Advanced Therapeutic Endoscopy for Pancreatico-Biliary Diseases

Tetsuya Mine
Rikiya Fujita
Editors

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Preface

Professor Rikiya Fujita asked me to write a book regarding the pancreatico-biliary system, and I accepted his offer, settling on the title *Advanced Therapeutic Endoscopy for Pancreatico-biliary Disease*. The editors were Rikiya Fujita and me. We divided the entire book into nine parts. Part I is about ERCP and includes an introduction, the cannulation method, the cannulation method on postoperative stomachs by balloon endoscopy, and ENBD. Next, EUS is described in Part II. It includes fine-needle aspiration and biopsies; the current situation and future of EUS-FNA, EUS-BD, and, furthermore, pancreatic gastrostomy focusing on WON; tumor ablation using EUS; and neurolysis of celiac ganglions using EUS. Part III includes intraductal ultrasonography. Part IV includes EST, and in Part V, EPLBD including EST is described. Part V includes how to treat biliary calculi. Mechanical lithotripsy and electrohydraulic shock wave lithotripsy are also described therein.

Moreover, we decided to include how to treat chronic pancreatitis in Part VI. In Part VII, we decided to include biliary drainage. We included peroral pancreatoscopy in Part VIII, and finally, endoscopic papillectomy is included in Part IX.

Isehara, Japan — Tetsuya Mine
Yokohama, Japan — Rikiya Fujita

Contents

Chapter 1
The History of ERCP and EUS

Rikiya Fujita

Abstract Initially, endoscopic retrograde cholangiopancreatography (ERCP) was developed based on the idea that diagnosis of pancreatic cancer would be possible by injecting a contrast medium retrogradely from Vater's papilla. After imaging diagnosis of pancreatic cancer became possible in the 1970s, ERCP gradually developed into interventional ERCP.

Around the same time, development of endoscopic ultrasonography (EUS) was underway, which was aimed at diagnosis of early stage pancreatic cancer. EUS development began in 1980, more than a decade after the development of ERCP had begun. Like ERCP, EUS was used for imaging diagnosis, and early applications took the form of endoscopic ultrasound fine-needle aspiration (EUS-FNA), later developing into interventional EUS. Today, the diagnostic and therapeutic applications of EUS have overtaken ERCP.

The capabilities of medical equipment reflect the scientific and technological conditions of the times. Today, both ERCP and EUS are indispensable for diagnosis and treatment of pancreatobiliary diseases.

Keywords Duodenoscope • ERCP • Endoscopic drainage • EUS • EUS-FNA

1.1 History of ERCP

ERCP was first reported by McCune in 1968 [1], although the fiberscope he used at the time had not yet been released commercially. Subsequently, Oi et al. of Tokyo Women's Medical University in cooperation with Machida Endoscope Co., Ltd. completed development of the FDS flexible duodenoscope, which was capable of observing Vater's papilla. With this new scope, endoscope-assisted imaging of the pancreatic duct was achieved in 1969 [2].

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Table 1.1 First-generation duodenoscopes

Development of duodenoscopes					
		Length and tip (mm)	Angulation		View-F degree
Machida 1969	FDSL	1465 and 28.5	u:120 d:90 Panning 60	Lateral	52
Olympus 1970	JF-B	1250 and 20	u:d: 120 r:l:90	Lateral	70
Fujinon 1975	FDQB	1500 and 17	u:d: 90 r:l:120	Lateral	64
Pentax 1981	FD32A	1600 and 21.4	u:d:135 r:l:100	Lateral	83 retroflex10

At about the same time, Takagi, et al. successfully performed intraoperative pancreatobiliary ultrasonography using the same fiberscope [3]. These successful cases were reported at the Japan Radiological Society Meeting of the Kanto Section in 1969.

A year later, in 1970, the Olympus group completed the JF-B fiberscope, which was designed specifically for the duodenum and was reported on by Shindo [4], Fujita [5], and Ogoshi et al. [6]. These groundbreaking developments were of such historical significance that they were reported on in 1970 at the World Congress of Gastroenterology (WCOG) co-hosted by Rome and Copenhagen. This marked a turning point in endoscopy and many endoscopists started visiting Japan. At the next WCOG held in Paris in 1972, reports on biliary and pancreatic endoscopy followed one another in rapid succession.

The standardization of the term "ERCP" was agreed upon at the symposium of the WCOG held in 1974 in Mexico City [7]. Up until then, it had been called "EPCG" in Japan, which stood for endoscopic pancreato-cholangiography. Subsequently, Fujinon and Pentax followed suit in the development of their endoscopes (Table 1.1).

In1973 and 1974, further progress was made in interventional ERCP when Kawai et al. [8], Classen et al. [9], and Soma, et al. [10] succeeded in performing endoscopic papillotomy, whose subsequent development is detailed in the corresponding chapters.

1.2 History of EUS

Ultrasonography was developed to facilitate diagnosis by obtaining images extracorporeally, but it was not easy to obtain images of a targeted pancreatic cancer. One of the world's leading experts in ultrasonographic diagnosis at that time, Dr. Fukuda came up with the idea of attaching an ultrasound transducer to the distal end of an endoscope to make it possible to diagnose early cancer within the body cavity [11]. Around the same time, DiMagno, Green et al. [12] also conceived the idea of combining endoscopy with ultrasonography—a combination that would later develop into EUS.

Table 1.2 First-generation ultrasound endoscopes

Development of EUS				
	Scope	Tip length mm	Diameter mm	Power MH
ACMI-national TV	FX-8 1980 Linear	80	13	10
Olympus-Aloka	GF-UM1 1982 Radial Convex	35	13.2	7.5 12
Machida-Toshiba	EPB-503FL 1983 Linear	45		10
Pentax (Hoya)-Hitachi	FG-32UA 1990 Convex	40	12	12
Fujifilm	EG-530UR 2007 Radial	35	15	20
	Convex		13.9	12

Research into this idea was soon undertaken by Olympus and Aloka. Subsequently, it was decided to transfer some Aloka engineers to Olympus. Soon, the project moved from the conceptual stage to concrete development. At this point, Japanese endoscopists such as Dr. Kawai, Dr. Nakazawa, and Dr. Takemoto participated in the project.

In 1980, work was completed on a model that could be used clinically, with the first report on successful cases coming from Classen et al. [13, 14] in Germany. This report can be found in English-language diagnostic books [15, 16].

Soon after, Wiersema and Vilmann et al. [17] performed fine-needle aspiration biopsy of pancreatic cancer. This technique was called EUS-FNA and marked the debut of interventional EUS. In addition to pathological examinations of pancreatobiliary diseases, EUS-FNA is now applied to drainage of pancreatic cysts and cystic lesions, as well as necrosectomy in cases of acute pancreatitis.

The first-generation models of ultrasound endoscopes from various manufacturers are shown in Table 1.2.

1.3 Conclusion

Development of something new starts from where there is dissatisfaction with the way things are. There is an old saying of Confucius that goes, “Study the past if you would define the future.” It is a saying that rings true in the sense that when old ways of doing things are no longer working, then things that have not existed before need to be created. The development of new products is influenced by the needs of the times.

Breakthroughs can occur no matter what the times. Breaking through to the other side requires courage and luck.

References

1. McCune WS, Shorb PE, Moskovitz H. Endoscopic cannulation of the ampulla of Vater: a preliminary report. Ann Surg. 1968;167(5):752–6.
2. Oi. Techniques of endoscopicancreato-cholangiography (in Japanese). Tokyo: Igakushoin; 1973.
3. Takagi K, Ikeda S, Nakagawa Y, et al. Retrograde pancreatography and cholangiography by fiberduodenoscope. Gastroenterology. 1970;59(3):445–52.
4. Shindo K, Ashizawa S. Fiberoptic duodenoscopy. Gastroenterol Endosc. 1970;12:70–8.
5. Fujita R, Sohma S, Kidokoro T. Endoscopy of the duodenum using the Olympus JFB2. Gastroenterol Endosc. 1970;12:97–106.
6. Ogoshi K, Tobita Y, Hara Y. Endoscopic observation of the duodenum and endoscopic pancreato-cholangiography. Gastroenterol Endosc. 1970;12:83–94.
7. Ogoshi K, Kasugai T. EPCG or ERCP(in Japanese). Stomach Intestine(I to Cho). 1975;10:538–539.
8. Kawai K, Nakajima M. Preliminary report on endoscopical papillotomy. J Kyoto Pref Univ Med. 1973;82:353.
9. Classen M, Demling L. Endoskopische Sphincterotomie der Papilla Vater und Steinextraktion aus dem Ductus Choledocus. Dtsch Med Wochenschr. 1974;99:496–7.
10. Sohma S, Fujita R. Endoscopic sphinctero-papillotomy. Gastroenterol Endosc. 1974;16(4): 446–53.
11. Fukuda M, Cosgrove D. Abdominal ultrasound, a basic textbook. Tokyo: Igakushoin; 1997.
12. DiMagno EP, Buxton JL, Green PS, et al. Ultrasonic endoscopy. Lancet. 1980;1:629–61.
13. Strohm WD, Phillip J, Hagenmueller F, Classen M. Ultrasonic tomography by means of an ultrasonic fiberendoscope. Endoscopy. 1980;12(5):241–4.
14. Vilardell F. Digestive endoscopy in the second millennium, part 2 endoscopic ultrasonography. Stuttgart: Thieme; 2006. p. 165–70.
15. Kawai K, editor. Endoscopic ultrasonography in gastroenterology. Tokyo: Igakushoin; 1988.
16. Fukuda M. Endoscopic ultrasonography. In: Gill RW, Dadd MJ, editors. WFUMB'85. Sydney: Pergamon Press; 1985. p. 13–6.
17. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine needle aspiration biopsy; diagnostic accuracy and complication assessment. Gastroenterology. 1997;112:1087–95.

Part I
ERCP

Chapter 2
Introduction of ERCP

Tetsuya Mine

Abstract Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic technique in which a side-viewing upper endoscope is guided into the duodenum, allowing for instruments to be passed into the bile and pancreatic ducts. Their new technique involves achieving opacification by the injection of contrast medium. It was developed by McCune et al., and two Japanese teams (Ohi et al. and Takagi et al.) followed separately. It is now a major technique employed worldwide. Recent advances have been made in the diagnosis and treatment of biliary duct and pancreas diseases. Their techniques are permitting radiologic visualization and allowing for a variety of therapeutic interventions.

Keywords ERCP • Cholangitis • Common bile duct stones

2.1 Indication

ERCP, magnetic resonance cholangiopancreatography, and endoscopic ultrasonography have comparable sensitivity and specificity in the diagnosis of choledocholithiasis. Patients undergoing cholecystectomy do not require an ERCP preoperatively if there is a low probability of having choledocholithiasis. ERCP with sphincterotomy and stone removal is a valuable therapeutic modality in choledocholithiasis with jaundice, dilated common bile duct, acute pancreatitis, or cholangitis. In patients with pancreatic or biliary cancer, the principal advantage of ERCP is palliation of biliary obstruction when surgery is not elected. Tissue sampling for patients with pancreatic or biliary cancer not undergoing surgery may be achieved by ERCP, but this is not always diagnostic. ERCP is the best means to diagnose ampullary cancers. ERCP has no role in the diagnosis of acute pancreatitis except when biliary pancreatitis is suspected. In patients with severe biliary pancreatitis, early intervention with ERCP reduces morbidity and mortality compared with

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delayed ERCP. ERCP with appropriate therapy is beneficial in selected patients who have either recurrent pancreatitis or pancreatic pseudocysts. Patients with type I sphincter of Oddi dysfunction (SOD) respond to sphincterotomy. Patients with type II SOD should not undergo diagnostic ERCP alone. If sphincter of Oddi manometric pressures are >40 mmHg, endoscopic sphincterotomy is beneficial in some patients. Avoidance of unnecessary ERCP is the best way to reduce the number of complications. ERCP should be avoided if there is a low likelihood of biliary stone or stricture, especially in women with recurrent pain, a normal bilirubin, and no other objective sign of biliary disease. Endoscopists performing ERCP should have appropriate training and expertise before performing advanced procedures.

Endoscope disinfection—in January 2014, the Centers for Disease Control and Prevention (CDC) reported that since January 2013, 69 cases of New Delhi metallo-beta-lactamase (NDM)-producing carbapenem-resistant *Enterobacteriaceae* (CRE; including *Escherichia coli*, *Klebsiella pneumoniae*) had been identified in the United States, 44 of which were from northeastern Illinois. Further investigation revealed 39 cases from one hospital. The source of infection was subsequently traced to the elevator channel of a single duodenoscope (the endoscopes used for endoscopic retrograde cholangiopancreatography [ERCP]). The procedure for cleaning the duodenoscopes was carefully reviewed, and no lapses in protocol were identified. It is theorized that the complex design of the elevator mechanism makes it more difficult to clean than other parts of endoscopes.

After changing duodenoscope reprocessing from high-level disinfection to gas sterilization with ethylene oxide, no new cases have been identified. Additional cases of CRE infection related to ERCP have been reported since the initial CDC report. With newer diagnostic imaging technologies emerging, ERCP is evolving into a predominantly therapeutic procedure.

2.2 EST

Furthermore, endoscopic sphincterotomy (EST) was developed in 1973. Three doctors, Classen M et al., Kawai K et al., and Sohma S et al., developed EST, independently.

After development of EST, ERCP is a tool of diagnosis as well as therapy.

Thereafter, the use of ERCP appears to be increasing with time. Average utilization of ERCP increased from 58 to 105 ERCPs per 100,000 person-years over a 10-year period. Similar to other endoscopic procedures, determinants of ERCP procedural safety include:

Sedation and monitoring practice
Patient age and clinical condition
Specific procedures performed
Setting and equipment of the endoscopy unit
Training and competence of endoscopic team

At least 180 procedures are required for a trainee to acquire a level of competence in diagnostic and therapeutic endoscopic retrograde cholangiopancreatography, defined by deep cannulation of the bile duct in 70–80% of cases.

This is still below the optimal standard of 90–95% success when the procedure is performed by experts. Cannulation is the only one diagnostic component of an ERCP, but ERCP has evolved from a diagnostic to a predominantly therapeutic procedure, and the procedural threshold has risen well above ASGE training guideline published in 2006 and updated in 2016.

Indications for ERCP have been proposed in consensus statements and guidelines with ASGE. The need for recognizing accepted indications for ERCP is underscored by the observation that malpractice litigation surrounding ERCP frequently involves disputes regarding the appropriateness of the indications. There is general consensus that ERCP should be done for good indications, by experienced endoscopists using standard techniques with well-documented, patient-informed consent, and communication before and after the procedure.

Complications should be recognized and managed early, and there should be honest and compassionate communication with the family and patients.

Complications are expected to occur in a predictable proportion of patients undergoing ERCP, even in expert hands. A number of patient-related and technique-related factors are known to increase the risk of complications.

Careful clinical monitoring of patients by the operator and assistance is mandatory, since ERCP is a complex procedure that is often performed for therapeutic purposes and requires sedation.

The patient is usually kept fasting before the procedure. Following the procedure, most experienced endoscopists will have patients who at high or moderate risk of complications continue to fast, or they will advance the diet to clear liquid only.

Such patients may resume their normal diet the next morning. Majority of complications appear during the first 6 h after the procedure. Therefore, patients should be carefully monitored during the recovery phase after ERCP to detect symptoms or signs suggestive of adverse events.

Several multicenter studies involving large numbers of patients in community and tertiary environment have identified risk factors associated with complications: operator-related factors (low numbers of ERCP done), method-related factors, (difficulty in cannulation, biliary sphincterotomy, and precut sphincterotomy), and patient-related factors (sphincter of Oddi dysfunction, periampullary diverticulum, and cirrhosis).

Definition and classification of complications—the spectrum of negative outcomes of endoscopic procedures includes the following: (1) complications, undesired events that require management by a clinician and unplanned admission or prolongation of planned hospital stay; (2) incidents, undesired events that do not qualify as complications; (3) adverse sequelae, adverse but inevitable results of the procedure, such as the loss of sphincter activity due to sphincterotomy; (4) technical failures, ERCP-related complications that can be divided into two main groups; (5) general complications common to all endoscopic procedures, like medication reactions, oxygen desaturation, cardiopulmonary accidents, and hemorrhage or

perforation induced by traumatic passage of the endoscope; and (6) selective complications specific to pancreatobiliary instrumentation, including pancreatitis, sepsis, and hemorrhage or retroperitoneal duodenal perforation following therapeutic procedures.

A 1991 consensus panel introduced a standardized, outcome-based set of definitions and grading system for the major complications of ERCP and endoscopic sphincterotomy. Complications may be focal, occurring at the point of endoscopic contact (e.g., perforation, bleeding, pancreatitis), or nonspecific, occurring in organs not traversed or touched (e.g., cardiopulmonary problems). With regard to timing, complications may be early or late, with a conventional cutoff at 30 days. The first group includes immediate, early, and delayed events, while the latter includes focal direct complications occurring after 30 days. The severity of complications can be expressed in terms of the length of hospital stay; the need for transfusions; intensive care unit assistance; surgical, radiologic or endoscopic interventions, and any resulting permanent disability; and death.

2.3 Incidence

Reporting complications—incidence rates of post-ERCP complications vary widely, depending largely upon the definition adopted, the methods of data collection, and the case mix (selection of the patients and techniques used). Retrospective surveys inevitably underestimate the frequency of adverse events. However, even prospective surveys are prone to measurement biases if the modality of data collection does not use strict criteria.

Prospective surveys from single referral centers ensure the highest accuracy but are unlikely to be representative of the frequency and severity of unfavorable events in practice. By comparison, prospective multicenter studies involving centers with different volumes of activity and operators with various degrees of expertise more reliably reflect the general effectiveness and safety of the endoscopic procedures on the pancreaticobiliary ducts.

Incidence rates—multiple studies have evaluated the incidence of post-ERCP complications: specific complications (pancreatitis, bleeding, sepsis, and perforation). In a summary of 21 studies involving 16,855 patients between 1987 and 2003, specific complications totaled 1154 (6.9%), with 55 deaths (0.33%). Mild-to-moderate events occurred in 872 patients (5.2%) and severe events in 282 (1.7%). Similar rates of specific complications (5.3%) and deaths (0.34%) were reported in two subsequent prospective studies involving a total of 7252 patients. Nonspecific complications—among 12,973 patients enrolled in 14 prospective studies, general complications totaled 173 (1.3%), with nine deaths (0.07%). A similar rate of nonspecific complications (0.87%) was noted in two subsequent prospective studies involving a total of 7252. Despite technological progress and recommendations of scientific societies, the incidence of complications and procedure-related mortality does not appear to have changed significantly with time. In the specific area, ERCPs

performed between 2002 and 2009, the overall complication and mortality rates were 11% and 0.4%, respectively. In a multicenter Austrian study that included 13,514 ERCPs performed between 2006 and 2009, the overall complication and mortality rates were 10% and 0.1%, respectively. Similarly, in a multicenter Norwegian study, ERCPs performed between 2007 and 2009, the overall complication and mortality rates were 12% and 1.4%, respectively. One possible reason why complication rates have not declined is that with time, ERCP has become a primarily therapeutic procedure. Specific complications are as follows:

Pancreatitis—The most frequent complication of ERCP is pancreatitis.

Bleeding—Bleeding during ERCP typically develops after sphincterotomy. As for all endoscopic procedures, patients should be screened for a history of excessive bleeding and the use of anticoagulants or antiplatelet agents. A platelet count and prothrombin time should be checked in patients undergoing ERCP.

Infection—Infections occurring after ERCP are most often due to manipulation of an obstructed biliary or pancreatic system. Less commonly, infection can be introduced by contaminated endoscopic equipment, which is unlikely if proper disinfection methods have been used. However, several cases of infection with carbapenem-resistant *Enterobacteriaceae* have been reported despite proper disinfection protocols having been followed. The American Heart Association and the American Society for Gastrointestinal Endoscopy (ASGE) have issued guidelines for antibiotic prophylaxis prior to endoscopic procedures. It is imperative to achieve effective drainage in patients with biliary obstruction. Thus, diagnostic ERCP should not be performed in such patients without the capability of providing immediate endoscopic drainage.

Perforation—ERCP may rarely be complicated by perforation of the esophagus, stomach, duodenum, or jejunum. The risk is increased in patients with stenosis of any of these segments and in patients who have undergone gastric resection. Retroperitoneal duodenal perforation can occur, usually secondary to sphincterotomy.

Nonspecific complications—ERCP is associated with a number of complications common to other procedures.

Chapter 3
Wire-Guided Cannulation

Hiroshi Kawakami and Yoshimasa Kubota

Abstract Selective bile duct cannulation (SBDC) is the most common technique for performing diagnostic and therapeutic biliary interventions. Wire-guided cannulation (WGC) is most commonly used in Western countries. A meta-analysis of randomized controlled trials (RCTs) found that WGC facilitates the primary SBDC and decreases the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). However, the RCTs involved one or at most two skilled endoscopists in a single-center setting. In more recent Japanese RCTs that were conducted at multiple centers by multiple endoscopists and using a crossover design, WGC did not improve the success rate of SBDC or the incidence of PEP compared with the conventional technique. We performed a multicenter RCT and found that WGC reduced the time required for SBDC, resulting in lower exposure to fluoroscopy. We conclude that WGC should be adopted for use in SBDC, leading to significantly less exposure to fluoroscopy. With a variety of SBDC techniques available, considerations for choice of technique should include operator, patient, and institutional factors. Endoscopists should be familiar with various techniques to allow flexibility depending upon each case. To improve the safety and efficacy of WGC, training and technique standardization are necessary. Here, we describe the novel use of WGC in SBDC, results of meta-analysis of WGC, results of the recent RCTs from Japan, and future perspectives.

Keywords Endoscopic retrograde cholangiopancreatography • Bile duct cannulation • Wire-guided cannulation

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3.1 Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard procedure for diagnostic and therapeutic interventions for pancreatobiliary diseases. Selective bile duct cannulation (SBDC) is the most effective technique for performing diagnostic and therapeutic biliary interventions. In 1968, McCune et al. reported the first use of endoscopic retrograde pancreatography [1] followed in 1970 by Takagi et al. reporting the first use of endoscopic retrograde cholangiography (ERC) [2]. Classen and Demling [3], Kawai et al. [4], and Sohma et al. [5] reported endoscopic sphincterotomy in 1974. The technical success rate of SBDC for trainees is suggested to be 80–90%, while that for expert endoscopists climbs to 95–100% [6]. Although there have been major advances in techniques, devices, and the sophistication of endoscopes, no standard SBDC technique has been established, and it is still a challenging procedure in difficult cases [7]. Cases of difficult or failed SBDC can be associated with post-ERCP pancreatitis (PEP). There are three important factors for successful SBDC: type of catheter, cannulation method, and skill of the endoscopist and the assistant. Complications arise due to patient factors (e.g., individual anatomy), procedural factors, and expertise of the endoscopist and the assistant [7].

Various endoscopic techniques for SBDC have been reported [6], such as contrast injection and wire-guided cannulation (WGC), the pancreatic guidewire technique (e.g., double-guidewire technique), precut sphincterotomy, endoscopic papillectomy [6], the endoscopic ultrasonography-guided rendezvous procedure, and the percutaneous transhepatic biliary drainage-guided procedure. In this text, WGC is reviewed and summarized.

3.2 Development of WGC

WGC is a technique for SBDC using a guidewire as a micro catheter. It is most widely utilized in Western countries [8].

Siegel and Pullano [9] reported the first use of WGC for SBDC in 1987. At that time, no dedicated guidewire for ERCP had been developed, preventing this technique from gaining widespread acceptance. The WGC technique was popularized as devices, particularly guidewires, were developed. The usefulness of a sphincterotome for SBDC was reported in 1993 [10]. In 1996, Schapiro et al. reported a high SBDC success rate when WGC was performed using a guidewire and sphincterotome [11]. Two randomized controlled trials (RCTs) compared guidewire thickness (0.025 in. vs. 0.035 in.) and assessed the SBDC success rate and incidence of complications, finding no significant differences [12, 13]. A prospective RCT compared an angled-tip guidewire and a J-tip guidewire for WGC, also reporting no significant differences in the incidence of successful SBDC [14]. Hybrid guidewires composed of a soft, hydrophilic-tipped guidewire with a nitinol shaft

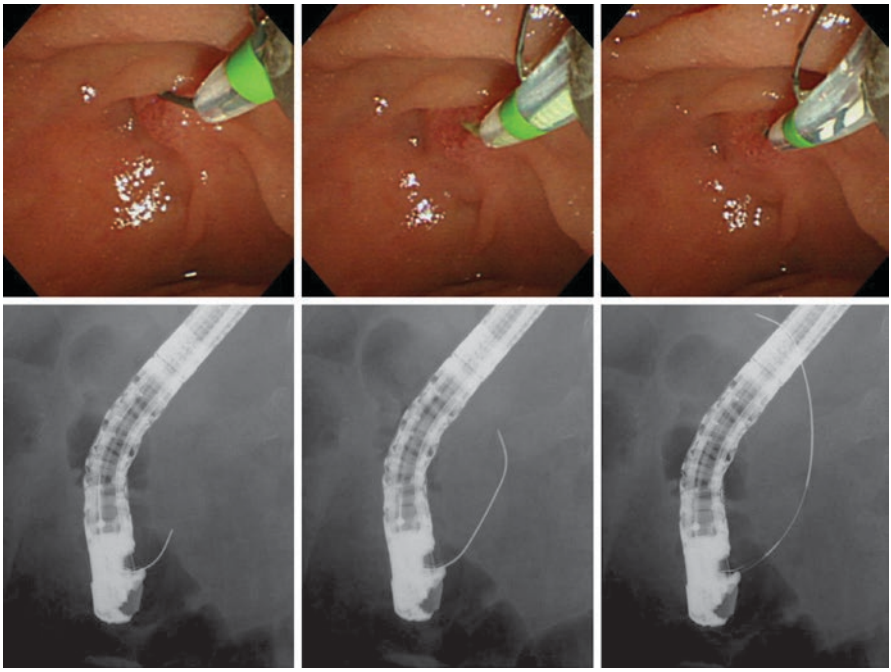

Fig. 3.1 Wire-guided cannulation technique (From ISBN 978-4-7581-1046-4 [in Japanese] with permission). Selective bile duct cannulation is usually performed facing the ampulla of Vater. An endoscopic retrograde cholangiopancreatography (ERCP) catheter or sphincterotome preloaded with a guidewire is inserted into the working channel of a duodenoscope. The tip of the guidewire or catheter is directed at the 11–12 o'clock position. Careful guidewire manipulation should be performed under endoscopic view and fluoroscopic guidance. An ERCP catheter or sphincterotome should not be cannulated before the guidewire is advanced to the common bile duct so as not to distort the ampulla of Vater and distal bile duct. The guidewire is controlled by an endoscopist or an assistant. The use of contrast is usually not allowed until the selective bile duct cannulation has been completed

engineered for optimal wire control and manipulation are currently widely used (Fig. 3.1).

The advantages of a guidewire technique are as follows: successful cannulation can be confirmed fluoroscopically, eliminating pancreatic duct opacification, and an appropriately directed, soft-tipped, hydrophilic wire, or a loop-tipped guidewire, may more easily overcome anatomical challenges presented by the distal bile duct and papilla than the more rigid sphincterotome or cannulating catheter [8]. Several RCTs [7, 15–21] state that WGC facilitates the primary SBDC and decreases the incidence of PEP (Table 3.1). The guidelines of the European Society of Gastrointestinal Endoscopy place WGC as the first-line SBDC technique and note that WGC is essential for reducing PEP, based on the results of Cennamo et al. [24]. In contrast, the guidelines of the American Society of Gastrointestinal Endoscopy do not recommend WGC as essential for PEP prevention [23].

Table 3.1 Summary of randomized controlled trials for wire-guided cannulation

Author	Ref.	Year	Study design	No. of institutions	No. of endoscopists	Enrolled patients	Time limit	Attempts limit
Lella F	[15]	2004	S vs. S + GW	1	1	200 vs. 200	None	None
Artifon EL	[16]	2007	S vs. S + GW	1	1	150 vs. 150	(–)	10
Bailey AA	[17]	2008	S vs. S + GW	1	2 and fellows	211 vs. 202	10 min 5 min fellow	(–)
Katsinelos P	[18]	2008	C vs. C + GW	1	1	165 vs. 167	10 min	(–)
Lee TH	[19]	2009	S vs. S + GW	1	1	150 vs. 150	10 min	(–)
Nambu T	[20]	2011	C vs. S + GW	1	Multiple	86 vs. 86	10 min	(–)
Kawakami H	[7]	2012	C vs. C + GW vs. S vs. S + GW	15	Multiple	101 vs. 102 vs. 100 vs. 97	10 min	(–)
Kobayashi G	[21]	2013	C vs. C + GW	9	Multiple	159 vs. 163	30 min	(–)

(From [26] with permission)

[a]*S* sphincterotome, *C.* ERCP catheter, *GW* guidewire, (–) not available, *NS* not significant, *SBDC* selective bile duct cannulation, *PEP* post-ERCP pancreatitis

3.3 Meta-Analysis of WGC (Table 3.1)

The efficacy of WGC has been shown in meta-analyses [24, 25] and reviewed elsewhere [26]. In 2009, Cennamo et al. [24] performed a meta-analysis comparing the contrast injection technique and WGC. After analyzing five RCTs [15–19], they showed that WGC improved the success rate of SBDC and reduced the risk of PEP compared with the standard contrast injection method. However, another meta-analysis by Shao et al. [25] that analyzed four RCTs [15–17, 19] did not find a significant association between the use of WGC and the reduction of PEP. An explanation for the discrepancy between findings was made by Shao et al. [25] as their subgroup analysis, including trials without a crossover design, showed that WGC significantly reduced the risk of PEP. A crossover design is more ideal than a noncrossover design in the clinical setting. Other SBDC techniques should be performed when a technique fails. Sticking to a technique is just time consuming [26]. Therefore, care should be taken to understand the study design when interpreting results of the studies included in each meta-analysis.

3.4 RCTs from Japan (Table 3.1)

Recent RCTs from Japan showed no superiority of WGC compared with the standard contrast injection method regarding the success rate of SBDC or the risk of PEP [7, 20, 21]. Nambu et al. [20] conducted a prospective RCT with a crossover design including 172 cases. A study by Kawakami et al. included 400 patients in a multicenter, prospective, randomized controlled design [7]. Kobayashi et al. [21] included 163 patients in a multicenter randomized controlled design. These studies did not reveal significant differences in the success rate of SBDC and the incidence of PEP between WGC and the contrast injection method. However, WGC reduced the time required for SBDC in one study, leading to significantly less exposure to fluoroscopy [7]. These results may indicate that WGC is a superior SBDC technique compared to the contrast injection method.

Factors that influenced results where no significant differences were found between WGC and the contrast injection method included crossover design and multiple endoscopists. There was also a difference in the backward oblique angle of the duodenoscope used in the RCTs that showed significant differences compared to those that did not. Japanese RCTs [7, 20] used a 15-degree backward oblique angle duodenoscope, which is the standard ERCP scope in Japan. In contrast, in Western countries, a 5-degree backward oblique angle duodenoscope is currently the standard ERCP scope. One report concluded that the 15-degree backward oblique angle duodenoscope was superior to the 5-degree backward oblique angle duodenoscope and did not require the bow-up function of the sphincterotome [27]. A 15-degree backward oblique angle duodenoscope can allow the endoscopist to adjust to the axis of the bile duct [27, 28].

To summarize, in a noncrossover study design conducted by multiple endoscopists, WGC for SBDC requires less time and less exposure to fluoroscopy.

3.5 Complications of WGC

Complications specific to WGC have not been well determined since it is difficult to distinguish WGC-specific complications from complications arising from the subsequent ERCP procedures. WGC may cause PEP similarly to the contrast injection method. Nakai et al. [29] retrospectively evaluated the incidence and risk factors of PEP in 800 consecutive patients with a native papilla who underwent WGC. They reported the incidence of PEP as 9.5%. In their report, a non-dilated common bile duct (diameter of <9 mm) and unintentional guidewire insertion into the main pancreatic duct were revealed as risk factors for PEP in biliary therapeutic ERCP with the use of WGC [29]. Sasahira et al. [30] compared early conversion to the double-guidewire method at first unintentional insertion of a guidewire into the pancreatic duct and repeated single-guidewire cannulation. In their study, PEP

incidences were not significantly different (17–20%). One characteristic complication of WGC is perforation of the ampulla of Vater [7]. A rare complication of WGC, portobiliary fistula, was reported by Kawakami et al. [31].

3.6 Roles of Assistants in WGC

The roles of the assistants, as well as the operators, are important in WGC, just like any ERCP. Manipulation of the guidewire and manual dexterity are essential for SBDC using WGC. The expertise and previous medical training of assistants is seldom described in published reports. Only Lee et al. [19] described the assistants as having 2 years of training. Since competence development and learning curves of ERCP are discussed in reports [32–34], training and experience of the assistants should also be discussed.

3.7 Differences Between Japan and Western Countries

As described, the contrast injection technique is the major SBDC technique utilized in Japan. ERCP is considered to be both an important diagnostic and therapeutic procedure in Japan. One problem with WGC is that ERC just above the papilla tends to be insufficient. However, this can be solved using ERCP catheters that are able to inject contrast agents without withdrawing the guidewire. The willingness of operators and assistants to utilize diagnostic ERC is what is required. The guidewire should not be immediately followed by the catheter after SBDC before ERC. ERC can be done with continuous suction to eliminate duodenal gas and leaking of the contrast agent. WGC is a relatively new technique in Japan introduced in 2007. Guidewires are not covered by medical payment methods in Japan. However, the use of a guidewire is essential as therapeutic ERCPs are becoming more commonly used. WGC should become a first-line SBDC technique in Japan. In contrast, WGC is already a first-line SBDC technique in Western countries. It should be emphasized that the most common method is physician-controlled WGC, in which the guidewire is manipulated by the operator himself/herself. The reasons for differences between Japan and Western countries with regard to WGC usage are as follows: (1) procedure time, (2) number of doctors and assistants, (3) insurance, and (4) training systems, which greatly differ between Western countries and Japan. A short procedure time is valued in Western countries. ERCP is typically only performed by the operator and assistants in Western countries, while two or more doctors usually participate in the procedure in Japan. Bundled payment has been adopted in Western countries. Finally, education is systematic in Western countries, while it is typically one-to-one in Japan.

3.8 Future Perspectives

WGC should become the first-line SBDC technique worldwide. However, WGC is not the perfect technique for SBDC. Therefore, other techniques should be considered as well, based on factors including the operator, patient, and institution. Pancreatobiliary endoscopists should be familiar with multiple techniques so that they can be flexible on a case-by-case basis. Standardization and training are necessary to improve the safety and efficacy of the technique.

References

1. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. Ann Surg. 1968;167:752–6.
2. Takagi K, Ikeda S, Nakagawa Y, Sakaguchi N, Takahashi T. Retrograde pancreatography and cholangiography by fiber duodenoscope. Gastroenterology. 1970;59:445–52.
3. Classen M, Demling L. Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl). Dtsch Med Wochenschr. 1974;99:496–7.
4. Kawai K, Akasaka Y, Murakami K, Tada M, Koli Y. Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc. 1974;20:148–51.
5. Sohma S, Tatekawa I, Okamoto Y, et al. Endoscopic papillotomy: a new approach for extraction of residual stones. Gastroenterol Endosc. 1974;16:446–53. (in Japanese).
6. Freeman ML, Guda NM. ERCP cannulation: a review of reported techniques. Gastrointest Endosc. 2005;61:112–25.
7. Kawakami H, Maguchi H, Mukai T, Hayashi T, Sasaki T, Isayama H, Nakai Y, Yasuda I, Irisawa A, Niido T, Okabe Y, Ryozawa S, Itoi T, Hanada K, Kikuyama M, Arisaka Y, Kikuchi S, Japan Bile Duct Cannulation Study Group. A multicenter, prospective, randomized study of selective bile duct cannulation performed by multiple endoscopists: the BIDMEN study. Gastrointest Endosc. 2012;75:362–72, 372.e1.
8. Bourke MJ, Costamagna G, Freeman ML. Biliary cannulation during endoscopic retrograde cholangiopancreatography: core technique and recent innovations. Endoscopy. 2009;41:612–7.
9. Siegel JH, Pullano W. Two new methods for selective bile duct cannulation and sphincterotomy. Gastrointest Endosc. 1987;33:438–40.
10. Rossos PG, Kortan P, Haber G. Selective common bile duct cannulation can be simplified by the use of a standard papillotome. Gastrointest Endosc. 1993;39:67–9.
11. Schapiro GD, Jaffe D, Ryder D, et al. Wire guided papillotomes increase the selective bile duct cannulation rate. Gastrointest Endosc. 1996;43:394.
12. Halttunen J, Kylänpää L. A prospective randomized study of thin versus regular-sized guide wire in wire-guided cannulation. Surg Endosc. 2013;27:1662–7.
13. Kitamura K, Yamamiya A, Ishii Y, Sato Y, Iwata T, Nomoto T, Ikegami A, Yoshida H. 0.025-inch vs. 0.035-inch guide wires for wire-guided cannulation during endoscopic retrograde cholangiopancreatography: a randomized study. World J Gastroenterol. 2015;21:9182–8.
14. Tsuchiya T, Itoi T, Maetani I, Shigoka H, Ikeuchi N, Umeda J, Sofuni A, Itokawa F, Ishii K, Kurihara T, Tsuji S, Tanaka R, Tonozuka R, Honjyo M, Mukai S, Moriyasu F. Effectiveness of the J-tip guidewire for selective biliary cannulation compared to conventional guidewires (The JANGLE Study). Dig Dis Sci. 2015;60:2502–8.
15. Lella F, Bagnolo F, Colombo E, Bonassi U. A simple way of avoiding post-ERCP pancreatitis. Gastrointest Endosc. 2004;59:830–4.

16. Artifon EL, Sakai P, Cunha JE, Halwan B, Ishioka S, Kumar A. Guidewire cannulation reduces risk of post-ERCP pancreatitis and facilitates bile duct cannulation. Am J Gastroenterol. 2007;102:2147–53.
17. Bailey AA, Bourke MJ, Williams SJ, Walsh PR, Murray MA, Lee EY, Kwan V, Lynch PM. A prospective randomized trial of cannulation technique in ERCP: effects on technical success and post-ERCP pancreatitis. Endoscopy. 2008;40:296–301.
18. Katsinelos P, Paroutoglou G, Kountouras J, Chatzimavroudis G, Zavos C, Pilpilidis I, Tzelas G, Tzovaras G. A comparative study of standard ERCP catheter and hydrophilic guide wire in the selective cannulation of the common bile duct. Endoscopy. 2008;40:302–7.
19. Lee TH, Park DH, Park JY, Kim EO, Lee YS, Park JH, Lee SH, Chung IK, Kim HS, Park SH, Kim SJ. Can wire-guided cannulation prevent post-ERCP pancreatitis? A prospective randomized trial. Gastrointest Endosc. 2009;69:444–9.
20. Nambu T, Ukita T, Shigoka H, Omuta S, Maetani I. Wire-guided selective cannulation of the bile duct with a sphincterotome: a prospective randomized comparative study with the standard method. Scand J Gastroenterol. 2011;46:109–15.
21. Kobayashi G, Fujita N, Imaizumi K, Irisawa A, Suzuki M, Murakami A, Oana S, Makino N, Komatsuda T, Yoneyama K. Wire-guided biliary cannulation technique does not reduce the risk of post-ERCP pancreatitis: multicenter randomized controlled trial. Dig Endosc. 2013;25:295–302.
22. Testoni PA, Mariani A, Aabakken L, Arvanitakis M, Bories E, Costamagna G, Devière J, Dinis-Ribeiro M, Dumonceau JM, Giovannini M, Gyokeres T, Hafner M, Halttunen J, Hassan C, Lopes L, Papanikolaou IS, Tham TC, Tringali A, van Hooft J, Williams EJ. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016;48(7):657–83.
23. ASGE Standards of Practice Committee, Anderson MA, Fisher L, Jain R, Evans JA, Appalaneni V, Ben-Menachem T, Cash BD, Decker GA, Early DS, Fanelli RD, Fisher DA, Fukami N, Hwang JH, Ikenberry SO, Jue TL, Khan KM, Krinsky ML, Malpas PM, Maple JT, Sharaf RN, Shergill AK, Dominitz JA. Complications of ERCP. Gastrointest Endosc. 2012;75: 467–73.
24. Cennamo V, Fuccio L, Zagari RM, Eusebi LH, Ceroni L, Laterza L, Fabbri C, Bazzoli F. Can a wire-guided cannulation technique increase bile duct cannulation rate and prevent post-ERCP pancreatitis?: a meta-analysis of randomized controlled trials. Am J Gastroenterol. 2009;104:2343–50.
25. Shao LM, Chen QY, Chen MY, Cai JT. Can wire-guided cannulation reduce the risk of post-endoscopic retrograde cholangiopancreatography pancreatitis? A meta-analysis of randomized controlled trials. J Gastroenterol Hepatol. 2009;24:1710–5.
26. Kawakami H, Kubota Y, Kawahata S, Kubo K, Kawakubo K, Kuwatani M, Sakamoto N. Transpapillary selective bile duct cannulation technique: review of Japanese randomized controlled trials since 2010 and an overview of clinical results in precut sphincterotomy since 2004. Dig Endosc. 2016;28(Suppl 1):77–95.
27. Kawakami H, Maguchi H, Hayashi T, Yanagawa N, Chiba A, Hisai H, Amizuka H. A prospective randomized controlled multicenter trial of duodenoscopes with 5 degrees and 15 degrees backward-oblique angle using wire-guided cannulation: effects on selective cannulation of the common bile duct in endoscopic retrograde cholangiopancreatography. J Gastroenterol. 2009;44:1140–6.
28. Kawakami H, Isayama H, Maguchi H, Kuwatani M, Kawakubo K, Kudo T, Abe Y, Kawahata S, Kubo K, Koike K, Sakamoto N. Is wire-guided selective bile duct cannulation effective for prevention of post-ERCP pancreatitis by all endoscopists? Endoscopy. 2014;46:163.
29. Nakai Y, Isayama H, Sasahira N, Kogure H, Sasaki T, Yamamoto N, Saito K, Umefune G, Akiyama D, Kawahata S, Matsukawa M, Saito T, Hamada T, Takahara N, Mizuno S, Miyabayashi K, Mohri D, Hirano K, Tada M, Koike K. Risk factors for post-ERCP pancreatitis in wire-guided cannulation for therapeutic biliary ERCP. Gastrointest Endosc. 2015;81:119–26.

30. Sasahira N, Kawakami H, Isayama H, Uchino R, Nakai Y, Ito Y, Matsubara S, Ishiwatari H, Uebayashi M, Yagioka H, Togawa O, Toda N, Sakamoto N, Kato J, Koike K. Early use of double-guidewire technique to facilitate selective bile duct cannulation: the multicenter randomized controlled EDUCATION trial. Endoscopy. 2015;47:421–9.
31. Kawakami H, Kuwatani M, Kudo T, Ehira N, Yamato H, Asaka M. Portobiliary fistula: unusual complication of wire-guided cannulation during endoscopic retrograde cholangiopancreatography. Endoscopy. 2011;43(Suppl 2 UCTN):E98–9.
32. Verma D, Gostout CJ, Petersen BT, Levy MJ, Baron TH, Adler DG. Establishing a true assessment of endoscopic competence in ERCP during training and beyond: a single-operator learning curve for deep biliary cannulation in patients with native papillary anatomy. Gastrointest Endosc. 2007;65:394–400.
33. Ekkelenkamp VE, Koch AD, Rauws EA, Borsboom GJ, de Man RA, Kuipers EJ. Competence development in ERCP: the learning curve of novice trainees. Endoscopy. 2014;46:949–55.
34. Cotton PB, Coté GA. ERCP (ensuring really competent practitioners). Endoscopy. 2014;46:922–4.

Chapter 4
Intrahepatic Selective Cannulation to the Left Bile Duct

Masami Ogawa, Yoshiaki Kawaguchi, and Tetsuya Mine

Abstract Selective cannulation to the left bile duct is essential for endoscopic management of biliary strictures caused by hilar cholangiocarcinoma, intrahepatic ductal calci, or primary sclerosing cholangitis.

However, selective placement of a guidewire or a catheter into the left bile duct is difficult. The cannula or guidewire tends to enter the right bile duct more easily than the left bile duct, probably because of the natural curve of the biliary system or the orientation of the accessories toward the right. So, several methods for insertion to the left bile duct have been described.

Keywords Selective cannulation • ERCP • Left bile duct

4.1 Intrahepatic Selective Cannulation to the Left Bile Duct

Selective cannulation to the left bile duct is essential for endoscopic management of biliary strictures caused by hilar cholangiocarcinoma, intrahepatic ductal calci, or primary sclerosing cholangitis.

However, selective placement of a guidewire or a catheter into the left bile duct is difficult, especially in the presence of the narrow biliary strictures typical of advanced hilar cholangiocarcinoma. The cannula or guidewire tends to enter the right bile duct more easily than the left bile duct, probably because of the natural curve of the biliary system or the orientation of the accessories toward the right. So, several methods for insertion to the left bile duct have been described.

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4.2 Guidewire

The initial attempt to access the desired duct involves various types of catheters and guidewires with various degrees of torque. Access to irregular or narrow strictures is usually facilitated by small-caliber, hydrophilic guidewires. Its hydrophilic properties result in tremendous flexibility and a reduction in frictional forces, making it possible to traverse strictures of various anatomic configurations.

Guide-wire with rounded tip sometimes easier to select the left bile duct (Fig. 4.1).

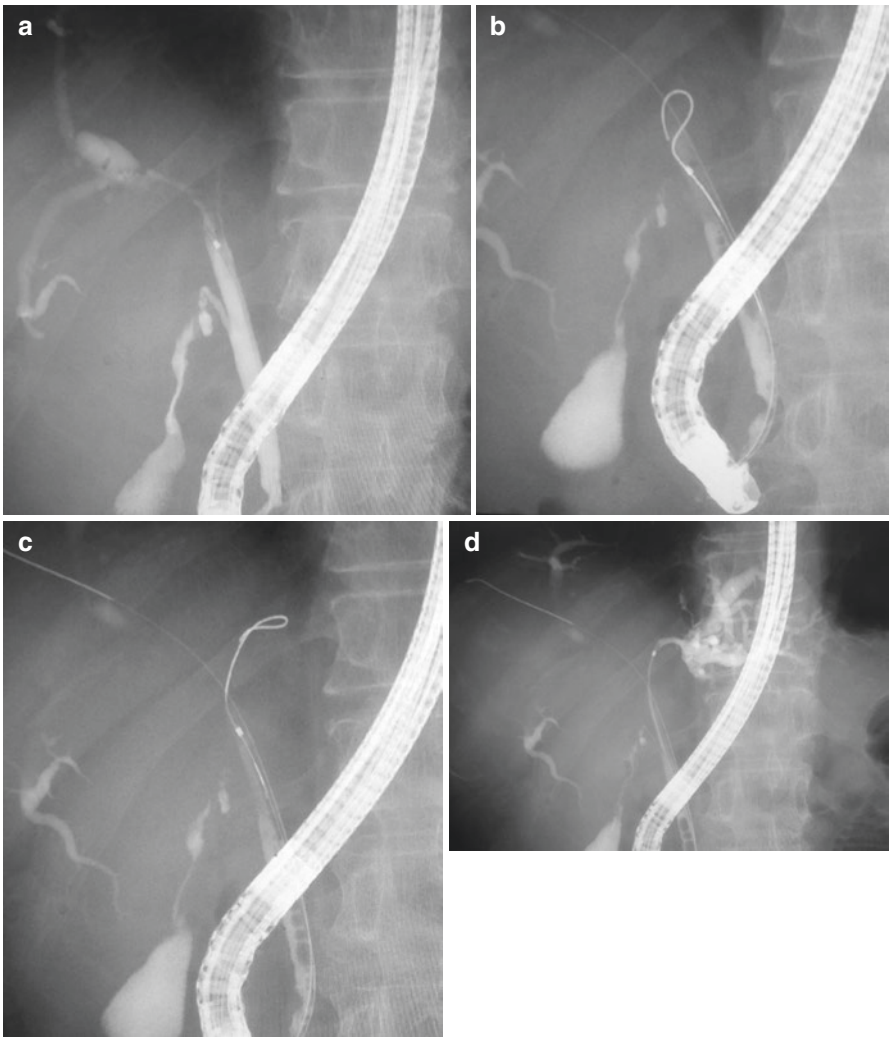

Fig. 4.1 Retrograde cholangiogram showing the strictures of hilar bile duct (**a**). Looping the tip of guidewire can selective cannulation to the left bile duct (**b**, **c**). Left bile duct was shown successfully (**d**)

4.3 Sphincterotome

Usefulness of a sphincterotome for selective cannulation for intrahepatic bile duct was reported [1, 2].

The tip of the sphincterotome has an intrinsic curve that orients it to the right; the orientation can be changed to the left by rotating the handle. Additionally, by tightening (bowing) the sphincterotome wire, the tip is easily deflected, up to 90°.

Although the rotatable sphincterotome has an advantage in directional control, it sometimes does not rotate well in the bile duct, especially in a narrow bile duct, and frequently twists instead of rotating. It also rotates sharply and does not always align with the intended duct.

SwingTip cannula (Olympus Co.) is similar device for selective cannulation. The tapered tip can be angulated as much as 90° when the handle is pulled and as much as 30° when pushed, ensuring easy insertion into the papilla and the biliary ducts, even in challenging cases.

4.4 Inflated Balloon Catheter

Balloon retrieval catheter was introduced over a guidewire into the right intrahepatic duct. The balloon was inflated in the right main hepatic duct under fluoroscopic guidance immediately proximal to the duct bifurcation. Subsequently a 0.035-in. guidewire was introduced alongside the balloon catheter via the 4.2-mm accessory channel of the therapeutic duodenoscope and into the bile duct. The guidewire was advanced across the CHD stricture and easily deflected off the inflated balloon into the left intrahepatic ductal system. The balloon was deflated and the balloon catheter withdrawn, leaving the two wires in place for bilateral access.

Directed balloon-assisted guidewire access is a procedure in which the opposite IHD is occluded by using an inflated balloon catheter before advancing the guidewire and deflecting it off the balloon and into the opposite duct. The balloon-occlusion method is time-consuming and requires a narrow ERCP catheter and a therapeutic duodenoscope because of the small diameter of the accessory channel.

4.5 Multi-lumen Catheter

Usefulness of a triple-lumen catheter (Haber Ramp; Cook Endoscopy, Winston-Salem, NC) for selective cannulation for intrahepatic bile duct was described (Fig. 4.2). To indicate the location of each opening, there are three radiopaque markings along the distal part of the triple-lumen catheter. One lumen exits at the tip of the catheter (distal opening), and the others exit at an angle on the either side of the catheter near the tip (side ramps; the middle opening is at the just proximal part of

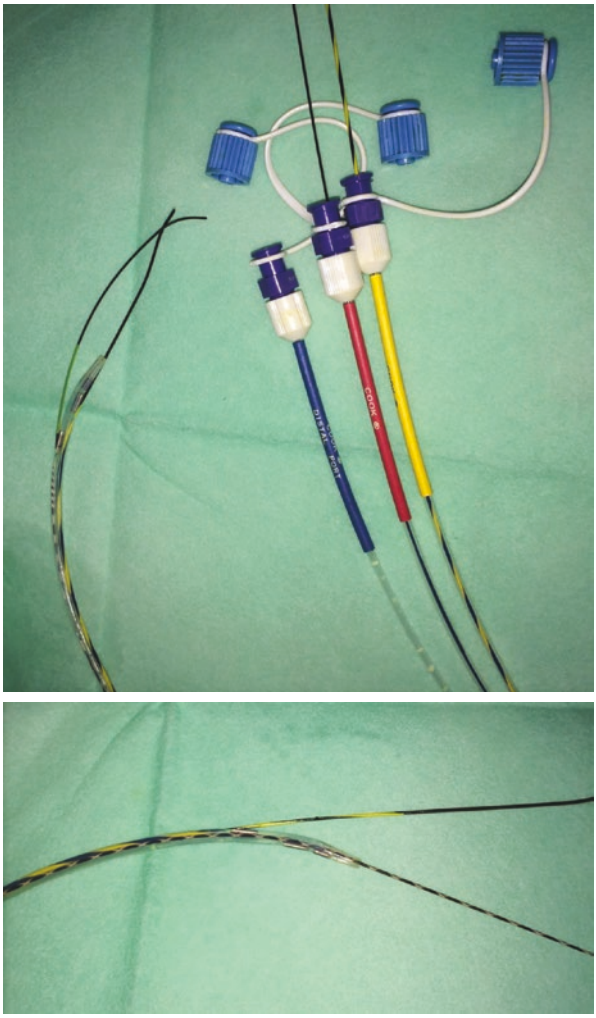

Fig. 4.2 The triple-lumen catheter (Haber Ramp; Cook Endoscopy, Winston-Salem, NC)

two distal radiopaque markings, and the proximal opening is at the proximal part of the most proximal marking) but at different distances (2 and 3 cm, respectively) from the tip. Kim et.al reported [3] that selective cannulation with the triple-lumen catheter was successful in10 of 15 patients (67%) in whom cannulation attempts were unsuccessful with conventional methods. The success rate of guidewire insertion into the bilateral IHD was 91% (53 patients) with the triple-lumen catheter, whereas it was 74% (43 patients) without the triple-lumen catheter.

References

1. Ching CK, Lai KC, Hu W, Lam SK. Cannulatome-aided selective intrahepatic bile duct cannulation. Gastrointest Endosc. 1996;43(6):632–3.
2. Moxon DR, Hong K, Brown RD, Venu RP. Selective intrahepatic ductal cannulation during ERCP with a sphincterotome. Gastrointest Endosc. 2003;57(6):738–43.
3. Kim JY, Kang DH, Choi CW, Kim HW, Park SB, Kim DU. Selective intrahepatic duct cannulation by using a triple-lumen catheter for endoscopic bilateral stenting in hilar cholangiocarcinoma. Gastrointest Endosc. 2010;72(1):192–8.

Chapter 5
Cannulation Through the Common Bile Duct to the Gallbladder

Nobuhito Ikeuchi and Takao Itoi

Abstract Endoscopic transpapillary gallbladder drainage (ETGBD) is a difficult procedure to perform, and its technical success rate is reportedly lower than that of percutaneous transhepatic gallbladder drainage (PTGBD). Therefore, ETGBD is regarded and positioned as an alternative to PTGBD, and advanced techniques and tips are often needed for a successful ETGBD. ETGBD is classified into two types, namely, endoscopic naso-gallbladder drainage (ENGBD) and endoscopic gallbladder stenting (EGBS). The selection of ENGBD or EGBS should be decided after carefully considering the situation and status of the patient as well as after a detailed examination and treatment planning for the patient. Importantly, prospective studies involving a large number of patients for long-term EGBS are needed. ETGBD is a useful alternative to PTGBD and should be performed at institutions with skilled endoscopists. In this section, we describe the status of ETGBD and provide valuable technical tips in effectively performing ETGBD.

Keywords ENGBD • EGBS • ETGBD

5.1 Introduction

Diseases that require gallbladder drainage include acute cholangitis and gallbladder tumors. There are three types of drainage routes for approaching the gallbladder. These include the transhepatic, transmural, and transpapillary approaches.

Percutaneous transhepatic gallbladder drainage (PTGBD) as a transhepatic approach is the most recommended drainage technique for acute cholecystitis in drainage guidelines. The first report of transhepatic drainage involving PTGBD was in 1977 [1], and many scholarly articles describing the safety and efficacy of PTGBD for acute cholecystitis have been published since then [2–5]. Therefore,

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PTGBD has become the most recommended drainage technique for acute cholecystitis. However, when the purpose of performing the drainage is to obtain bile juice for the differentiation between benign or malignant disease and when the cause of the acute cholecystitis requiring gallbladder drainage points to a malignant disease, PTGBD poses a risk of needle tract seeding. If the condition is acute cholecystitis caused by a benign disease, there are situations wherein PTGBD cannot always be recommended. These situations include patients with hemorrhagic diathesis, ascites, and Chilaiditi syndrome. Therefore, an alternative to PTGBD is highly anticipated.

Endoscopic ultrasonography (EUS)-guided gallbladder duodenostomy (EUS-GBD) as a transmural approach is a relatively new method of gallbladder drainage, with the first EUS-GBD report published in 2007 [6]. The efficacy of EUS-GBD has recently been reported by some endoscopists including our group [7, 8]. EUS-GBD has become widely recognized to date. However, the specific procedure involved in EUS-GBD has not yet been clearly established. Thus, many EUS-GBD studies are expected in the future.

On the other hand, the possible uses of endoscopic transpapillary gallbladder drainage (ETGBD) have been suggested by Kozarek in 1984 [9], paving the way for many reports on the efficacy and safety of ETGBD. The success rate of ETGBD has been reported to range from 64 to 100% [10–15]. However, the success rates of ETGBD vary for each report, and many of these previous works were retrospective studies and case reports. Moreover, these studies were reported from high-volume centers. In addition, the technical success rate of ETGBD is lower than that of PTGBD [16]. In fact, ETGBD requires a high-endoscopic and guidewire technique. Moreover, ETGBD should be performed at institutions with skilled endoscopists as stipulated in the ETGBD guidelines [17]. Therefore, ETGBD is regarded and positioned as an alternative to PTGBD, and advanced techniques and guidelines are often needed for a successful ETGBD. Herein, we describe the status of ETGBD and provide technical tips in effectively performing ETGBD.

5.2 Classifications and Characteristics of Transpapillary Drainage

ETGBD is classified into two types, namely, endoscopic naso-gallbladder drainage (ENGBD) and endoscopic gallbladder stenting (EGBS).

In ENGBD, the outflow of bile juice can be checked directly after the procedure, and the clogging in a tube can be released by washing out with saline. Moreover, ENGBD can repeatedly obtain bile juice for cytology. On the other hand, nasal discomfort and a risk of self-removal of the naso-drainage tube are associated with the use of ENGBD.

In the case of EGBS, there are no nasal discomfort and risk of self-removal of the naso-drainage tube because the tube does not come out of the body. However, there is difficulty in checking and releasing the stent clogging. Therefore, when acute cholecystitis recurs because of stent clogging, reintervention may be required.

5.3 Actual Techniques and Tips for Endoscopic Transpapillary Gallbladder Drainage

After successful bile duct cannulation, a 0.025- or 0.035-in. guidewire is advanced into the cystic duct and subsequently into the gallbladder. Before the guidewire is advanced into the cystic duct, it may be necessary to perform cholangiography by injection of a contrast medium to locate the bifurcation of the cystic duct. When the cystic duct is located with a guidewire, a hydrophilic guidewire (Radifocus; Terumo Co., Ltd., Tokyo, Japan) or a guidewire with hydrophilic coating on the distal end (VisiGlide2; Olympus Medical Systems, Tokyo, Japan) is helpful.

The bifurcation forming the cystic duct has a variety of distribution or deformation. In fact, there are some cases that require the use of devices except a catheter for the cannulate guidewire from the bile duct to the cystic duct. For example, in patients with a left-side distribution or deformation of the cystic duct, a catheter with a flexible tip (Swing-tip; Olympus Medical Systems, Tokyo, Japan) may be useful (Fig. 5.1). A sphincterotome (Ellipsotom; MTW Endoscopie, Wesel, Germany) is occasionally used, particularly for a downward look diverging of the cystic duct. The sphincterotome usually bows toward the cystic duct when the cystic duct takeoff is heading toward the right side. The tip of the sphincterotome is positioned downward to facilitate a flexed look, and then the guidewire may fall into the cystic duct opening (Fig. 5.2a-1, a-2, b-1, b-2, c). A rotatable sphincterotome (TRUEtome; Boston Scientific, Massachusetts, USA) may be helpful for cannulating left-sided cystic duct takeoffs (Fig. 5.3).

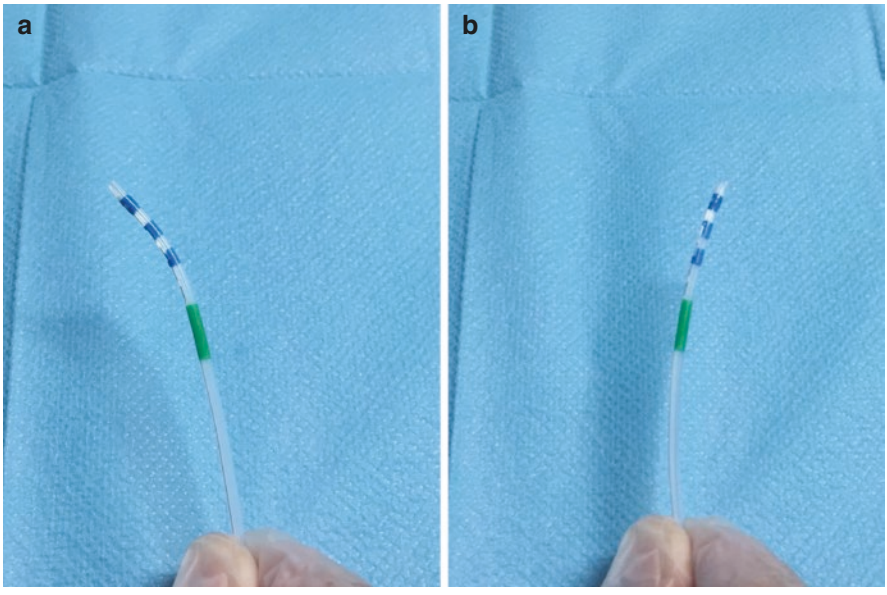

Fig. 5.1 (**a**) The neutral form of Swing-tip catheter. (**b**) The bended backward form of Swing-tip catheter by pulling the handle

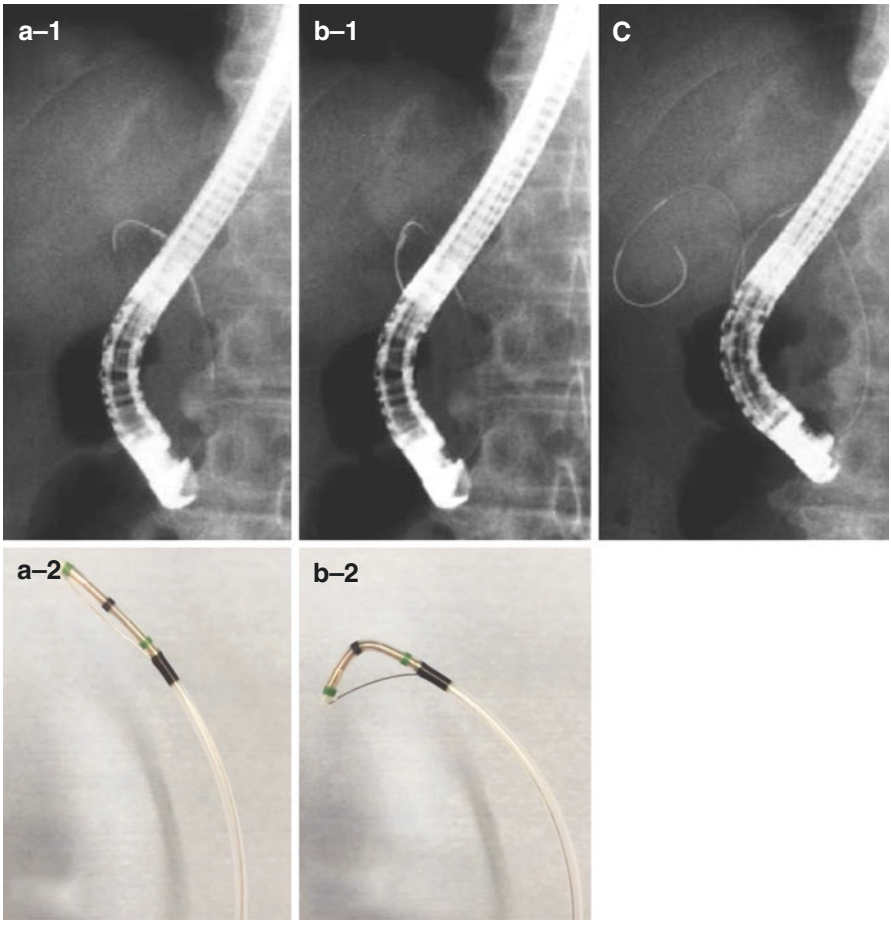

Fig. 5.2 (**a-1**) The cystic duct is diverged as right-sided and downward looking. (**a-2**) The neutral form of Elipsotome. (**b-1**) Elipsotome is bended toward the cystic duct, and the guidewire is advanced to the cystic duct. (**b-2**) The tip of Elipsotome is bended to arrow by pushing the handle. (**c**) The guidewire is advanced into the gallbladder

Fig. 5.3 The mobility of TRUEtome. © 2012 Boston Scientific or its affiliates. All rights reserved

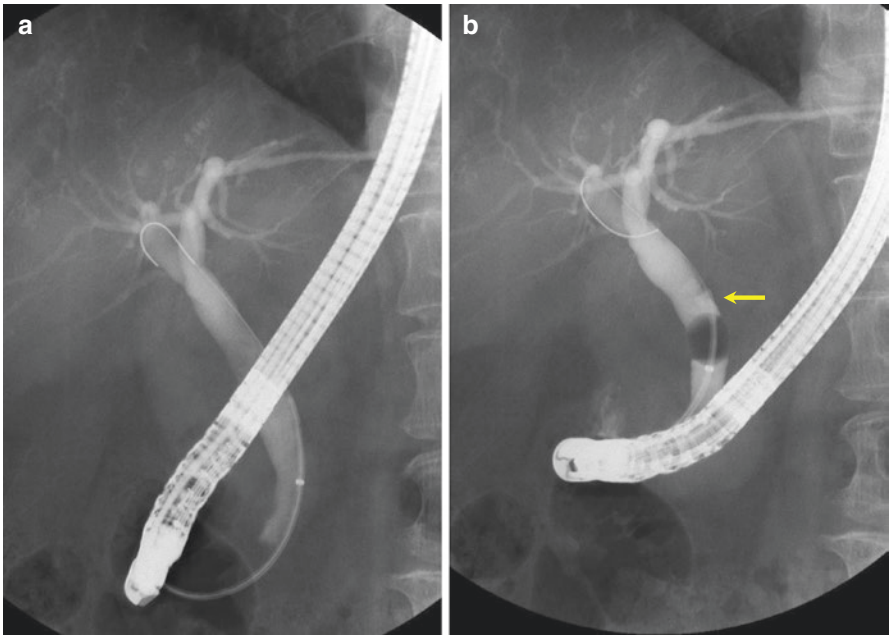

Fig. 5.4 (**a**) There is no visualization of the cystic duct on cholangiography. (**b**) After an occlusion balloon is inflated below the expected level of the cystic duct and contrast medium injection under pressure, the cystic duct is projected (*arrow*)

Notably, in all patients who undergo ETGBD, the gallbladder and cystic duct are not always visualized on cholangiography because of cholecystitis. In such cases, an occlusion balloon is often helpful. The occlusion balloon is inflated below the expected level of the cystic duct bifurcation, and contrast medium injection under pressure may project some fillings of the cystic duct. In particular, a triple-lumen balloon may be useful because of the requirement for injection into a larger guidewire port (Extractor TM Pro RX; Boston Scientific, Massachusetts, USA) (Fig. 5.4a, b).

When contrast medium injection under pressure is performed, we recommend the administration of steroids such as hydrocortisone sodium succinate (500 mg) before the procedure to prevent cholangio-venous reflux from an increase in the bile duct content brought about by the contrast medium injection under pressure.

After successfully inserting the guidewire into the cystic duct, the cystic duct is negotiated by the guidewire. The rotating manipulation of the guidewire is important because the stricture of the cystic duct is spiral. Specifically, the loop technique is effective and involves pushing the cystic duct with the guidewire forming a loop (Fig. 5.5a–d). This technique can reduce the rate of cystic ductal perforation more than negotiating the cystic duct with the tip of the guidewire. Moreover, the loop technique can alleviate the effect of stone obstruction in the cystic duct or neck of the gallbladder.

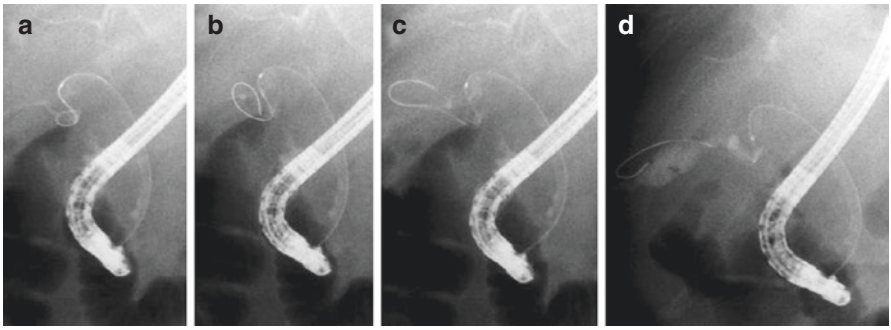

Fig. 5.5 (**a**) The tip of the guidewire formed the loop in the cystic duct. (**b**) The guidewire is advanced forming the loop into the cystic duct. (**c**) The guidewire is advanced forming the loop into the gallbladder. (**d**) The guidewire is placed in the gallbladder

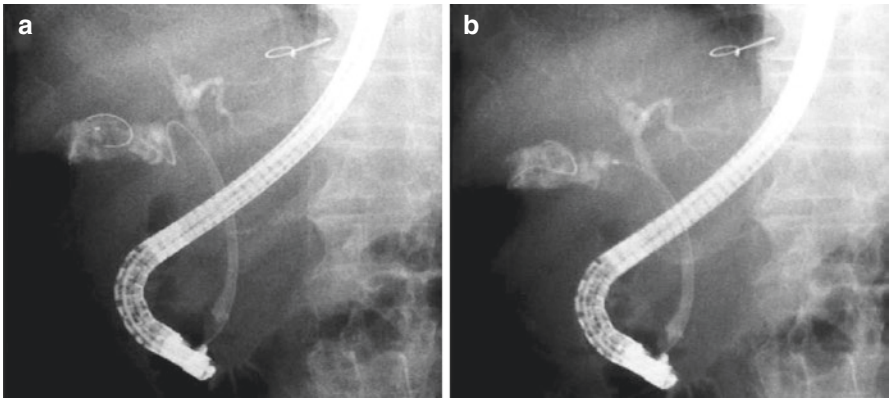

Fig. 5.6 (**a**) The catheter and the guidewire are inserted with a loop into the gallbladder. (**b**) After the catheter and guidewire have been pulled out a few centimeters coincidently, the loop is removed and straightened

When attempts are made to place the guidewire and catheter into the gallbladder, the cystic duct occasionally forms loops which usually interfere with the insertion of a stent or a naso-drainage tube. Therefore, these loops must be removed as much as possible. When the guidewire and catheter are inserted through and placed over the loops, the guidewire and catheter are then pulled out by a few centimeters (Fig. 5.6a, b). At this point, it is important for the guidewire to be sufficiently placed into the gallbladder because the guidewire may be withdrawn when the loops are removed.

When ENGBD is selected, the catheter is withdrawn leaving behind the guidewire in the gallbladder. Then, a 5F to 7F pigtail naso-gallbladder drainage tube (NB tube; Hanako Medical, Co., Ltd., Tokyo, Japan) is inserted into the gallbladder, and the endoscope is withdrawn (Fig. 5.7a). The tube is then rerouted to the nose. The nasal discomfort from the indwelling naso-gallbladder drainage tube may be reduced using tubes with a smaller diameter (5F or 6F).

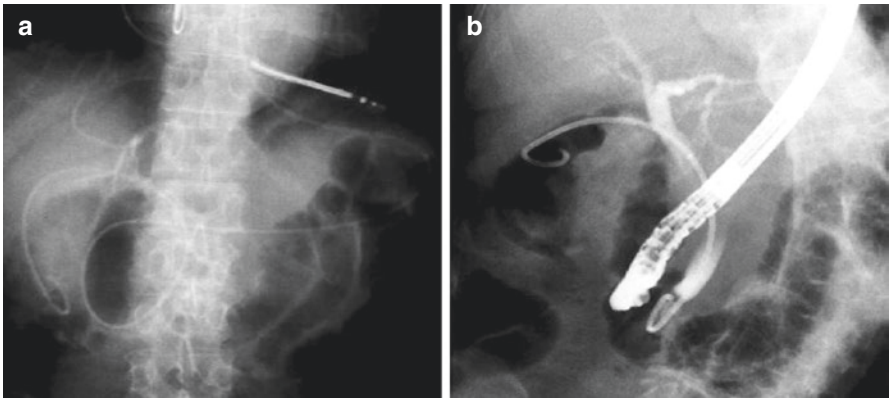

Fig. 5.7 (**a**) A 5F naso-gallbladder drainage tube is placed into the gallbladder as ENGBD. (**b**) A 7F double pigtail stent is placed into the gallbladder as EGBS

When EGBS is selected, a 7F to 10Fr double pigtail stent (Zimmon; Cook Medical, NC, USA) is placed (Fig. 5.7b). When stents of over 7F diameter are selected, endoscopic sphincterotomy should be considered to prevent post-ERCP pancreatitis caused by large diameter stents.

5.4 Selection of Procedures According to the Type of ETGBD

Studies comparing the efficacy and safety of ENGBD with those of EGBS are extremely rare. To the best of our knowledge, only one randomized and controlled study comparing the efficacy and safety of ENGBD with those of EGBS has been reported [18]. This previous study showed that there were no significant differences in the technical success rate, clinical success rate, and adverse event rate between the ENGBD group and the EGBS group. However, the mean visual analog score of the post-procedure pain in the ENGBD group was significantly higher than that in the EGBS group ($p < 0.001$). Although there was a small difference in terms of the post-procedure discomfort, there was no difference in the efficacy and safety of the procedures between ENGBD and EGBS [18]. Therefore, the selection of either ENGBD or EGBS should be decided after carefully considering the situation and status of the patient as well as after the examination and treatment planning for the patient.

5.5 Recurrence Rate of Acute Cholecystitis After EGBS

The long-term outcome of EGBS remains unknown because of the scarcity of studies regarding this technique. Moreover, most of the available reports have thus far been retrospective studies [19–22]. In particular, the critical question as to whether EGBS

should be performed or not for acute cholecystitis to prevent recurrence after improving the inflammation remains unanswered. Moreover, the safety of long-term EGBS has not been established to date. Although the recurrence rate in patients who underwent long-term EGBS was reported to range from 3 to 16% in previous retrospective studies, prospective studies on the safety of long-term EGBS are rare. Lee et al. prospectively followed up 20 patients who underwent EGBS without stent removal [23]. Their study showed that late complications occurred in 20% (4/20) of the patients and that there was no patient who had recurrence of acute cholecystitis during the median follow-up period of 586 days (range 11–1403 days). Although the study of Lee et al. may show the feasibility of long-term EGBS, another study reported the occurrence of a liver abscess after EGBS during the follow-up period [19]. Overall, the safety of long-term EGBS has not been definitively established to date. Therefore, prospective studies of long-term EGBS involving a large number of patients are needed.

5.6 Conclusion

We described the status of ETGBD and provided important technical tips in performing ETGBD. The selection of either ENGBD or EGBS should be decided after carefully considering the situation and status of the patient as well as after examination and treatment planning for the patient. Prospective studies on long-term EGBS involving a large number of patients are warranted. Taken together, ETGBD is a useful alternative to PTGBD and should be performed at institutions with skilled endoscopists.

References

1. Glenn F. Cholecystectomy in high risk patients with biliary tract disease. Ann Surg. 1977;185:185–91.
2. Davis CA, Landercasper J, Gundersen LH, Lambert PJ. Effective use of percutaneous cholecystostomy in high-risk surgical patients: techniques, tube management, and results. Arch Surg. 1999;134:727–31.
3. Ito K, Fujita N, Noda Y, Kobayashi G, Kimura K, Sugawara T, Horaguchi J. Percutaneous cholecystostomy versus gallbladder aspiration for acute cholecystitis: a prospective randomized controlled trial. AJR Am J Roentgenol. 2004;183(1):193–6.
4. Winbladh A, Gullstrand P, Svanvik J, Sandström P. Systematic review of cholecystostomy as a treatment option in acute cholecystitis. HPB (Oxford). 2009;11:183–93.
5. Melloul E, Denys A, Demartines N, Calmes JM, Schäfer M. Percutaneous drainage versus emergency cholecystectomy for the treatment of acute cholecystitis in critically ill patients: does it matter? World J Surg. 2011;35:826–33.
6. Baron TH, Topazian MD. Endoscopic transduodenal drainage of the gallbladder: implications for endoluminal treatment of gallbladder disease. Gastrointest Endosc. 2007;65:735–7.
7. Itoi T, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, et al. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with video). Gastrointest Endosc. 2012;75:870–6.

8. Jang JW, Lee SS, Song TJ, Hyun YS, Park do H, Seo DW, et al. Endoscopic ultrasound-guided transmural and percutaneous transhepatic gallbladder drainage are comparable for acute cholecystitis. Gastroenterology. 2012;142:805–11.
9. Kozarek RA. Selective cannulation of the cystic duct at the time of ERCP. J Clin Gastroenterol. 1984;6:37–40.
10. Baron TH, Schroeder PL, Schwartzberg MS, Carabasi MH. Resolution of Mirizzi's syndrome using endoscopic therapy. Gastrointest Endosc. 1996;44:343–5.
11. Feretis C, Apostolidis N, Mallas E, Manouras A, Papadimitriou J. Papadimitriou endoscopic drainage of acute obstructive cholecystitis in patients with increased operative risk. Endoscopy. 1993;25(6):392–5.
12. Itoi T, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, Ishii K, Tsuji S, Ikeuchi N, Tsukamoto S, Takeuchi M, Kawai T, Moriyasu F. Endoscopic transpapillary gallbladder drainage in patients with acute cholecystitis in whom percutaneous transhepatic approach is contraindicated or anatomically impossible (with video). Gastrointest Endosc. 2008;68(3):455–60.
13. Kjaer DW, Kruse A, Funch-Jensen P. Endoscopic gallbladder drainage of patients with acute cholecystitis. Endoscopy. 2007;39(4):304–8.
14. Nakatsu T, Okada H, Saito K, Uchida N, Minami A, Ezaki T, et al. Endoscopic transpapillary gallbladder drainage (ETGBD) for the treatment of acute cholecystitis. J Hepatobiliary Pancreat Surg. 1977;4:31–5.
15. Ogawa O, Yoshikumi H, Maruoka N, Hashimoto Y, Kishimoto Y, Tsunamasa W, Kuroki Y, Yasuda H, Endo Y, Inoue K, Yoshiba M. Predicting the success of endoscopic transpapillary gallbladder drainage for patients with acute cholecystitis during pretreatment evaluation. Can J Gastroenterol. 2008;22:681–5.
16. Itoi T, Coelho-Prabhu N, Baron TH. Endoscopic gallbladder drainage for the management of acute cholecystitis. Gastrointest Endosc. 2010;71:1038–5.
17. Tsuyuguchi T, Itoi T, Takada T, Strasberg SM, Pitt HA, Kim MH, Supe AN, Mayumi T, Yoshida M, Miura F, Gomi H, Kimura Y, Higuchi R, Okamoto K, Yamashita Y, Gabata T, Hata J, Kusachi S, Tokyo Guideline Revision Committee. TG13 indications and techniques for gallbladder drainage in acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2013;20:81–8.
18. Itoi T, Kawakami H, Katanuma A, Irisawa A, Sofuni A, Itokawa F, Tsuchiya T, Tanaka R, Umeda J, Ryozawa S, Doi S, Sakamoto N, Yasuda I. Endoscopic nasogallbladder tube or stent placement in acute cholecystitis: a preliminary prospective randomized trial in Japan (with video). Gastrointest Endosc. 2015;81:111–8.
19. Maekawa S, Nomura R, Murase T, Ann Y, Oeholm M, Harada M. Endoscopic gallbladder stenting for acute cholecystitis: a retrospective study of 46 elderly patients aged 65 years or older. BMC Gastroenterol. 2013;12:13–65.
20. Conway JD, Russo MW, Shrestha R. Endoscopic stent insertion into the gallbladder for symptomatic gallbladder disease in patients with end-stage liver disease. Gastrointest Endosc. 2005;61:32–6.
21. Schlenker C, Trotter JF, Shah RJ, Everson G, Chen YK, Antillon D, Antillon MR. Endoscopic gallbladder stent placement for treatment of symptomatic cholelithiasis in patients with end-stage liver disease. Am J Gastroenterol. 2006;101:278–83.
22. Mutignani M, Iacopini F, Perri V, Familiari P, Tringali A, Spada C, Ingrosso M, Costamagna G. Endoscopic gallbladder drainage for acute cholecystitis: technical and clinical results. Endoscopy. 2009;41(6):539–46.
23. Lee TH, Park DH, Lee SS, Seo DW, Park SH, Lee SK, Kim MH, Kim SJ. Outcomes of endoscopic transpapillary gallbladder stenting for symptomatic gallbladder diseases: a multicenter prospective follow-up study. Endoscopy. 2011;43:702–8.

Chapter 6
ERCP with Device-Assisted Enteroscopy in Patients with Altered Gastrointestinal Anatomy

Takashi Sasaki and Naoki Sasahira

Abstract Diagnosis and treatment using ERCP in patients with altered gastrointestinal anatomy have progressed greatly since the emergence of the double-balloon enteroscope in 2001. The balloon-assisted enteroscope has improved steadily over time, and a short-type balloon-assisted enteroscope with a large working channel became commercially available in 2016. These short-type balloon-assisted enteroscopes accommodate most ERCP accessories, and many kinds of ERCP intervention can be performed, such as conventional ERCP for patients with normal anatomy. Although the success rate of ERCP with balloon-assisted enteroscopy in patients with altered gastrointestinal anatomy has increased to approximately 68–98%, it is still a challenging procedure for many endoscopists. Because ERCP with a balloon-assisted enteroscope is time-consuming, mandates specialized training, and requires special endoscopes and accessories, these factors limit the widespread availability outside tertiary endoscopic referral centers. Other types of device-assisted enteroscopies, including spiral enteroscopy and through-the-scope balloon-assisted enteroscopy, have also been developed to make it easier to perform ERCP in patients with altered gastrointestinal anatomy. These novel device-assisted enteroscopy instruments are still immature compared with balloon-assisted enteroscopy for ERCP in patients with altered gastrointestinal anatomy. Therefore, both device-assisted enteroscopy and ERCP accessories must be improved for this challenging procedure to become a more general procedure.

Keywords ERCP • Altered gastrointestinal anatomy • Enteroscope

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6.1 Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) in patients with altered gastrointestinal (GI) anatomy is still a challenging procedure. Many challenges have been overcome to perform this difficult procedure. Several types of endoscopes (side-viewing duodenoscope, forward-viewing endoscope, pediatric- or adult-use colonoscope, and enteroscope) have been used to perform ERCP. An endoscopic approach in patients with Billroth II anatomy was first reported by Katon et al. in 1975 [1]. The success rates of ERCP in patients with Billroth II anatomy have been reported to be 52–92% [2–5]. Roux-en-Y reconstruction is a more challenging situation in which to perform ERCP. ERCP in patients with Roux-en-Y reconstruction was first reported by Gostout and Bender in 1988 [6]. The success rates of ERCP in patients with Roux-en-Y reconstruction have been reported to range from 33 to 67% [7–9]. Because the success rates of these procedures in patients with altered GI anatomy are extremely low, the endoscopic approach has not become a standard of care. Percutaneous transhepatic cholangiograms or even surgical approaches have been required even for basic diagnostic and therapeutic purposes. Therefore, a new endoscopic approach is required to overcome the low success rate of ERCP in patients with altered GI anatomy.

In 2001, Yamamoto et al. developed a double-balloon enteroscope (DBE) for the diagnosis and treatment of small intestinal disease [10]. The DBE could be inserted into the deep small intestine by anchoring the bowel with an inflated balloon attached to both the tip of enteroscope and the overtube. A Fujinon DBE became commercially available in 2003. The use of a DBE for ERCP in a patient with altered GI anatomy was first reported in 2005 [11]. An Olympus single-balloon enteroscope (SBE) was another type of balloon-assisted enteroscope (BAE); it was developed in 2006 and became commercially available in 2007 [12]. ERCP with SBE has also been attempted in patients with altered GI anatomy [13]. A spiral enteroscope was developed in 2007 to potentially provide a simpler and faster technique than the BAE [14]. The use of a spiral enteroscope was also attempted for ERCP in patients with altered GI anatomy [15–17]. Because the DBE, SBE, and spiral enteroscope are all time-consuming, mandate specialized training, and require special endoscopes and accessories, a new concept of a through-the-scope balloon-assisted enteroscope was developed, and its use was reported in 2008 [18]. Deep enteroscopy with standard endoscopes and a novel through-the-scope balloon system (NaviAid AB) was first reported in 2014 [19, 20]. ERCP with this NaviAid AB system in patients with altered GI anatomy was also reported in 2016 [21]. These device-assisted enteroscopy instruments facilitate ERCP in patients with altered GI anatomy compared with conventional push enteroscopy. In this chapter, we reviewed ERCP with these device-assisted enteroscopes in patients with altered GI anatomy.

6.2 Device-Assisted Enteroscope

6.2.1 Double-Balloon Enteroscope

The double-balloon enteroscope (DBE) was first introduced in 2001 and became commercially available in 2003. The DBE uses a specially coupled enteroscope and overtube apparatus with latex balloons mounted on the distal ends of each component. The balloons are intended to anchor the endoscope in position during insertion to allow the pleating of the bowel over the endoscope shaft, which reduces loop formation and allows a greater insertion depth. Several types of DBEs have been developed for several purposes. The main features that discriminate each enteroscope are the working length of the enteroscope and the size of working channel. The conventional BAE has been designed to have a 200-cm working length (long-type DBE). In the early days, the most commonly used long-type DBE system was EN-450T (Fujinon Co, Saitama, Japan), which has a 2.8-mm working channel and a 200-cm working length. Although it is easier to approach the target lesion by using a long-type DBE, various ERCP accessories cannot be used because the working length of these accessories is approximately 190 cm. Therefore, the need for short-type DBE increased when DBE-assisted ERCP became widely performed. EC-450BI5 (Fujifilm Co, Tokyo, Japan), which has a 2.8-mm working channel and a 152-cm working length, was made for colonoscopy use but was instead used as an enteroscope for balloon-assisted ERCP. EI-530B (Fujifilm Co, Tokyo, Japan) was also developed as a short-type DBE, and it has a 2.8-mm working channel and a 152-cm working length. EI-530B was widely used for balloon-assisted ERCP. To perform more complicated ERCP procedures with BAE, a larger working channel is required. In 2016, EI-580BT (Fujifilm Co, Tokyo, Japan) became commercially available. EI-580BT has a 3.2-mm working channel and a 155-cm working length. This new DBE is equipped with the advanced force transmission function and the adaptive bending system, which allows better scope maneuverability. This DBE is designed so the working channel is in the 5:30 direction of the screen and the catheter can be easily adjusted to the axis of the biliary duct. This new DBE has a large working channel that permits the performance of almost all types of ERCP procedures, including self-expandable metallic stent (SEMS) insertion.

6.2.2 Single-Balloon Enteroscope

A single-balloon enteroscope (SBE) was developed in 2006 and became commercially available in 2007. In contrast to the DBE, only the disposable overtube has a non-latex balloon at its distal end. The SBE can be inserted into the deep small

bowel by manipulating the balloon on the distal end of the splinting tube and the angulation mechanism of the scope. Three SBE systems have become available. SIF-Q180 (Olympus Co, Center Valley, PA, USA) and SIF-Q260 (Olympus Medical Systems, Tokyo, Japan) are the conventional SBEs; each has a 2.8-mm working channel and a 200-cm working length. The SIF-Q180 was mainly used in Western countries, whereas the SIF-Q260 was mainly used in Japan. These two SBEs were categorized as long-type SBEs because they have 200-cm working lengths. When a long-type SBE is used for balloon-assisted ERCP, various ERCP accessories cannot be used as they are with a long-type DBE. Therefore, the need for a short-type SBE has also increased. In 2016, the SIF-H290S (Olympus Medical Systems, Tokyo, Japan) became commercially available in Japan. The SIF-H290S has a 3.2-mm working channel and a 155-cm working length. This enteroscope has a passive bending design and a high force transmission design, both of which facilitate a smoother passage through the flexures of altered GI anatomy. Moreover, the large size of the working channel makes it possible to perform almost all types of ERCP procedures, including SEMS insertion.

6.2.3 Spiral Enteroscope

A spiral enteroscope was developed in 2007 to potentially provide a simpler and faster technique compared with BAE. The spiral enteroscope uses a helical overtube that allows deep insertion by pleating the small bowel over the enteroscope as the overtube is rotated clockwise. The overtube is 118-cm long and has a soft raised spiral helix at its distal end that is either 4.5 mm or 5.5 mm in height. The overtube is compatible with enteroscopes that are 200 cm in length and between 9.1 and 9.5 mm in diameter. Two different overtubes are available for antegrade or retrograde examinations. The overtube has a coupling device on its proximal end that affixes itself to the enteroscope. This permits the free rotation of the overtube independent of the enteroscope but prevents independent movement of the enteroscope relative to the overtube. When the overtube is uncoupled, the enteroscope can then be advanced or withdrawn independent of the overtube. A motorized spiral enteroscopy system is in development [22]. When a spiral overtube is used to perform ERCP in patients with altered GI anatomy, a long-type enteroscope is used for the insertion to reach the target sight. A long-type enteroscope is sometimes exchanged for a short-type enteroscope to use most of the ERCP accessories if needed.

6.2.4 Through-the-Scope Balloon-Assisted Enteroscope

The new concept of through-the-scope BAE was reported in 2008. Through-the-scope BAE was marketed as the NaviAid system (SMART Medical Systems Ltd., Ra'anana, Israel). This new device consists of a disposable balloon component that

is advanced through the working channel of an endoscope or colonoscope and an air supply unit. The NaviAid AB (Advancing Balloon) has a working length of 350 cm with a balloon diameter of 40 mm. The minimum endoscope working channel diameter needed for passage of the device is 3.7 mm. The deflated balloon was passed through the working channel 20–30 cm ahead of the standard endoscope. It was then inflated to anchor itself to the small bowel. Once it was inflated ahead of the endoscope and anchored in the bowel, the device was used as a rail on which the endoscope was advanced, replacing pushing with guidance. Once the endoscope met the balloon catheter, the balloon was deflated to allow the next cycle of advancement. When the endoscope reached the target sight, the balloon catheter was removed from the working channel to allow the accessories to perform the procedure. Either an adult colonoscope or a therapeutic gastroscope, which has a large working channel, is chosen when this balloon system is used for ERCP.

6.3 ERCP Using Device-Assisted Enteroscopy

6.3.1 Treatment Outcomes

Recently, there have been an increasing number of patients with altered GI anatomy following gastric surgery, pancreatobiliary surgery, liver transplantation, and bariatric surgery. With the increase in altered GI anatomy patients, the frequency at which pancreatobiliary interventions are performed in such patients has increased. The difficulty of performing ERCP is influenced by the type of surgically altered anatomy. Recently, a high success rate of ERCP in patients with Billroth II reconstruction was reported [23]. However, it is still difficult to reach the target site and perform ERCP in patients with Roux-en-Y reconstruction and hepaticojejunostomy [24]. In a questionnaire survey at the Endoscopic Forum Japan 2013, it was reported that the success rates of reaching the target site were 89.6% for Roux-en-Y reconstruction, 94.8% for pancreaticoduodenectomy, 86.4% for hepaticojejunostomy, 90.0% for liver transplantation, and 98.6% for Billroth II reconstruction. In the systematic review of 945 procedures (DBE, SBE, and spiral enteroscopy-assisted ERCP) in 679 patients, an overall success rate was reported to be 70–90%, and the success rates were highest in patients with Billroth II reconstruction and lowest in patients with Roux-en-Y gastric bypass [25]. According to the success rate of reaching the target sight, the length to the target sight and the angulation of the afferent limb are usually the main factors. Roux-en-Y reconstruction with gastric bypass is particularly challenging due to the long limb (often greater than 100 cm) that must be traversed from the gastrojejunal anastomosis to the jejunojejunal orifice. Recently, a short-type DBE and SBE have been introduced and have advantages because most ERCP accessories can be used with these instruments. However, it is sometimes difficult to reach the target sight using these short-type BAEs when the length of target site is long. For the angulation of the afferent limb, the new types of DBE (EI-580BT) and SBE (SIF-H290S) have been introduced to facilitate smoother passage through the flexures of altered GI anatomy.

From the data of the systematic review, which included 945 procedures (DBE, SBE, and spiral enteroscopy-assisted ERCP), the overall ERCP success rate of all procedures was reported to be 74% [25]. When the enteroscopes were compared, the success rates were highest in DBE and lowest in spiral enteroscopy. Regarding the data of DBE, the success rate of reaching the target site was 89% (73–100%), the success rate of cannulation was 93% (85–100%), and the overall success rate was 82% (63–95%). When SBE was used, the success rate of reaching the target site was 82% (75–100%), the success rate of cannulation was 86% (75–100%), and the overall success rate was 68% (60–100%). For the spiral enteroscope, the success rate of reaching the target site was 72%, and the overall success rate was 65%. However, the data for spiral enteroscopy-assisted ERCP were limited. A multicenter experience of through-the-scope BAE showed that the success rate of reaching the target site was 58%, the success rate of cannulation was 94%, and the overall success rate was 55% [21]. Through-the-scope BAE is shown to be an effective modality with which to successfully deliver intervention despite a slightly lower target success rate compared to other device-assisted enteroscopy instruments. Therefore, through-the-scope BAE may not yet be able to replace the current methods because of the lower overall target success rate.

Short-type DBE and SBE are preferred for ERCP in patients with altered GI anatomy. A Japanese multicenter prospective study that included 311 patients and used a short-type DBE with 2.8-mm working channel (EI-530B) showed high success rates that were comparable to the success rates of conventional ERCP in patients with normal anatomy. The success rate of reaching the target site was 97.7%, the success rate of cannulation was 96.4%, and the therapeutic success rate was 97.9% [26]. In this prospective study, only patients with biliary indication were included. The efficacy of a new short-type DBE (EI-580BT) with a 3.2-mm working channel was reported in 2016 [27]. When this new short-type DBE was used to treat 112 procedures, the success rate of reaching the target site was 99.1%, the diagnostic success rate was 98.2%, and the overall success rate was 97.3%. The median time to complete ERCP with DBE was 54 min. Therefore, this new short-type DBE is very useful for ERCP in patients with altered GI anatomy. A large Japanese retrospective observational case series that included 203 procedures with the short-type prototype SBE with a 3.2-mm working channel also showed high success rates [28]. The success rate of reaching the target sight was 92.6%, and the procedural success rate was 81.8%. In this retrospective study, the pancreatic indication was also included. From the multivariate analysis, the pancreatic indication (odds ratio, 4.35), first ERCP (odds ratio, 6.03), and no transparent hood (odds ratio, 4.61) were reported to be potential risk factors for procedural failure.

Biliary cannulation of the intact papilla in patients with altered GI anatomy remains challenging, especially in the case of Roux-en-Y reconstruction. The success rate of the standard cannulation of the intact papilla was reported to be 67.8% [29]. Therefore, several advanced cannulation methods, including the double-guidewire technique, precutting, and percutaneous transhepatic cholangiography-guided rendezvous technique, are required to improve the deep cannulation rate. When these techniques were used, the final cannulation success rate became 95.6%.

Several complications occurred from ERCP with device-assisted enteroscopy. From the data of a systematic review that included 945 procedures, major complications occurred in 3.4% of the procedures. Major adverse events included cholangitis (0.1%), pancreatitis (1.2%), bleeding (0.3%), perforation (1.4%), and death (0.1%), which was attributed to an embolic stroke [25]. From a Japanese multicenter prospective study that used a short-type DBE, adverse events occurred in 10.6% of procedures [26]. The most common adverse event was pancreatitis (3.5%), followed by cholangitis (2.6%). Obvious perforation that required surgical repair occurred in 0.3% of the cases, and microperforations, as identified by escaped air, occurred in 1.9% of the cases. The perforation rate of ERCP with device-assisted enteroscopy is not as high. ERCP in patients with altered GI anatomy could be performed safely, similar to conventional ERCP in patients with normal anatomy.

6.3.2 Therapeutic ERCP

Bilioenteric anastomotic stricture can now be treated with device-assisted enteroscopy [11, 30–32]. A practical classification proposed by Mönkemüller and Jovanovic is used to assess the type of the anastomotic stricture [33]. When the guidewire passes through the stricture, the stricture is usually treated with balloon dilation and/or stent placement (Fig. 6.1). The use of a Soehendra stent retriever and wire-guided diathermic dilator is useful when the balloon cannot pass through the stricture [34, 35]. It is occasionally difficult to determine the orifice of bilioenteric anastomosis. In such cases, a rendezvous technique via percutaneous transhepatic biliary drainage route is usually useful [36, 37].

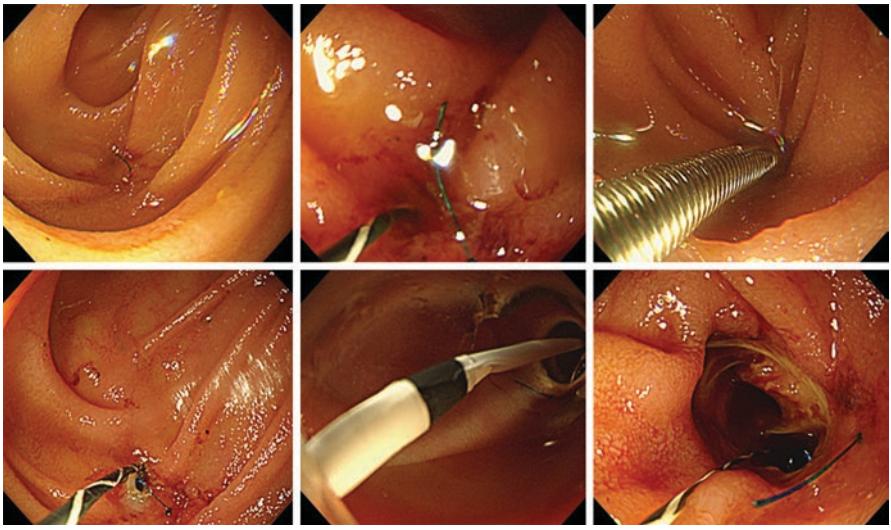

Fig. 6.1 Treatment of bilioenteric anastomotic stricture using short-type single-balloon enteroscope (SIF-H290S)

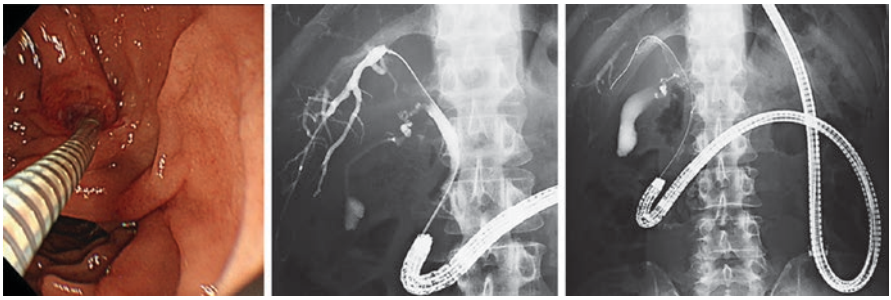

Fig. 6.2 Self-expandable metallic stent placement for malignant biliary obstruction using short-type single-balloon enteroscope (SIF-H290S)

The extraction of a biliary stone is also a major treatment in patients with altered GI anatomy [38]. Endoscopic papillary large-balloon dilation is performed such as a conventional ERCP and shows good efficacy [39, 40]. Direct cholangioscopy with an ultra-slim endoscope or a SpyGlass Direct Visualization System is useful for the detection and treatment of biliary stones and biliary tumors [41–43]. Electrohydraulic lithotripsy could be used to treat a large stone under direct cholangioscopy [44–46].

Biliary drainage via an endoscopic approach is less invasive in patients with altered GI anatomy compared with percutaneous and surgical drainage. Iatrogenic biliary injury and bile leakage from choledochojejunostomy could be treated with biliary drainage with device-assisted enteroscopy [47, 48]. The insertion of SEMS for malignant biliary obstruction was a difficult procedure when a long-type BAE was used [49]. With the introduction of the short-type BAE, it became easier to deploy SEMS, as with conventional ERCP, even in situations of multiple stenting (Fig. 6.2) [50–52].

Pancreatic intervention is more difficult than biliary intervention in cases of altered GI anatomy. Identifying the pancreaticojejunal anastomotic site is difficult because of the location and small size of the anastomosis and interference from the jejunal folds. Therefore, dilation and/or stenting of pancreaticodigestive tract anastomotic stricture showed a relatively low success rate (38%) [53]. The use of the EUS-guided or US-guided rendezvous method may improve the success rate of these difficult cases [53, 54]. Pancreatitis caused by the pancreaticojejunal anastomotic stricture and pancreatic duct stones is a confusing problem in patients with pancreaticoduodenectomy. A short-type BAE with a transparent hood might be useful for the detection of the pancreaticojejunal anastomotic site and the successful removal of the pancreatic duct stone [55].

6.4 Conclusions

The emergence of a BAE has changed the treatment of pancreatobiliary disorders in patients with altered GI anatomy. Due to the improvement of device-assisted enteroscopy, ERCP with device-assisted enteroscopy has become the mainstay of

management in patients with altered GI anatomy. However, it is still a challenging procedure for many endoscopists. Therefore, both the device-assisted enteroscopy and ERCP accessories need to be improved for this challenging procedure to become a more general procedure.

Another approach for the treatment of pancreatobiliary disorders in patients with altered GI anatomy is the EUS-guided approach. EUS-guided intervention techniques have also progressed over the past several decades. This novel technique also helps manage pancreatobiliary disorders in patients with altered GI anatomy in combination with a BAE. Because of the improvement of the prognosis of patients with altered GI anatomy, the demand for ERCP for such patients will increase further. The treatment of pancreatobiliary disorders in patients with altered GI anatomy should be improved with the combination of these kinds of novel approach, and each procedure should become more sophisticated.

References

1. Katon RM, Bilbao MK, Parent JA, et al. Endoscopic retrograde cholangiopancreatography in patients with gastrectomy and gastrojejunostomy (Billroth II), a case for the forward look. Gastrointest Endosc. 1975;21:164–5.
2. Thon HJ, Löffler A, Buess G, et al. Is ERCP a reasonable diagnostic method for excluding pancreatic and hepatobiliary disease in patients with a Billroth II resection? Endoscopy. 1983;15:93–5. https://doi.org/10.1055/s-2007-1021476.
3. Forbes A, Cotton PB. ERCP and sphincterotomy after Billroth II gastrectomy. Gut. 1984;25:971–4.
4. Osnes M, Rosseland AR, Aabakken L. Endoscopic retrograde cholangiography and endoscopic papillotomy in patients with a previous Billroth-II resection. Gut. 1986;27:1193–8.
5. Kim MH, Lee SK, Lee MH, et al. Endoscopic retrograde cholangiopancreatography and needle-knife sphincterotomy in patients with Billroth II gastrectomy: a comparative study of the forward-viewing endoscope and the side-viewing duodenoscope. Endoscopy. 1997;29:82–5. https://doi.org/10.1055/s-2007-1004080.
6. Gostout CJ, Bender CE. Cholangiopancreatography, sphincterotomy, and common duct stone removal via Roux-en-Y limb enteroscopy. Gastroenterology. 1988;95:156–63.
7. Hintze RE, Adler A, Veltzke W, et al. Endoscopic access to the papilla of Vater for endoscopic retrograde cholangiopancreatography in patients with billroth II or Roux-en-Y gastrojejunostomy. Endoscopy. 1997;29:69–73. https://doi.org/10.1055/s-2007-1004077.
8. Elton E, Hanson BL, Qaseem T, et al. Diagnostic and therapeutic ERCP using an enteroscope and pediatric colonoscope in long-limb surgical bypass patients. Gastrointest Endosc. 1998;47:62–7.
9. Wright BE, Cass OW, Freeman ML. ERCP in patients with long-limb Roux-en-Y gastrojejunostomy and intact papilla. Gastrointest Endosc. 2002;56:225–32.
10. Yamamoto H, Sekine Y, Sato Y, et al. Total enteroscopy with a nonsurgical steerable double-balloon method. Gastrointest Endosc. 2001;53:216–20.
11. Haruta H, Yamamoto H, Mizuta K, et al. A case of successful enteroscopic balloon dilation for late anastomotic stricture of choledochojejunostomy after living donor liver transplantation. Liver Transpl. 2005;11:1608–10. https://doi.org/10.1002/lt.20623.
12. Ohtsuka K, Kashida H, Kodama K, et al. Observation and treatment of small bowel diseases using single balloon endoscope. Gastrointest Endosc. 2008;67:AB271.
13. Dellon ES, Kohn GP, Morgan DR, et al. Endoscopic retrograde cholangiopancreatography with single-balloon enteroscopy is feasible in patients with a prior Roux-en-Y anastomosis. Dig Dis Sci. 2009;54:1798–803. https://doi.org/10.1007/s10620-008-0538-x.

14. Akerman PA, Agrawal D, Cantero D, et al. Spiral enteroscopy with the new DSB overtube: a novel technique for deep peroral small-bowel intubation. Endoscopy. 2008;40:974–8. https://doi.org/10.1055/s-0028-1103402.
15. Kogure H, Watabe H, Yamada A, et al. Spiral enteroscopy for therapeutic ERCP in patients with surgically altered anatomy: actual technique and review of the literature. J Hepatobiliary Pancreat Sci. 2011;18:375–9. https://doi.org/10.1007/s00534-010-0357-2.
16. Lennon AM, Kapoor S, Khashab M, et al. Spiral assisted ERCP is equivalent to single balloon assisted ERCP in patients with Roux-en-Y anatomy. Dig Dis Sci. 2012;57:1391–8. https://doi.org/10.1007/s10620-011-2000-8.
17. Wagh MS, Draganov PV. Prospective evaluation of spiral overtube-assisted ERCP in patients with surgically altered anatomy. Gastrointest Endosc. 2012;76:439–43. https://doi.org/10.1016/j.gie.2012.04.444.
18. Adler SN, Bjarnason I, Metzger YC. New balloon-guided technique for deep small-intestine endoscopy using standard endoscopes. Endoscopy. 2008;40:502–5.
19. Kumbhari V, Storm AC, Khashab MA, et al. Deep enteroscopy with standard endoscopes using a novel through-the-scope balloon. Endoscopy. 2014;46:685–9. https://doi.org/10.1055/s-0034-1365464.
20. Ali R, Wild D, Shieh F, et al. Deep enteroscopy with a conventional colonoscope: initial multicenter study by using a through-the-scope balloon catheter system. Gastrointest Endosc. 2015;82:855–60. https://doi.org/10.1016/j.gie.2015.04.037.
21. Cai JX, Diehl DL, Kiesslich R, et al. A multicenter experience of through-the-scope balloon-assisted enteroscopy in surgically altered gastrointestinal anatomy. Surg Endosc. 2016. https://doi.org/10.1007/s00464-016-5282-2.
22. Neuhaus H, Beyna T, Schneider M. Novel motorized spiral enteroscopy: first clinical case. Gastrointest Endosc. 2016;83:AB637.
23. Park CH, Lee WS, Joo YE, et al. Cap-assisted ERCP in patients with a Billroth II gastrectomy. Gastrointest Endosc. 2007;66:612–5. https://doi.org/10.1016/j.gie.2007.04.024.
24. Katanuma A, Isayama H. Current status of endoscopic retrograde cholangiopancreatography in patients with surgically altered anatomy in Japan: questionnaire survey and important discussion points at Endoscopic Forum Japan 2013. Dig Endosc. 2014;26(Suppl 2):109–15. https://doi.org/10.1111/den.12247.
25. Skinner M, Popa D, Neumann H. ERCP with the overtube-assisted enteroscopy technique: a systematic review. Endoscopy. 2014;46:560–72. https://doi.org/10.1055/s-0034-1365698.
26. Shimatani M, Hatanaka H, Kogure H, et al. Diagnostic and therapeutic endoscopic retrograde cholangiography using a short-type double-balloon endoscope in patients with altered gastrointestinal anatomy: a multicenter prospective study in Japan. Am J Gastroenterol. 2016;111:1750–8. https://doi.org/10.1038/ajg.2016.420.
27. Shimatani M, Tokuhara M, Kato K, et al. Utility of newly developed short type double balloon endoscopy for endoscopic retrograde cholangiography in postoperative patients. J Gastroenterol Hepatol. 2016. https://doi.org/10.1111/jgh.13713.
28. Yane K, Katanuma A, Maguchi H, et al. Short-type single-balloon enteroscope-assisted ERCP in postsurgical altered anatomy: potential factors affecting procedural failure. Endoscopy. 2017;49:69–74. https://doi.org/10.1055/s-0042-118301.
29. Ishii K, Itoi T, Tonozuka R, et al. Balloon enteroscopy-assisted ERCP in patients with Roux-en-Y gastrectomy and intact papillae (with video). Gastrointest Endosc. 2016;83:377–386. e6. https://doi.org/10.1016/j.gie.2015.06.020.
30. Sanada Y, Mizuta K, Yano T, et al. Double-balloon enteroscopy for bilioenteric anastomotic stricture after pediatric living donor liver transplantation. Transpl Int. 2011;24:85–90. https://doi.org/10.1111/j.1432-2277.2010.01156.x.
31. Sakakihara I, Kato H, Muro S, et al. Double-balloon enteroscopy for choledochojejunal anastomotic stenosis after hepato-biliary-pancreatic operation. Dig Endosc. 2015;27:146–54. https://doi.org/10.1111/den.12332.

32. Tomoda T, Tsutsumi K, Kato H, et al. Outcomes of management for biliary stricture after living donor liver transplantation with hepaticojejunostomy using short-type double-balloon enteroscopy. Surg Endosc. 2016;30:5338–44. https://doi.org/10.1007/s00464-016-4886-x.
33. Mönkemüller K, Jovanovic I. Endoscopic and retrograde cholangiographic appearance of hepaticojejunostomy stricture: a practical classification. World J Gastrointest Endosc. 2011;3:213–9. https://doi.org/10.4253/wjge.v3.i11.213.
34. Tsutsumi K, Kato H, Sakakihara I, et al. Dilation of a severe bilioenteric or pancreatoenteric anastomotic stricture using Soehendra stent retriever. World J Gastrointest Endosc. 2013;5:412–6. https://doi.org/10.4253/wjge.v5.i8.412.
35. Miyata E, Yamauchi H, Kida M, et al. Successful endoscopic dilation of severe bilioenteric strictures with a wire-guided diathermic dilators and short-type single-balloon enteroscope. Endoscopy. 2015;47(Suppl 1):E94–5. https://doi.org/10.1055/s-0034-1391240.
36. Mönkemüller K, Popa D, McGuire B, et al. Double-balloon enteroscopy-ERCP rendezvous technique. Endoscopy. 2013;45(Suppl 2):E333–4. https://doi.org/10.1055/s-0033-1344329.
37. Shimatani M, Takaoka M, Ikeura T, et al. Rendezvous technique: double-balloon endoscopy and SpyGlass direct visualization system in a patient with severe stenosis of a choledochojejunal anastomosis. Endoscopy. 2014;46(Suppl 1):E275–6. https://doi.org/10.1055/s-0034-1365785.
38. Ito K, Masu K, Kanno Y, et al. Ampullary intervention for bile duct stones in patients with surgically altered anatomy. Dig Endosc. 2014;26(Suppl 2):116–21. https://doi.org/10.1111/den.12250.
39. Itoi T, Ishii K, Sofuni A, et al. Large balloon dilation following endoscopic sphincterotomy using balloon enteroscope for the bile duct stone extractions in patients with Roux-en-Y anastomosis. Dig Liver Dis. 2011;43:237–41. https://doi.org/10.1016/j.dld.2010.09.002.
40. Cheng CL, Liu NJ, Tang JH, et al. Double-balloon enteroscopy for ERCP in patients with Billroth II anatomy: results of a large series of papillary large-balloon dilation for biliary stone removal. Endosc Int Open. 2015;3:E216–22. https://doi.org/10.1055/s-0034-1391480.
41. Takaoka M, Shimatani M, Ikeura T, et al. Diagnostic and therapeutic procedure with a short double-balloon enteroscope and cholangioscopy in a patient with acute cholangitis due to hepatolithiasis. Gastrointest Endosc. 2009;70:1277–9. https://doi.org/10.1016/j.gie.2009.04.018.
42. Mou S, Waxman I, Chennat J. Peroral cholangioscopy in Roux-en-Y hepaticojejunostomy anatomy by using the SpyGlass Direct Visualization System (with video). Gastrointest Endosc. 2010;72:458–60. https://doi.org/10.1016/j.gie.2009.11.017.
43. Itoi T, Sofuni A, Itokawa F, et al. Diagnostic and therapeutic peroral direct cholangioscopy in patients with altered GI anatomy (with video). Gastointest Endosc. 2012;75:441–9. https://doi.org/10.1016/j.gie.2011.09.038.
44. Baron TH, Saleem A. Intraductal electrohydraulic lithotripsy by using SpyGlass cholangioscopy through a colonoscope in a patient with Roux-en-Y hepaticojejunostomy. Gastrointest Endosc. 2010;71:650–1. https://doi.org/10.1016/j.gie.2009.08.016.
45. Kao KT, Batra B. Single-balloon-assisted ERCP with electrohydraulic lithotripsy for the treatment of a bile duct stone in a patient with a hepaticojejunostomy. Gastrointest Endosc. 2014;80:1173. https://doi.org/10.1016/j.gie.2014.02.1022.
46. Hakuta R, Kogure H, Isayama H, et al. Electrohydraulic lithotripsy of large bile duct stones under direct cholangioscopy with a double-balloon endoscope. Endoscopy. 2015;47(Suppl 1):E519–20. https://doi.org/10.1055/s-0034-1392669.
47. Pinto-Pais T, Pinho R, Proença L, et al. Iatrogenic biliary injury in a patient with Roux-en-Y hepaticojejunostomy: stenting repair with single-balloon enteroscopy-assisted ERCP. Endoscopy. 2014;46(Suppl 1):E506–7. https://doi.org/10.1055/s-0034-1365431.
48. Nagai K, Yane K, Katanuma A, et al. Successful less-invasive endoscopic treatment for bile leakage from choledochojejunostomy site using short-type single-balloon enteroscopy. Endoscopy. 2016;48(Suppl 1):E140–1. https://doi.org/10.1055/s-0042-105208.
49. Skinner M, Guttierrez JP, Wilcox CM, et al. Overtube-assisted placement of a metal stent into the bile duct of a patient with surgically altered upper-gastrointestinal anatomy during

double-balloon enteroscopy-assisted ERCP. Endoscopy. 2013;45(Suppl 2):E418–9. https://doi.org/10.1055/s-0033-1358806.
50. Tsutsumi K, Kato H, Tomoda T, et al. Partial stent-in-stent placement of biliary metallic stents using a short double-balloon enteroscopy. World J Gastroenterol. 2012;18:6674–6. https://doi.org/10.3748/wjg.v18.i45.6674.
51. Kogure H, Yamada A, Isayama H, et al. Multiple metal stenting using a double-balloon endoscope for malignant biliary obstruction in a patient with hepaticojejunostomy. Endoscopy. 2014;46(Suppl 1):E472–3. https://doi.org/10.1055/s-0034-1377541.
52. Yamauchi H, Kida M, Okuwaki K, et al. A case series: outcomes of endoscopic biliary self-expandable metal stent for malignant biliary obstruction with surgically altered anatomy. Dig Dis Sci. 2016;61:2436–41. https://doi.org/10.1007/s10620-016-4148-8.
53. Kikuyama M, Itoi T, Ota Y, et al. Therapeutic endoscopy for stenotic pancreatodigestive tract anastomosis after pancreatoduodenectomy (with videos). Gastrointest Endosc. 2011;73:376–82. https://doi.org/10.1016/j.gie.2010.10.015.
54. Itoi T, Kikuyama M, Ishii K, et al. EUS-guided with single-balloon enteroscopy for treatment of stenotic pancreaticojejunal anastomosis in post-Whipple patients (with video). Gastrointest Endosc. 2011;73:398–401. https://doi.org/10.1016/j.gie.2010.07.010.
55. Yane K, Katanuma A, Osanai M, et al. Successful removal of a pancreatic duct stone in a patient with Whipple resection, using a short single-balloon enteroscope with a transparent hood. Endoscopy. 2014;46(Suppl 1):E86–7. https://doi.org/10.1055/s-0033-1344832.

Chapter 7
ENBD

Chun-Tao Liu, Peng Li, and Shu-Tian Zhang

Abstract Endoscopic nasobiliary drainage (ENBD) was developed on the basis of diagnostic endoscopic retrograde cholangio-pancreatography (ERCP). The nasobiliary catheter was inserted with the help of a guidewire for the drainage of the biliary system. ENBD provides effective decompression for obstructive jaundice and allows sequential cholangiography, bile culture, and irrigation. Emergent ENBD is essential for severe obstructive cholangitis cases, whereas patients with mild to moderate conditions should also receive ENBD as soon as possible if they do not respond to conservative treatment. The nasobiliary catheter is relatively easy to insert once deep cannulation of the bile duct is achieved. And it is well tolerated for a short term. Biliary drainage can be achieved via three different routes/procedures: endoscopic, percutaneous transhepatic cholangiography, and surgery. Compared with surgical or percutaneous transhepatic approaches, endoscopic drainage is associated with a low morbidity rate and shorter duration of hospitalization. Thus, ENBD has been widely used for the initial decompression in patients with acute cholangitis. It also facilitates further interventional procedures of the biliary and pancreatic system.

Keywords Endoscopic nasobiliary drainage • External drainage • Nasobiliary catheter • Cholangitis • Choledocholithiasis

7.1 Indications and Contraindications

7.1.1 Indications for ENBD

1. Urgent drainage for suppurative cholangitis
2. Temporary drainage for incomplete ductal clearance
3. Lithotripsy for large bile duct stones
4. Preoperative biliary drainage in malignant biliary obstruction

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5. Therapy for benign intrahepatic cholestasis
6. Treatment of biliary adverse events following surgery

7.1.2 Contraindications to ENBD

1. Contraindications include those specific to ERCP.
2. Severe esophageal and gastric varices.

7.2 Endoscope Requirements

7.2.1 Duodenoscopes

Therapeutic duodenoscopes with a working channel of larger than 2.8 mm are needed for the procedure of ENBD.

7.2.2 Guidewires

During ERCP, guidewires are used for cannulation and for achieving and maintaining access to the bile duct. And they are also used for placing and exchanging devices. A variety of guidewires are currently available, and these vary in materials, length, diameter, and design to optimize performance. A 0.035 inch guidewire (400 cm in length) is needed for the insertion of the nasobiliary catheters.

7.2.3 Nasobiliary Catheters (Fig. 7.1)

Nasobiliary catheters are polyethylene tubes (250 cm in length) of 5–7-French gauge, with some shaping of the distal end or tip to prevent dislocation. Multiple tip configurations are available. Common configurations are straight and pigtail. The straight tip can be inserted into the hepatic duct, while the pigtail tip is suitable for a dilated common bile duct. Pigtails (especially in 7-French tubing) do not reform well unless the duct is dilated. The pigtail tip has to be straightened over a guidewire before insertion and remain straightened within the endoscope during cannulation. There is a preformed alpha curve loop about 15 cm from the tip which corresponds to the loop of the duodenum. Multiple side holes are placed over the distal 10 cm of the catheter to facilitate drainage, and the proximal end is connected to a drainage bag. A nasal transfer tube is needed for rerouting the tube from the mouth to the nose. A connecting tube is needed for gravity drainage.

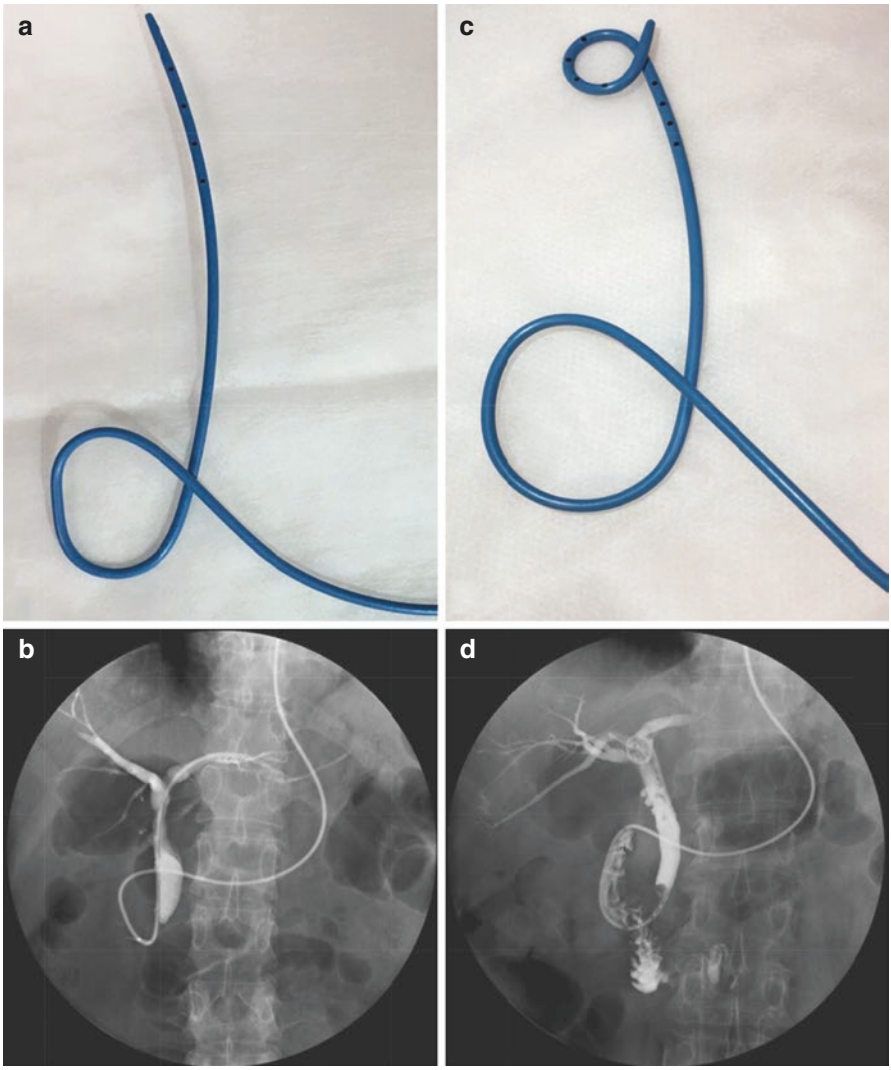

Fig. 7.1 (**a**) A straight-tip nasobiliary catheter; (**b**) a straight-tip nasobiliary catheter inserted into the hepatic duct; (**c**) a pigtail-tip nasobiliary catheter; (**d**) a pigtail-tip nasobiliary catheter inserted into the common bile duct

7.3 Procedures

During ERCP, a 0.035 inch guidewire is used to achieve deep cannulation of the bile duct. The guidewire helps to bypass the bile duct strictures or obstructing stones and to position the tip of the nasobiliary catheter deep in the bile duct. Then the nasobiliary catheter is inserted into the bile duct over the guidewire with or without a prior

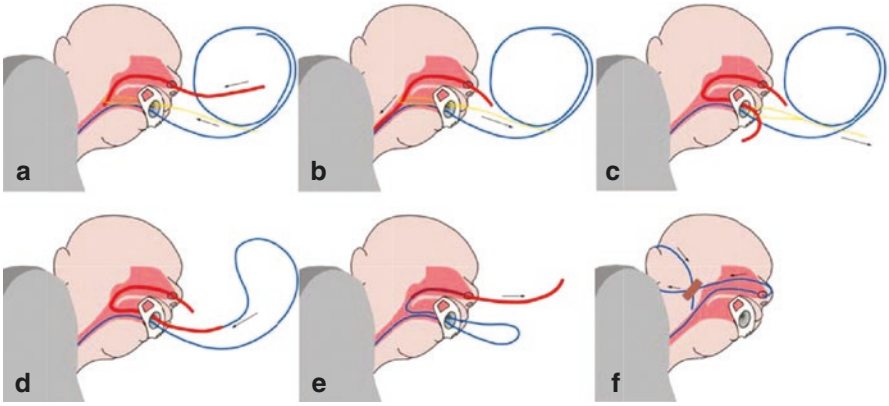

Fig. 7.2 The oral-nasal transfer process of nasobiliary catheter

sphincterotomy. Under fluoroscopic monitoring, slowly advance drainage catheter to the desired position in biliary duct above obstruction. Anchorage of the catheter within the bile duct is provided by the pigtail tip or by hooking the bent tip into one of the intrahepatic ducts. Once the nasobiliary catheter is in the desired place, the endoscope is withdrawn slowly from the patient while simultaneously advancing the catheter. This exchange will make sure that the catheter and guidewire are staying in the right place of the bile duct. When the endoscope is retrieved to the stomach, additional advancement of the nasobiliary catheter allows it to be in a long position along the greater curvature, which allows a safety margin so that the tube is not accidentally dislodged during endoscope withdrawal and oral-nasal transfer (Fig. 7.2). The whole procedure is performed under fluoroscopic control to avoid excess looping of the catheter in the stomach and duodenum, since loop formation may cause the intraductal portion to be dislodged. After the endoscope is removed from the patient, a nasal transfer tube is inserted through a nostril and brought out through the mouth. The end of the nasobiliary catheter is inserted into this tube, and then the nasobiliary catheter together with the nasal transfer tube is pulled back through the nose. The loop in the posterior pharynx is straightened to avoid kinking. The final position of the nasobiliary catheter is checked under fluoroscopy. The catheter is taped onto the nose and face for anchorage. The proximal end is then connected to a drainage bag. The endoscopists need to check the amount and color of the bile in the drainage bag after the procedure.

7.4 Clinical Applications

7.4.1 Urgent Drainage for Suppurative Cholangitis

Patients presenting with acute cholangitis caused by stone obstruction of the biliary system carry a significant morbidity and mortality, especially in elderly patients. Complete biliary obstruction and infection may lead to suppurative cholangitis. The

raised intrabiliary pressure leads to cholangiovenous reflux resulting in septicemia and shock with an increased risk of fatality. Conservative treatment with antibiotics is poorly effective for these patients. Decompression of the biliary system is mandatory. Before the introduction of ERCP and endoscopic drainage, the mortality rate of operation for acute suppurative cholangitis was around 40%. The clinical outcomes have been improved with urgent endoscopic biliary decompression using a nasobiliary catheter or a biliary stent. In 1989, emergency ENBD was shown to be effective in controlling sepsis of patients presenting with suppurative cholangitis [1]. Since then, ERCP has established its role in urgent drainage for suppurative cholangitis. Patients with coagulopathy due to prolonged cholestasis have a high risk of complications after biliary sphincterotomy. ENBD can be achieved without a sphincterotomy, thus avoiding the risk of bleeding in patients with coagulopathy. It has been shown by a randomized controlled trial that ENBD is a safe and effective measure for the initial control of severe acute cholangitis due to choledocholithiasis and to reduce the mortality associated with the condition, when compared with emergency open surgery and CBD exploration [2]. Sphincterotomy and stone extraction can be performed after sepsis is controlled. With successful drainage of the biliary system, abdominal pain and fever subside, and the patient's hemodynamic status stabilizes. The mortality rate of cholangitis has been brought down to 5–8% in recent years.

There are several randomized controlled trials comparing ENBD and endoscopic retrograde biliary drainage (ERBD) by using a plastic biliary stent in patients with acute suppurative cholangitis. The results showed that endoscopic biliary decompression, either by ENBD or ERBD, was equally effective for patients with acute suppurative cholangitis caused by bile duct stones. There is no significant difference in the success rate, effectiveness, and complications between the two procedures [3–6]. ENBD suffers the disadvantage of patient discomfort and risk for dislodgement; thus it is mainly selected for the patients with multiple biliary strictures, hemorrhage tendency, and excessive purulent bile in Western countries. Advantages of ENBD over internal stents are the ability to obtain noninvasive cholangiograms and cholecystogram and to provide irrigation for hemobilia, mucin, or debris. In the authors' center, we currently still prefer ENBD for urgent decompression for patients with acute suppurative cholangitis. On the other hand, the internal stent is associated with less postprocedure discomfort and avoidance of the potential problem of inadvertent removal of the nasobiliary catheter. The major drawback of internal stent is that its patency and adequacy of drainage cannot be monitored. Furthermore, a higher rate of blockage and more frequent hyperamylasemia in the ERBD group has been found [4, 6]. Thus, the choice of endoscopic drainage, ENBD or ERBD, depends on the specific circumstances of each patient.

7.4.2 Temporary Drainage for Incomplete Ductal Clearance

After successful cannulation and decompression of the bile duct is achieved, there are several potential strategies in the treatment of bile duct stones. A one-step approach with endoscopic sphincterotomy and stone extraction is the treatment of

choice for patients with stable clinical conditions. A prospective randomized study has assessed whether routine ENBD improves the clinical course in patients with choledocholithiasis-induced acute cholangitis after clearance of choledocholithiasis. The results showed that a routinely inserted ENBD tube did not improve the clinical course, despite patients having to endure increased procedure time and discomfort, and the insertion would therefore be unnecessary [7]. However, in patients with large or multiple common bile duct stones and failure of complete clearance of the stones, insertion of a nasobiliary catheter prevents stone impaction and provides drainage for the biliary system [8]. Complete ductal clearance is also difficult for patients with poor cardiopulmonary function, while the complication rate of ERCP and stone extraction is high. During the first ERCP, complete ductal clearance may only be achieved in 57–85% of patients [9]. Prolonged procedure and increasing sedation pose unnecessary challenges to these patients. For patients that are not suitable for prolonged endoscopic intervention, temporary ENBD followed by elective ERCP and stone extraction is recommended. Continuous bile duct irrigation via the nasobiliary catheter may be useful for management of patients with purulent cholangitis. Post-sphincterotomy cholangitis can occur in patients with failed or incomplete stone extraction. In patients with uncertain duct clearance, a check cholangiogram can be performed via the nasobiliary catheter. Through successful drainage, stone extraction can be achieved after the edema around the sphincterotomy has settled. The nasobiliary catheter can be safely removed without the need for a repeat ERCP [10].

7.4.3 Lithotripsy for Large Bile Duct Stones

Large bile duct stones, particularly those larger than 2 cm in diameter, are difficult to remove and usually need stone fragmentation prior to removal with baskets or balloons. There are many methods for stone fragmentation, including mechanical lithotripsy using metal baskets, intraductal electrohydraulic or laser lithotripsy, and extracorporeal shock wave lithotripsy (ESWL) [11–13]. The process of lithotripsy generates a lot of stone fragments which tend to obscure the endoscopic view. Furthermore, stone fragments may cause bile duct impaction and subsequent cholangitis. A nasobiliary catheter inserted into the common bile duct may be useful during fragmentation of large stones. Flushing the bile ducts with normal saline via the nasobiliary catheter removes the stone fragments and debris generated during the process of stone fragmentation and hence provides a clear endoscopic view. Adequate immersion of the probe and stones in normal saline is also necessary for effective electrohydraulic lithotripsy. In cases in which the stone is impacted within the bile duct, it is important to ensure the bile drainage by placing a nasobiliary catheter to avoid subsequent cholangitis. A pernasal cholangiogram by injecting contrast through the nasobiliary catheter helps to localize the bile duct stones in patients undergoing ESWL. The indwelling nasobiliary catheter also serves to drain the biliary system and prevents acute cholangitis after lithotripsy. Endoscopic

papillary balloon dilatation (EPBD) has been reported to increase the risk of post-ERCP pancreatitis (4–11%). Application of ENBD after EPBD prevents pancreatic duct obstruction by residual stones or papillary edema and decreases the incidence of post-ERCP pancreatitis [14, 15]. In the event that the stone is too large and endoscopic stone extraction fails, a nasobiliary catheter needs to be placed and additional endoscopic attempts can be performed at a later time.

7.4.4 Preoperative Biliary Drainage in Malignant Biliary Obstruction

Malignant biliary obstruction (MBO) is most frequently encountered in the setting of pancreatic adenocarcinoma, followed by cholangiocarcinomas, ampullary adenocarcinoma, duodenal adenocarcinoma, gallbladder adenocarcinoma, lymphoma, and compressive metastatic proximal lymph nodes [16]. The highest incidence of MBO is in Asia. The prognosis of MBO is poor with a median survival of 1–4 years after surgery [17]. Obstructive jaundice resulting from MBO may serve as the initial sign of disease, such as in the classic presentation of painless jaundice in pancreatic adenocarcinoma. Obstructive jaundice may lead to coagulopathy, abnormal liver function, and pre- or postoperative cholangitis. As the disease develops, other complications may occur, such as renal dysfunction and hepatic failure. The only curative treatment for MBO is surgical resection. However, both pancreatic cancer and cholangiocarcinoma usually progress to an advanced stage at diagnosis when radical surgery is contraindicated. Treatment goals for these patients include downstaging of the tumor with chemoradiotherapy or strictly palliative measures. Biliary drainage is recommended to resolve jaundice, improve clinical outcomes, and reduce postoperative complications. Functional impairment caused by jaundice increases the risk of surgery; therefore, preoperative biliary drainage (PBD) has been suggested. There are three types of biliary drainage: ENBD, ERBD, and percutaneous transhepatic cholangial drainage (PTCD). A lot of studies have assessed the outcomes of the different types of biliary drainage in MBO patients. Kumar et al. [18] prospectively compared the efficacy of endoscopic drainage for severe acute cholangitis in biliary obstruction as a result of malignant and benign diseases. They found endoscopic biliary drainage is equally effective in patients with either malignant or benign biliary diseases. PTCD is not recommended as the first choice of biliary drainage due to the risk of tumor seeding and other adverse events, in addition to the patient discomfort caused by such invasive treatment [19]. Lin et al. [16] performed a meta-analysis to compare the safety and efficacy of ENBD and ERBD in MBO treatment, showing that ENBD is better than ERBD for MBO in terms of the preoperative cholangitis rate, the postoperative pancreatic fistula rate, the incidence of stent dysfunction, and morbidity. A multicenter retrospective study was conducted to determine the optimal method of endoscopic preoperative biliary drainage (ENBD or ERBD) for malignant distal biliary obstruction. The results showed that ENBD/ERBD shared the same jaundice resolution rate (85%). However,

stent/catheter dysfunction rate was higher in the ERBD group (35%) than in the ENBD group (18%), suggesting that ERBD has insufficient patency for PBD [20].

However, the role of biliary drainage in patients who will undergo pancreaticoduodenectomy for biliary obstruction remains controversial. The choice of biliary drainage is also affected by the location of MBO. Sugiyama et al. [21] assessed the use of preoperative drainage for distal biliary obstruction and demonstrated that PBD should not be routinely performed because of higher risk for postoperative complications. PBD should only be considered in carefully selected patients, particularly in those whose surgery had to be delayed. PBD may be needed in patients with severe jaundice, concomitant cholangitis, or severe malnutrition. The optimal method of biliary drainage has yet to be confirmed. PBD should be performed by endoscopic routes rather than by percutaneous routes to avoid metastatic tumor seeding. ENBD or ERBD can be selected. Van der Gaag et al. [22] reported a randomized trial of 202 patients demonstrating that preoperative biliary drainage with stents was linked to increased complications compared to surgery alone in resectable pancreatic cancer. This study suggests PBD for distal biliary obstruction is not recommended except for treatment of cholangitis or intractable pruritus.

Treatment of distal MBO is typically managed by an endoscopically placed single biliary prosthesis, whereas hilar MBO can be more challenging to manage due to the need to access the left and right systems of the biliary tree. Hilar cholangiocarcinoma is a tumor of the extrahepatic bile duct involving the left main hepatic duct, the right main hepatic duct, or their confluence. Biliary drainage in hilar cholangiocarcinoma is sometimes clinically challenging because of complexities associated with the level of biliary obstruction. This may result in some adverse events, especially acute cholangitis. Hence the decision on the indication and methods of biliary drainage in patients with hilar cholangiocarcinoma should be carefully evaluated. Under certain conditions such as right lobectomy for Bismuth type IIIA or IV hilar cholangiocarcinoma, or preoperative portal vein embolization with chemoradiation therapy, PBD should be strongly recommended. Several studies compared the outcomes of ENBD, ERBD, and PTCD in patients with hilar cholangiocarcinoma. Jo et al. reveals that PTCD, ERBD, and ENBD showed comparable results regarding initial technical success rates, complication rates, and surgical outcomes [23]. However, ENBD was significantly associated with a lower risk of biliary reintervention [24]. Drainage tube occlusion with cholangitis was a frequent complication of ERBD. PTCD was associated with serious complications such as vascular injury and cancer dissemination. Thus, ENBD proves to be the most appropriate method for initial PBD management in patients with hilar cholangiocarcinoma [25–27].

In patients with suspicious malignant biliary strictures, ENBD cytology may be used to assist the pathological diagnosis. Bile cytology via an ENBD tube is often performed, in addition to aspirated bile cytology, brush cytology, and forceps biopsy, during the initial ERCP. Yagioka et al. [28] assessed the sensitivities of various sample acquisition methods in 214 patients with malignant biliary strictures. The results showed that the sensitivities were as follows: 30% (28/93) for aspirated bile cytology, 48% (62/130) for brush cytology, 41% (47/114) for forceps biopsy,

and 24% (19/79) for ENBD cytology. Although the sensitivity was inferior to that of the other methods used, ENBD cytology may contribute to the improvement of the total diagnostic sensitivity for malignancy.

7.4.5 Therapy for Benign Intrahepatic Cholestasis

Benign recurrent intrahepatic cholestasis (BRIC) is a rare disease characterized by repeated episodes of cholestasis and pruritus. It is an autosomal recessive disorder associated with the mutation of two hepatic transporter genes: the ATP8B1 gene, coding for familial intrahepatic cholestasis-1 (FIC1; BRIC type 1), and the ABCB11 gene, coding for the bile salt export pump (BSEP; BRIC type 2). Pruritus and jaundice are the only subjective symptoms, and cholestasis generally improves within a few months. The therapeutic aim is to relieve pruritus and other complications of severe cholestasis until the episode resolves spontaneously. Ursodeoxycholic acid is used as the first-line treatment for jaundice and pruritus in most cases of BRIC, but it is not necessarily effective. Several studies have demonstrated that ENBD is highly effective in the treatment of jaundice and pruritus in BRIC [29, 30]. ENBD forces external bile drainage, blocks the enterohepatic circulation, and results in the subsequent restoration of the function of bile excretion transporters. It suggests that patients with BRIC attacks can be treated with temporary ENBD.

Pruritus is a common and prominent symptom of cholestatic diseases such as primary biliary cholangitis (PBC), primary sclerosing cholangitis, and other less common cholestatic conditions including BRIC, progressive familial intrahepatic cholestasis, and drug-induced liver injury. A retrospective multicenter European study assessed the efficacy of nasobiliary drainage in relieving cholestatic pruritus [31]. The median duration of ENBD was 7 days. Pruritus was decreased in 89.6% of cases, suggesting ENBD is effective in relieving cholestatic pruritus. Prospective studies are needed to confirm these findings.

7.4.6 Treatment of Biliary Adverse Events Following Surgery

Biliary adverse events are relatively common following biliary and liver surgery, including cholecystectomy, hepatectomy, and liver transplantation. Bile duct injury during surgery may cause bile leak, biliary strictures, hemobilia, and so on. These complications result in morbidity and mortality following surgery. Endoscopic management remains to be the first choice for these biliary adverse events associated with surgery.

Bile leaks may result from various conditions after biliary and liver surgery. Patients usually present with persistent bile drainage or formation of a biloma. Clinically significant bile leak after surgery is a serious complication and poses difficulties in management. Surgery or PTCD has been used to treat bile leaks after

surgery. However, surgical repair has a higher rate of adverse events and death, and PTCD has a lower rate of success. ERCP is a safe and effective treatment for bile leakage. Several studies have reported the use of ERCP for the endoscopic treatment of bile leakage, with a success rate of approximately 65–80% [32–34]. ENBD or ERBD which bypasses the sphincter may serve to decompress the biliary system and reduce the bile flow through the leak site. This contributes indirectly to the healing of the leak. A small leak can be closed off easily by ENBD for a few days. Closure of the leak can be monitored by repeating cholangiography, low pressure suction can be applied, and the removal of ENBD tube does not require an additional endoscopy [35]. Bile leak associated with CBD damage may require drainage for several weeks. Since ENBD is not proper for long-term drainage, ERBD is often performed after initial emergency ENBD for these patients.

Hemobilia is an uncommon biliary complication after liver transplantation. Park et al. [36] investigated the frequency of spontaneous hemobilia after liver transplantation and assessed the outcomes of endoscopic management. The results showed that the frequency of spontaneous hemobilia was 1.22% (33/2701). ENBD was achieved in all 33 cases (100%). In 29 of 33 patients (87.9%), hemobilia was improved. Thus ENBD is a feasible method for the management of spontaneous hemobilia after liver transplantation.

7.5 Complications of ENBD

ENBD is a rather safe procedure, with patient discomfort and risk for dislodgement being the main disadvantages. Patients may complain of retropharyngeal discomfort. Most patients can tolerate the nasobiliary catheter well and consume a normal diet. The insertion and rerouting of the nasobiliary catheter through the nose may be difficult in septic patients with confusion. The catheter may be pulled out either accidentally or intentionally by the unconscious or uncooperative patient. In such cases, the catheter needs to be carefully taped onto the nose and face for anchorage, and the patients need to be constrained. In patients that require prolonged drainage, the fluid and electrolytes loss through the external drainage could be a potential problem for patients. Thus, ENBD is not proper for long-term external drainage. Improper positioning of the nasobiliary catheter, such as excessive looping in the stomach and duodenum, may cause the intraductal portion to be dislodged. Furthermore, kinking of the catheter in the posterior pharynx due to improper rerouting technique may result in failed drainage. Thus, the whole procedure needs to be performed under fluoroscopic control. The final position of the nasobiliary catheter needs to be checked under fluoroscopy after the procedure.

Severe complications of ENBD are extremely rare. Furuzono et al. [37] reported a case of cannulation and placement of an ENBD tube in the portal vein during ERCP and sphincterotomy. Immediate withdrawal of the tube inserted in the portal vein did not cause serious bleeding. Yu et al. [38] reported a case of gangrene of cystic duct due to the insertion of ENBD tube into the cystic duct by mistake. The

patient experienced right upper quadrant pain, along with fever, shivering, hypotension, jaundice, and leukocytosis, and then received emergency surgical exploration subsequently. Therefore, the location of the catheter must be repeatedly checked to avoid such complications.

References

1. Leung JW, Chung SC, Sung JJ, et al. Urgent endoscopic drainage for acute suppurative cholangitis. Lancet. 1989;1:1307–9.
2. Lai EC, Mok FP, Tan ES, et al. Endoscopic biliary drainage for severe acute cholangitis. N Engl J Med. 1992;326:1582–6.
3. Lee DW, Chan AC, Lam YH, et al. Biliary decompression by nasobiliary catheter or biliary stent in acute suppurative cholangitis: a prospective randomized trial. Gastrointest Endosc. 2002;56:361–5.
4. Park SY, Park CH, Cho SB, et al. The safety and effectiveness of endoscopic biliary decompression by plastic stent placement in acute suppurative cholangitis compared with nasobiliary drainage. Gastrointest Endosc. 2008;68:1076–80.
5. Sharma BC, Kumar R, Agarwal N, et al. Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis. Endoscopy. 2005;37:439–43.
6. Zhang RL, Cheng L, Cai XB, et al. Comparison of the safety and effectiveness of endoscopic biliary decompression by nasobiliary catheter and plastic stent placement in acute obstructive cholangitis. Swiss Med Wkly. 2013;w13823:143.
7. Lee JK, Lee SH, Kang BK, et al. Is it necessary to insert a nasobiliary drainage tube routinely after endoscopic clearance of the common bile duct in patients with choledocholithiasis-induced cholangitis? A prospective, randomized trial. Gastrointest Endosc. 2010;71:105–10.
8. Leung JW, Chung SC, Mok SD, et al. Endoscopic removal of large common bile duct stones in recurrent pyogenic cholangitis. Gastrointest Endosc. 1988;34:238–41.
9. Garcia-Cano J. Success rate for complete choledocholithiasis extraction by means of endoscopic retrograde cholangiopancreatography. Surg Endosc. 2004;18:1681–2.
10. Lauri A, Horton RC, Davidson BR, et al. Endoscopic extraction of bile duct stones: management related to stone size. Gut. 1993;34:1718–21.
11. Hakuta R, Kogure H, Isayama H, et al. Electrohydraulic lithotripsy of large bile duct stones under direct cholangioscopy with a double-balloon endoscope. Endoscopy. 2015;47(Suppl 1):E519–20.
12. Ogura T, Higuchi K. A review of treatment options for bile duct stones. Expert Rev Gastroenterol Hepatol. 2016;10:1271–8.
13. Tandan M, Reddy DN. Extracorporeal shock wave lithotripsy for pancreatic and large common bile duct stones. World J Gastroenterol. 2011;17:4365–71.
14. Sato D, Shibahara T, Miyazaki K, et al. Efficacy of endoscopic nasobiliary drainage for the prevention of pancreatitis after papillary balloon dilatation: a pilot study. Pancreas. 2005;31:93–7.
15. Yang J, Peng JY, Pang EJ, et al. Efficacy of endoscopic nasobiliary drainage for the prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis and cholangitis after repeated clearance of common bile duct stones: experience from a Chinese center. Dig Endosc. 2013;25:453–8.
16. Lin H, Li S, Liu X. The safety and efficacy of nasobiliary drainage versus biliary stenting in malignant biliary obstruction: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95:e5253.
17. Rerknimitr R, Kladcharoen N, Mahachai V, et al. Result of endoscopic biliary drainage in hilar cholangiocarcinoma. J Clin Gastroenterol. 2004;38:518–23.

18. Kumar R, Sharma BC, Singh J, et al. Endoscopic biliary drainage for severe acute cholangitis in biliary obstruction as a result of malignant and benign diseases. J Gastroenterol Hepatol. 2004;19:994–7.
19. Choi SH, Gwon DI, Ko GY, et al. Hepatic arterial injuries in 3110 patients following percutaneous transhepatic biliary drainage. Radiology. 2011;261:969–75.
20. Sasahira N, Hamada T, Togawa O, et al. Multicenter study of endoscopic preoperative biliary drainage for malignant distal biliary obstruction. World J Gastroenterol. 2016;22:3793–802.
21. Sugiyama H, Tsuyuguchi T, Sakai Y, et al. Current status of preoperative drainage for distal biliary obstruction. World J Hepatol. 2015;7:2171–6.
22. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362:129–37.
23. Jo JH, Chung MJ, Han DH, et al. Best options for preoperative biliary drainage in patients with Klatskin tumors. Surg Endosc. 2017;31:422–9.
24. Kawakubo K, Kawakami H, Kuwatani M, et al. Lower incidence of complications in endoscopic nasobiliary drainage for hilar cholangiocarcinoma. World J Gastrointest Endosc. 2016;8:385–90.
25. Paik WH, Loganathan N, Hwang JH. Preoperative biliary drainage in hilar cholangiocarcinoma: when and how? World J Gastrointest Endosc. 2014;6:68–73.
26. Kawashima H, Itoh A, Ohno E, et al. Preoperative endoscopic nasobiliary drainage in 164 consecutive patients with suspected perihilar cholangiocarcinoma: a retrospective study of efficacy and risk factors related to complications. Ann Surg. 2013;257:121–7.
27. Kawakami H, Kuwatani M, Onodera M, et al. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. J Gastroenterol. 2011;46:242–8.
28. Yagioka H, Hirano K, Isayama H, et al. Clinical significance of bile cytology via an endoscopic nasobiliary drainage tube for pathological diagnosis of malignant biliary strictures. J Hepatobiliary Pancreat Sci. 2011;18:211–5.
29. Stapelbroek JM, van Erpecum KJ, Klomp LW, et al. Nasobiliary drainage induces long-lasting remission in benign recurrent intrahepatic cholestasis. Hepatology. 2006;43:51–3.
30. Yakar T, Demir M, Gokturk HS, et al. Nasobiliary drainage for benign recurrent intrahepatic cholestasis in patients refractory to standard therapy. Clin Invest Med. 2016;39:27522.
31. Hegade VS, Krawczyk M, Kremer AE, et al. The safety and efficacy of nasobiliary drainage in the treatment of refractory cholestatic pruritus: a multicentre European study. Aliment Pharmacol Ther. 2016;43:294–302.
32. Oh DW, Lee SK, Song TJ, et al. Endoscopic management of bile leakage after liver transplantation. Gut Liver. 2015;9:417–23.
33. Ishii H, Ochiai T, Murayama Y, et al. Risk factors and management of postoperative bile leakage after hepatectomy without bilioenteric anastomosis. Dig Surg. 2011;28:198–204.
34. Ichiya T, Maguchi H, Takahashi K, et al. Endoscopic management of laparoscopic cholecystectomy-associated bile duct injuries. J Hepatobiliary Pancreat Sci. 2011;18:81–6.
35. Elmi F, Silverman WB. Nasobiliary tube management of postcholecystectomy bile leaks. J Clin Gastroenterol. 2005;39:441–4.
36. Park TY, Lee SK, Nam K, et al. Spontaneous hemobilia after liver transplantation: frequency, risk factors, and outcome of endoscopic management. J Gastroenterol Hepatol. 2016;32(3):583–8.
37. Furuzono M, Hirata N, Saitou J, et al. A rare complication during ERCP and sphincterotomy: placement of an endoscopic nasobiliary drainage tube in the portal vein. Gastrointest Endosc. 2009;70:588–90.
38. Yu H, Chen H, Jin X. A rare case of gangrene of cystic duct due to the insertion of endoscopic nasobiliary drainage (ENBD) tube into the cystic duct by mistake. Rev Esp Enferm Dig. 2016;108:168–9.

Part II
EUS

Chapter 8
Endoscopic Ultrasound: Introduction and How to Educate Operators

Akio Katanuma, Hiroyuki Maguchi, Kuniyuki Takahashi, Kei Yane, and Toshifumi Kin

Abstract Endoscopic ultrasound (EUS) is used to obtain ultrasound images from the gastrointestinal (GI) lumen by inserting an endoscope with a US transducer mounted at the tip. Recently, electronic scanning EUS has been developed, markedly improving the quality of conventional B-mode images. Moreover, EUS comes with various functions, including tissue harmonic imaging, Doppler function, elastography, and contrast harmonic echo using contrast agents. There are two types of EUS: the radial scanning (RS) and the curved linear array (CL). CL is now widely used for not only the pathological diagnosis through the collection of specimens but also various therapeutic applications. To perform both radial and curved array EUS, visualization of the target is necessary. Moreover, the EUS technique is operator dependent, and an operator must acquire a certain level of skill including interventional procedures. Nowadays, there are some training models which include living animal, ex vivo animal model, phantom, and computer-based simulator that are developed. With the expansion of indications, more complex skills will be required for EUS procedures, and appropriate training systems will play an increasingly vital role.

Keywords Endoscopic ultrasound • Endoscopic ultrasound-guided fine needle aspiration • Interventional EUS • Training model

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8.1 Introduction

8.1.1 Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is used to obtain ultrasound (US) images from the gastrointestinal (GI) lumen by inserting an endoscope with a US transducer mounted at the tip. Compared with abdominal US, EUS produces fewer artifacts from gas in the GI tract and provides superior images with high spatial resolution [1–3]. For this reason, EUS is considered to be an important modality for the diagnosis of pancreaticobiliary diseases. The utility of EUS has been noted in the differential diagnosis of tumors and the visualization of small lesions [4, 5]. EUS is also extremely useful in the visualization of nodules and the septum within a cyst in pancreatic cystic diseases [6, 7]. It can also be used for tumor staging, particularly in the visualization of vascular invasion and enlarged lymph nodes [8].

EUS has been used mostly for diagnostic purposes through observation and visualization. However, with the advent of curved linear array (CL) echoendoscopes, EUS is now widely used for the pathological diagnosis of tumors through the collection of specimens or the so-called endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) [9–12]. Because of its high sampling and diagnostic accuracy rates and low incidence of accidental injury, EUS-FNA is used for the histopathological diagnosis of various conditions. The interventional applications of EUS-FNA are not limited to pancreatic cyst drainage but have been expanded to biliary and pancreatic ductal drainage and approaches. Similarly to endoscopic ultrasound-guided celiac plexus neurolysis, EUS-FNA is also used for the localized injection of medications to treat pain.

However, although EUS plays a central role in the diagnosis of pancreaticobiliary diseases, the procedure is largely operator dependent. Moreover, interventional EUS requires a high level of technical skill. In this chapter, we provide an appraisal of EUS in terms of the techniques, educational aspects, and training models used for this important procedure.

8.1.2 Equipment

8.1.2.1 Echoendoscope

EUS scopes can be classified into two types: radial (Fig. 8.1a) and linear (Fig. 8.1b) types. A radial echoendoscope (RS) produces images by transmitting a US signal radially from the transducer in the center, whereas a CL produces US images in a plane parallel to the long axis of the echoendoscope. The advantages of using an RS are the 360° scanning range and the ease of obtaining long axis images of the pancreas, bile duct, and gallbladder. In contrast, the scanning range of a CL is limited; its field of view ranges from 180° to 270°, which is narrower than that of an RS (Table 8.1). However, with a CL, the EUS needle can be advanced from the distal

Fig. 8.1 Echoendoscope. (**a**) Radial echoendoscope. (**b**) Curved linear echoendoscope. (**c**) Forward-viewing echoendoscope

Table 8.1 Advantages and disadvantages of radial and curved linear array endoscopic ultrasound

	Radial array	Curved linear array
Advantages	The scanning range is 360° The pancreas and bile duct are easily seen as a longitudinal and continuous image	Histological diagnosis is possible The junction between the pancreatic head and the pancreatic body can be seen from the stomach The aorta, celiac artery, and superior mesenteric artery (SMA) are easily seen in a single longitudinal image
Disadvantage	Histological diagnosis is not possible Operator dependent	The scanning range is from 180° to 270° Images of the pancreatic body and tail easily become cross-sectional images A continuous image of the bile duct, cystic duct, and gallbladder is difficult to capture

tip of the echoendoscope in the same plane as the US image. This allows for the simultaneous visualization of the target lesion and the EUS needle as it is advanced [13]. Although most CL are oblique viewing, forward-viewing linear echoendoscopes have also been developed in recent years and have been clinically applied (Fig. 8.1c) [14, 15]. Although the scanning range is small, treatment accessories extend straight from the channel, which is reportedly useful in interventional procedures.

Several manufacturers market echoendoscopes, but these echoendoscopes all have different tip diameters and frequencies. Therefore, it is important to fully understand the characteristics of each product. According to a randomized controlled trial that compared RS and CL in terms of observation and visualization, both types had the same level of visualization capabilities; however, the RS was superior in the visualization of the papillary area and gallbladder, whereas the CL was superior in the visualization of the pancreatic neck and celiac artery as well as the upper mesenteric artery [16].

8.1.2.2 EUS Processors

When EUS was first developed, it used only a mechanical scanning method. Recently, however, electronic scanning EUS has also been developed, markedly improving the quality of conventional B-mode images. Moreover, the US processors sold for use with EUS come with various functions, including tissue harmonic imaging to produce images with fewer artifacts, Doppler to provide information on blood flow, elastography to visualize tissue stiffness, and contrast harmonic echo to allow detailed observation of blood flow in the tissue with the use of US contrast agents.

8.1.2.3 FNA Needles and Devices for Interventional EUS

EUS-FNA procedures require a needle. Needles are available in different outer diameters, namely, 19-gauge, 22-gauge, and 25-gauge needles. Some of the needles used in EUS-FNA have side holes or a core trap at the tip. The 25-gauge needle is easy to insert through the accessory channel and is superior in terms of the ease of pass in locations where an echoendoscope needs to be bent to target a lesion, such as when puncturing via the transduodenal route. The drawback of the 25-gauge needle is the limited amount of tissue samples it can collect because of its very small diameter. On the other hand, the 19-gauge needle can collect larger amounts of tissue samples but is inferior in terms of the ease of insertion through the channel and pass owing to its larger diameter [17, 18].

When performing interventional EUS, particularly drainage, it is ideal to use therapeutic accessories specifically designed for the procedure, including tools used for dilation of the transmural tract and drainage tubes. However, there are currently few dedicated accessories that are available for EUS-guided drainage.

8.1.3 EUS-FNA and Interventional EUS Procedures

Since the first report of Vilmann et al. [9] regarding the use of linear EUS for the tissue diagnosis of pancreatic tumors, the indications for linear EUS have expanded to include the histological diagnosis of various diseases. Moreover, a study in 1992 reported on the EUS-guided drainage of a pancreatic pseudocyst [19].

Diagnostic EUS-FNA is often indicated for the definitive histopathologic diagnosis of lesions in cases of pancreatic tumors, gastrointestinal submucosal tumors, and lymphadenopathy and in cases where tissue diagnosis may influence the subsequent treatment. On the other hand, EUS-FNA is contraindicated in the following cases: (1) when a target cannot be visualized by EUS, (2) when blood vessels in the needle path cannot be avoided, and (3) when a bleeding tendency is noted. In patients who are taking oral antithrombotic drugs, careful considerations should be given to all pertinent factors, including drug discontinuation, to determine whether or not EUS-FNA is feasible. Lesions such as paragangliomas may cause an elevated blood pressure when passed and thus need to be identified before performing FNA [20].

There are various kinds of EUS-FNA needles that are commercially available. Needles with a larger diameter may be more difficult to insert into the channel of an echoendoscope and pass through a target, although they can collect a larger amount of tissue samples. After the needle tip reaches a target, the stylet is removed, and the needle is moved to and fro within the target, while negative pressure is applied to collect tissue samples. Regarding the needle movement within a target, the fanning technique changes the direction of a needle within a lesion by the movements of the elevator and echoendoscope to collect tissue. Various clinical trials have been conducted to determine the optimal method of collecting tissue samples. The focus of these trials has been on whether to use a stylet or not [21] or whether to sample with or without suction [22, 23], among others. However, a prevailing consensus has not been obtained for any of these methods; thus, further investigation is necessary.

The diagnostic accuracy of EUS-FNA is in fact high ranging from 88 to 95% as reported by most studies [24–26]. Its common complications include bleeding, perforation, and pancreatitis, but the rate of complications is only from 1 to 3% [25–28], and, therefore, EUS-FNA is considered to be a safe procedure. Although needle tract seeding after FNA of a malignant lesion has been reported [29–31], the incidence is extremely low.

EUS-guided interventions are divided into two types: (1) drainage (Table 8.2) and (2) injection. There are several types of drainage procedures, namely, pancreatic pseudocyst drainage, biliary drainage, pancreatic duct drainage, and pelvic abscess drainage. In all of these procedures, needle puncture is performed, followed by dilation of the transmural tract and placement of a stent or a drainage tube at the target site.

Among all linear EUS-guided drainage procedures, drainage of pancreatic pseudocysts is performed most frequently. Recently, the usefulness of endoscopic necrosectomy has also been reported for the treatment of walled-off necrosis following necrotizing pancreatitis [32, 33]. In this procedure, the transmural tract is dilated, and a forward-viewing endoscope is advanced directly into the necrotic cavity to remove the necrotic material.

Table 8.2 EUS-guided drainage technique

Pancreatic cyst drainage
– Pseudocyst
– Walled-off necrosis
Biliary drainage
– Choledocoduodenostomy
– Hepaticogastrostomy
– Antegrade stenting
– Rendezvous technique
– Gallbladder drainage
Pancreatic drainage
– Pancreaticogastrostomy
– Pancreaticoduodenostomy
– Antegrade stenting
– Rendezvous technique
Pelvic abscess drainage

EUS-guided biliary drainage is a useful alternative to endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous biliary drainage in cases of difficult endoscopic insertion, such as those with intestinal obstruction and surgically altered anatomy, and in cases of difficult transpapillary biliary cannulation. EUS-guided biliary drainage is performed by either EUS-guided choledochoduodenostomy to puncture the bile duct from the duodenal bulb or EUS-guided hepaticogastrostomy (EUS-HGS) to puncture the intrahepatic bile duct from the stomach. The EUS-HGS technique is applied to EUS-guided antegrade stenting, in which a guidewire is introduced anterograde from the intrahepatic bile duct across a stenosis for stent placement. Additionally, an EUS-guided rendezvous technique is used for difficult biliary cannulation. In EUS-guided rendezvous drainage, the bile duct is punctured, and a guidewire is advanced across the papilla. Then, while the guidewire is left in place, the echoendoscope is replaced with a duodenoscope, which is inserted into the channel to perform biliary cannulation.

EUS-guided pancreatic duct drainage is performed in the same manner as EUS-guided biliary drainage. However, the pancreatic duct drainage requires a higher level of technical skill because dilation of the pancreatic parenchyma is difficult. Moreover, the pass route from the transmural tract tends to have a steep angle at the main pancreatic duct.

8.2 Educational Aspects

8.2.1 Standard Visualization Technique

To perform both radial and curved array EUS, visualization of the target is necessary. The EUS-guided observation technique is operator dependent, and an operator must start with the acquisition of a certain level of skill and a proper visualization

technique to make an accurate diagnosis. Factors contributing to the difficulty in performing EUS-guided observation include the following: (1) the operator needs to maneuver the echoendoscope while watching the ultrasound images; (2) the images are not endoscopic images, making it difficult to check the orientation of the US transducer within the GI lumen; (3) the images obtained can change greatly by subtle movement of the echoendoscope; and (4) it is difficult to grasp the three-dimensional positioning within the GI lumen.

For EUS visualization, standard techniques for radial EUS and linear EUS were reported in 2003 and 2007, respectively [34, 35]. In the report, radial EUS techniques can be performed via the transgastric and transduodenal approaches. The transduodenal approach involves pull and push maneuvers. The pull maneuver employs the ERCP stretch technique to make an observation from the pancreatic head, whereas the push maneuver involves the pushing of the EUS scope through the stomach and its advancement across the pylorus to be maneuvered from the duodenal bulb. Specifically, the pull maneuver from the descending limb of the duodenum is divided into the longitudinal method and transverse method (Fig. 8.2a, b). The longitudinal approach uses the up angle to initially obtain a longitudinal image of the aorta before maneuvering the scope. The transverse approach obtains a transverse image of the aorta without using the up angle.

Linear EUS techniques can also be divided into the transgastric and transduodenal approaches. As with radial EUS, the transduodenal approach involves pull and push maneuvers (Fig. 8.3a, b). In both radial EUS and linear EUS, the orientation of the transducer in the duodenal approach changes between the pull and push maneuvers, which may alter the positional relationship on the EUS images displayed on the monitor.

Taken together, a thorough knowledge of the standard visualization techniques is very essential in mastering the skills required to perform EUS-guided procedures.

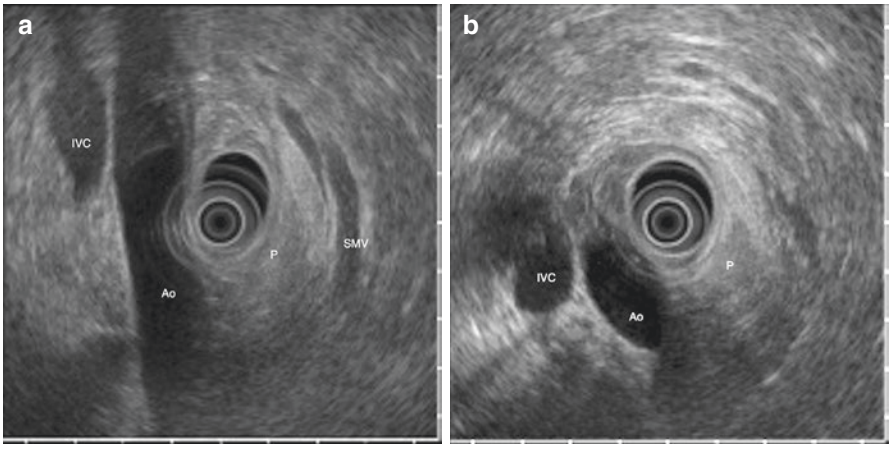

Fig. 8.2 Scanning of the pancreatic head from the duodenum by radial EUS. (**a**) Longitudinal method. Uses the up angle to obtain a longitudinal image of the aorta. (**b**) Transverse method (*P* pancreatic head, *Ao* aorta, *IVC* inferior vena cava, *SMV* superior mesenteric vein)

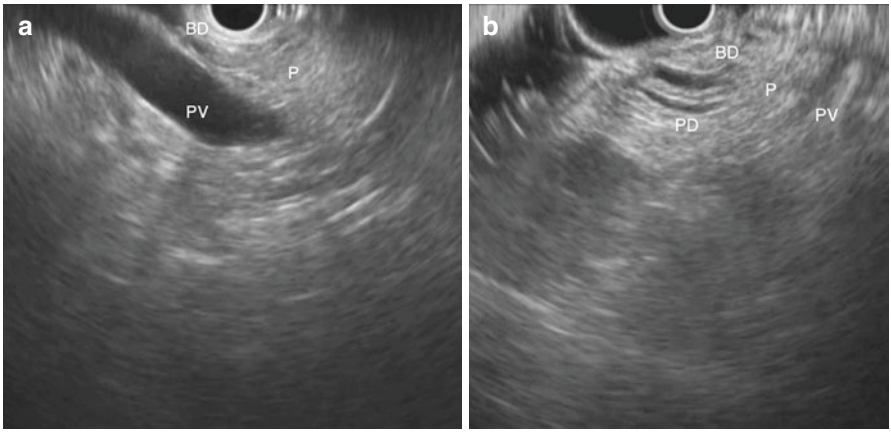

Fig. 8.3 Scanning of the pancreatic head from the duodenum by linear EUS. On the image, the left and right directions are opposed. (**a**) Push method. (**b**) Pull method. (*P* pancreatic head, *PV* portal vein, *BD* bile duct, *PD* pancreatic duct)

8.2.2 Training and Learning Curve

To master EUS observation and FNA techniques, proper training and learning opportunities are necessary. The number of cases required for training varies depending on the technical competence of each trainee. Studies have been conducted to explore learning curves for acquiring an adequate level of skills and expertise.

The American Society for Gastrointestinal Endoscopy (ASGE) recommends that for comprehensive competence in all aspects of EUS, at least 150 supervised EUS procedures should be performed; 50 of them must be EUS-FNA, and at least 75 should include pancreaticobiliary indications. More specifically, these guidelines recommend that for pancreatic EUS-FNA competence, the trainee should be competent in performing pancreaticobiliary EUS and must have performed at least 25 supervised FNAs of pancreatic lesions [36].

Therefore, it is essential that trainees carry out a sufficient number of procedures under the supervision of an attending doctor to master EUS techniques.

Wani et al. [37] in their study of prospectively defining learning curves in EUS among advanced endoscopy trainees observed a substantial variability in achieving competency and a consistent need for more supervision in all advanced endoscopy trainees than current recommendations (150 cases). Mohamad et al. [38] addressed the importance of a proper training program to master the techniques for performing EUS-FNA in pancreatic tumors. Wasan et al. [39] investigated the EUS training status in multiple facilities and reported that most EUS operators are in academic practice. Those with advanced training obtained higher training volumes and perform higher volumes of EUS. The majority of respondents felt well trained regardless of the training type and the number of procedures performed during the training.

To master the techniques for performing EUS procedures, proper training is a must. This should be performed under the supervision of an attending doctor who possesses sufficient levels of technical skills and proficiency.

8.2.3 Training Models

Currently, most facilities and endoscopists conduct EUS training in actual clinical settings. Clinical training is certainly important; however, when considering recent medical circumstances, it may be necessary to use training models first, rather than using patients from the start. In fact, various EUS training models have been reported, and their utility has been demonstrated. These models include live animal models, ex vivo animal models, phantoms, and computer-based simulators.

Barthet [40] reported the utility of EUS training using living pig models. In 17 trainees who had undergone EUS training using living pig models, improvement was observed in their EUS observation and FNA techniques after the training.

Ex vivo animal models are prepared from a combination of explanted animal organs and artificial parts to overcome some limitations of living animal models. The most well-known ex vivo model for endoscopy is the Erlangen Active Simulator for Interventional Endoscopy (EASIE) (ECETraining GmbH, Erlangen, Germany) [41, 42]. This was the first model to simulate spurting blood realistically, and it was developed for therapeutic endoscopy training in 1997 [43]. The EASIE model is a human-shaped mannequin consisting of an anatomical torso, a pivotal suspension frame with an external perfusion system. This mannequin is adapted to connection devices and fixation elements for topographically implanting the prepared special swine organs.

The EUS visualization model (Ikuma model) (Fig. 8.4a) is one of the well-known phantoms that is used for simulating real-life human anatomy. This model was designed through collaboration between Olympus Corporation (Tokyo, Japan) and Kyoto Kagaku (Kyoto, Japan). Structures, organs, and blood vessels surrounding the gastric region can be viewed under EUS (Fig. 8.4b) [44]. It is considered to be a good model for teaching the localization of structures and the navigation of stations.

The GI endoscopic ultrasound training phantom (ATS Laboratories, Inc., Bridgeport, CT, USA) is also a well-designed phantom which provides training of EUS-FNA procedure (Fig. 8.5a, b). This training phantom is a low-cost, practical, hands-on, easy-to-use device. The target structures or spheres are continued within a soft rubber-based tissue-mimicking material. The number, placement, and contrast of these spheres vary between the three models offered.

In recent years, a new training phantom for EUS-guided biliary drainage has been developed. This model contains a bile duct created by 3D printing (Fig. 8.6a, b) which allows passage and drainage of tube inserted, and its utility has been demonstrated [45].

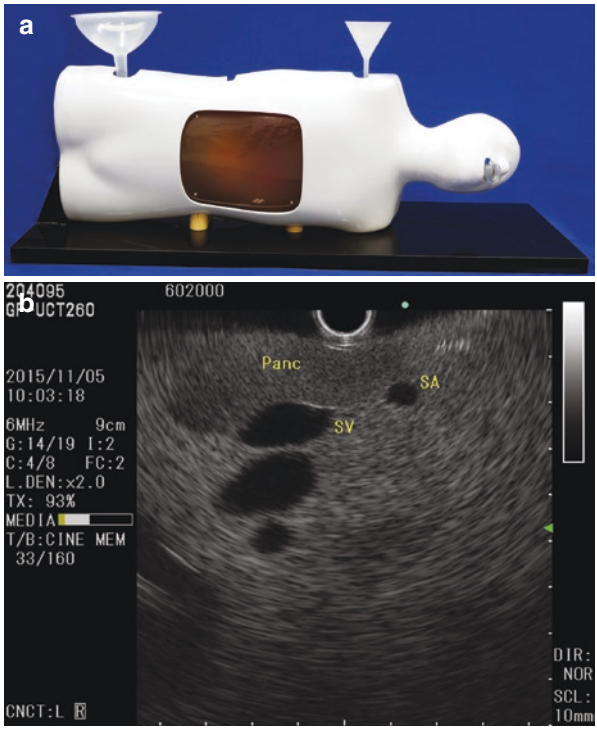

Fig. 8.4 (**a**) EUS visualization model (Ikuma model) (Olympus Co. Tokyo, Japan, and Kyoto Kagaku, Kyoto, Japan). (**b**) Structures, organs, and blood vessels surrounding the gastric region can be viewed under EUS. (*Panc* pancreas, *SA* splenic artery, *SV* splenic vein)

As for computer-based simulators, there are reports of the GI Mentor™ (Simbionix, Tel Hashomer, Israel), which is based on a flight simulator technology. The simulator endoscope tip has a sensor that allows the computer to generate a dynamic real-time endoscopic view according to the user's movements. A module for EUS (EUS Mentor) is available on the GI Mentor [46, 47]. The EUS Mentor represents an addition to a computer-based endoscopic simulator platform and was developed for radial and linear array EUS.

As described above, various EUS training models have been developed. However, each model has its own advantages and disadvantages (Table 8.3). Living animal models and ex vivo animal models provide a realistic sense of how to perform EUS on living bodies, and these models are similar to living bodies in terms of actually having blood flow. However, the use of living animal models and ex vivo animal models also involves ethical concerns and requires special facilities and equipment. Particularly for living animal models, a facility to perform veterinary anesthesia is absolutely necessary. Furthermore, animal models are not anatomically the same as humans. They are also costly and thereby not practical for repeated use in training.

Computer simulators are capable of creating various situations and are free from ethical issues or the need for special facilities. However, they are expensive, and EUS performed on a computer simulator does not provide a sense of reality compared with a living body. To overcome these issues, phantoms have been developed. Unlike computer simulators, phantoms can be created at a relatively low cost.

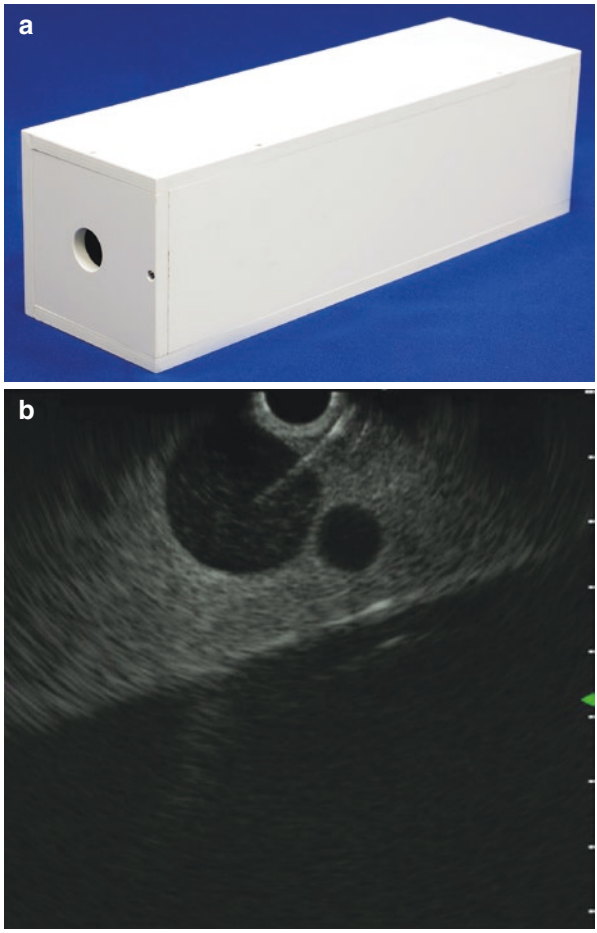

Fig. 8.5 (**a**) GI endoscopic ultrasound training phantom (ATS Laboratories, Inc., Bridgeport, CT, USA). (**b**) Image of EUS-FNA using GI endoscopic ultrasound training phantom

However, they are still not realistic compared with living bodies. It is also difficult to replicate a complete model for EUS procedures without blood flow. With further advancement in technology, the emergence of new training models that can provide a more realistic sense of how to perform EUS on living bodies is eagerly anticipated.

8.2.4 Limitations of Training Models

With the expansion of indications, more complex skills will be required for EUS procedures, and appropriate training models will undoubtedly play an increasingly vital role. However, it is difficult to definitively assess whether these models are truly useful for acquiring practical EUS skills, thus necessitating further investigations. In most of the studies that evaluated EUS training models, the results were

Fig. 8.6 (**a**) 3D printing model (Mumbai model) for EUS-guided hepaticogastrostomy. (**b**) Hands-on training using Mumbai model (Courtesy by prof. Takao Itoi, Tokyo Medical University)

based only on questionnaire surveys and skill improvement observed over a short period of time; therefore, additional studies are necessary. Despite the various training models that have been developed, many of these models are unfortunately not practical to be used for daily EUS education. Moreover, shortages of facilities and instructors capable of providing proper EUS training are a reality.

In conclusion, EUS is an essential modality for the diagnosis and treatment of pancreaticobiliary diseases, and its role is expected to become increasingly vital. However, effective EUS training systems are currently far from being established; thus, further development and upgrading of such systems are required.

Table 8.3 Characteristics of training models for endoscopic ultrasonography and endoscopic ultrasonography-guided fine needle aspiration

	Advantages	Disadvantages
Living animal model	Realistic	High cost Ethical issues Needs special facilities and equipment Anatomy is not completely the same
Ex vivo model	Realistic Lower cost than living animal model	Longer preparation time No vital tissue characteristics
Phantom	Simple Easy to use Minimal preparation Reusable	Not realistic Not actual anatomy or conditions
Computer-based simulator	Easy to use Reusable Feedback and alert function Various situations are possible	High cost Not realistic

References

1. Maguchi H. The roles of endoscopic ultrasonography in the diagnosis of pancreatic tumors. J Hepato-Biliary-Pancreat Surg. 2004;11:1–3.
2. Tierney WM, Adler DG, Chand B, et al. Echoendoscopes. Gastrointest Endosc. 2007;66:435–42.
3. Tierney WM, Kochman ML, Scheiman JM. Computed tomography versus endoscopic ultrasonography for staging of pancreatic cancer. Ann Intern Med. 2005;142:590–1.
4. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol. 2004;2:606–21.
5. Liu CL, Lo CM, Chan JK, et al. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc. 2000;51:28–32.
6. Koshita S, Fujita N, Noda Y, et al. Invasive carcinoma derived from “flat type” branch duct intraductal papillary mucinous neoplasms of the pancreas: impact of classification according to the height of mural nodule on endoscopic ultrasonography. J Hepatobiliary Pancreat Sci. 2015;22:301–9.
7. Lee KH, Lee SJ, Lee JK, et al. Prediction of malignancy with endoscopic ultrasonography in patients with branch duct-type intraductal papillary mucinous neoplasm. Pancreas. 2014;43:1306–11.
8. Li JH, He R, Li YM, et al. Endoscopic ultrasonography for tumor node staging and vascular invasion in pancreatic cancer: a meta-analysis. Dig Surg. 2014;31:297–305.
9. Vilmann P, Jacobsen GK, Henriksen FW, et al. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreas disease. Gastrointest Endosc. 1992;38:172–3.
10. Wiersema MJ, Kochman ML, Cramer HM, et al. Endosonography-guided real-time fine-needle aspiration biopsy. Gastrointest Endosc. 1994;40:700–7.
11. Chang KJ, Katz KD, Durbin TE, et al. Endoscopic ultrasound-guided fine- needle aspiration. Gastrointest Endosc. 1994;40:694–9.
12. Chang KJ, Nguyen P, Erickson RA, et al. The clinical utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of pancreas carcinoma. Gastrointest Endosc. 1997;45:387–93.

13. Katanuma A, Maguchi H, Osanai M, et al. The difference in the capability of delineation between convex and radial arrayed echoendoscope for pancreas and biliary tract; case reports from the standpoint of both convex and radial arrayed echoendoscope. Dig Endosc. 2011;23:S2–8.
14. Eloubeidi MA. Initial evaluation of the forward-viewing echoendoscope prototype for performing fine-needle aspiration, Trucut biopsy, and celiac plexus neurolysis. J Gastroenterol Hepatol. 2011;26:63–7.
15. Kida M, Araki M, Miyazawa S, et al. Fine needle aspiration using forward-viewing endoscopic ultrasonography. Endoscopy. 2011;43:796–801.
16. Kaneko M, Katanuma A, Maguchi H, et al. Prospective, randomized, comparative study of delineation capability of radial scanning and curved linear array endoscopic ultrasound for the pancreaticobiliary region. Endosc Int Open. 2014;2:E160–70.
17. Sakamoto H, Kitano M, Komaki T, et al. Prospective comparative study of the EUS guided 25-gauge FNA needle with the 19-gauge Trucut needle and 22-gauge FNA needle in patients with solid pancreatic masses. J Gastroenterol Hepatol. 2009;24:384–90.
18. Siddiqui UD, Rossi F, Rosenthal LS, et al. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. Gastrointest Endosc. 2009;70:1093–7.
19. Grimm H, Binmoeller KF, Soehendra N. Endosonography-guided drainage of a pancreatic pseudocyst. Gastrointest Endosc. 1992;38:170–1.
20. Akdamar MK, Eltoum I, Eloubeidi MA. Retroperitoneal paraganglioma: EUS appearance and risk associated with EUS-guided FNA. Gastrointest Endosc. 2004;60:1018–21.
21. Sahai AV, Paquin SC, Gariépy G. A prospective comparison of endoscopic ultrasound-guided fine needle aspiration results obtained in the same lesion, with and without the needle stylet. Endoscopy. 2010;42:900–3.
22. Wallace MB, Kennedy T, Durkalski V, et al. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. Gastrointest Endosc. 2001;54:441–7.
23. Puri R, Vilmann P, Săftoiu A, et al. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. Scand J Gastroenterol. 2009;44:499–504.
24. Moller K, Papanikolaou IS, Toermer T, et al. EUS-guided FNA of solid pancreatic masses: high yield of 2 passes with combined histologic-cytologic analysis. Gastrointest Endosc. 2009;70:60–9.
25. Iglesias-Garcia J, Dominguez-Munoz E, Lozano-Leon A, et al. Impact of endoscopic ultrasound-guided fine needle biopsy for diagnosis of pancreatic masses. World J Gastroenterol. 2007;13:289–93.
26. O'Toole D, Palazzo L, Arotçarena R, et al. Assessment of complications of EUS-guided fine-needle aspiration. Gastrointest Endosc. 2001;53:470–4.
27. Adler DG, Jacobson BC, Davila RE, et al. ASGE guideline: complications of EUS. Gastrointest Endosc. 2005;61:8–12.
28. Katanuma A, Maguchi H, Yane K, et al. Factors predictive of adverse events associated with endoscopic ultrasound-guided ne needle aspiration of pancreatic solid lesions. Dig Dis Sci. 2013;58:2093–9.
29. Shah JN, Fraker D, Guerry D, et al. Melanoma seeding of an EUS-guided fine needle track. Gastrointest Endosc. 2004;59:923–4.
30. Doi S, Yasuda I, Iwashita T, et al. Needle tract implantation on the esophageal wall after EUS-guided FNA of metastatic mediastinal lymphadenopathy. Gastrointest Endosc. 2008;67:988–90.
31. Katanuma A, Maguchi H, Hashigo S, et al. Tumor seeding after endoscopic ultrasound-guided fine-needle aspiration of cancer in the body of the pancreas. Endoscopy. 2012;44:E160–1.
32. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307:1053–61.

33. Yasuda I, Nakashima M, Iwai T, et al. Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: the JENIPaN study. Endoscopy. 2013;45:627–34.
34. Fujita N, Inui K, Kida M, et al. Standard imaging techniques in the pancreatobiliary region using radial scanning endoscopic ultrasonography. Dig Endosc. 2004;16:S118–33.
35. Yamao K, Irisawa A, Inoue H, et al. Standard imaging techniques of endoscopic ultrasound-guided fine-needle aspiration using a curved linear array echoendoscope. Dig Endosc. 2007;19:S180–205.
36. Eisen GM, Dominitz JA, Faigel DO, et al. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc. 2001;54:811–4.
37. Wani S, Coté GA, Keswani R, et al. Learning curves for EUS by using cumulative sum analysis: implications for American Society for Gastrointestinal Endoscopy recommendations for training. Gastrointest Endosc. 2013;77:558–65.
38. Mohamad A, Eloubeidi MA, Tamhane A. EUS-guided FNA of solid pancreatic masses: a learning curve with 300 consecutive procedures. Gastrointest Endosc. 2005;61:700–8.
39. Wasan SM, Kapadia AS, Adler DG. EUS training and practice patterns among gastroenterologists completing training since 1993. Gastrointest Endosc. 2005;62:914–20.
40. Barthet M. Endoscopic ultrasound teaching and learning. Minerva Med. 2007;98:247–51.
41. Neumann M, Mayer G, Ell C, et al. The Erlangen Endo-Trainer: life-like simulation for diagnostic and interventional endoscopic retrograde cholangiography. Endoscopy. 2000;32:906–10.
42. Hochberger J, Maiss J, Magdeburg B, et al. Training simulators and education in gastrointestinal endoscopy: current status and perspectives in 2001. Endoscopy. 2001;33:541–9.
43. Hochberger J, Neumann M, Hohenberger W, Hahn EG. Neuer Endoskopie-Trainer für die therapeutische flexible Endoskopie. Z Gastroenterol. 1997;35:722–3.
44. Wang MH, Dy F, Vu VK, et al. Structured endoscopic ultrasonography (EUS) training program improved knowledge and skills of trainees: results from the Asian EUS Group. Dig Endosc. 2015;27:687–91.
45. Dhir V, Itoi T, Fockens P, et al. Novel ex vivo model for hands-on teaching of and training in EUS-guided biliary drainage: creation of "Mumbai EUS" stereolithography/3D printing bile duct prototype (with videos). Gastrointest Endosc. 2015;81:440–6.
46. Bar-Meir S. A new endoscopic simulator. Endoscopy. 2000;32:898–900.
47. Desilets DJ, Banerjee S, Barth BA, et al. Endoscopic simulators. Gastrointest Endosc. 2011;73:861–7.

Chapter 9
Endoscopic Ultrasound-Guided Fine Needle Aspiration and Biopsy

Charilaos Papafragkakis, Sayam Thaiudom, and Manoop S. Bhutani

Abstract Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and biopsy (FNB) has been widely accepted as a fundamental procedure for the diagnosis and staging of lesions of the gastrointestinal tract or non-gastrointestinal lesions within reach of the aspiration needle. EUS-FNA has been used in lesions of the esophagus, mediastinal lesions, lymph node (LN) sampling, lung cancer diagnosis and other less common conditions (such as tuberculosis and sarcoidosis), gastrointestinal subepithelial lesions, pancreatic solid cystic lesions and neuroendocrine tumors, liver and bile duct lesions (such as cholangiocarcinoma and hepatocellular carcinoma), rectal and pelvic lesion, and lesions of extra-gastrointestinal organs (such as the adrenals and the prostate). Continued improvements in the technology and the technical aspects of EUS-guided FNA and FNB aim to improve the diagnostic accuracy and sensitivity and at the same time reduce the adverse events associated with the procedure. This chapter focuses on common technical aspects of EUS-FNA and FNB, such as the choice of needle and use of the stylet and suction, and performs a short review of the current applications of EUS-guided FNA in gastrointestinal and extra-intestinal lesions, along with a brief review of the adverse events that have been associated with the procedure.

Keywords Endoscopic ultrasound • Fine needle aspiration • Biopsy

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9.1 Technical Aspects of Endoscopic Ultrasound-Guided Aspiration and Biopsy

9.1.1 The Choice of Needle

The imaging plane of linear echoendoscopes allows acquisition of tissue by various needles and devices (Fig. 9.1). Multiple needles have been marketed for use in endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) and biopsy (FNB), with different gauges, needle composition, penetration features, ability to reshape after bending (metal memory properties), reverse bevel technology for histology, and variable durability (Fig. 9.2). The appropriate needle in EUS-FNA/FNB has been evaluated in multiple studies. The currently available needles are listed in Table 9.1.

The choice of needle is largely dependent on the location and type of lesion. Two meta-analyses of pancreatic EUS-FNA using 22 and 25 gauge needles demonstrated increased sensitivity of the 25 gauge needle in the diagnosis of pancreatic malignancy (93% vs. 85%, respectively, $p = 0.003$) [1, 2]. Besides pancreatic lesions, solid data comparing different needle types are lacking. In subepithelial lesions both the 22 and 25 gauge needles have shown similar diagnostic yield [3]. The use of a 19 gauge needle for pancreatic lesions is falling out of favor, mainly when a transduodenal approach is preferred. A recent study compared the 22 gauge core needle with the 25 gauge aspiration needle for the diagnosis of solid pancreatic lesions. The proportion of adequate sampling was nearly 82% for the 25 gauge and 74% for the FNB needle. The diagnostic yield was slightly higher for the FNB needle (77% vs. 75%). The FNB needle had 68% sensitivity compared to 60% of the FNA needle, achieved, however, with fewer passes (1.7 vs. 3.5). The authors concluded that there are nonsignificant differences in FNA versus FNB for diagnosing solid pancreatic lesions [4]. A new 25 gauge FNB needle was studied in solid pancreatic, liver, bile

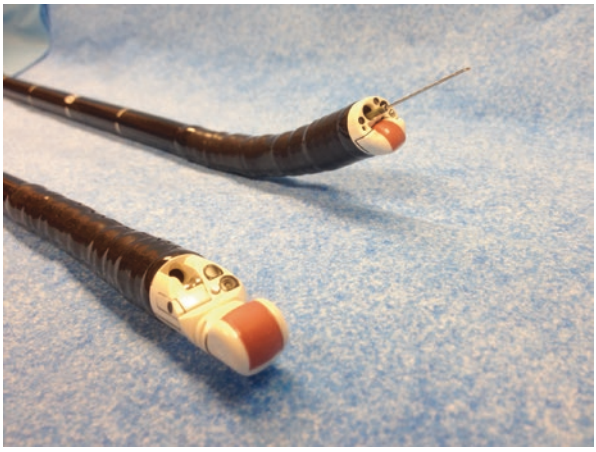

Fig. 9.1 Forward viewing curved linear array (TGF-UC 180 J) and curved linear array (GF-UC 140P-AL5), Olympus

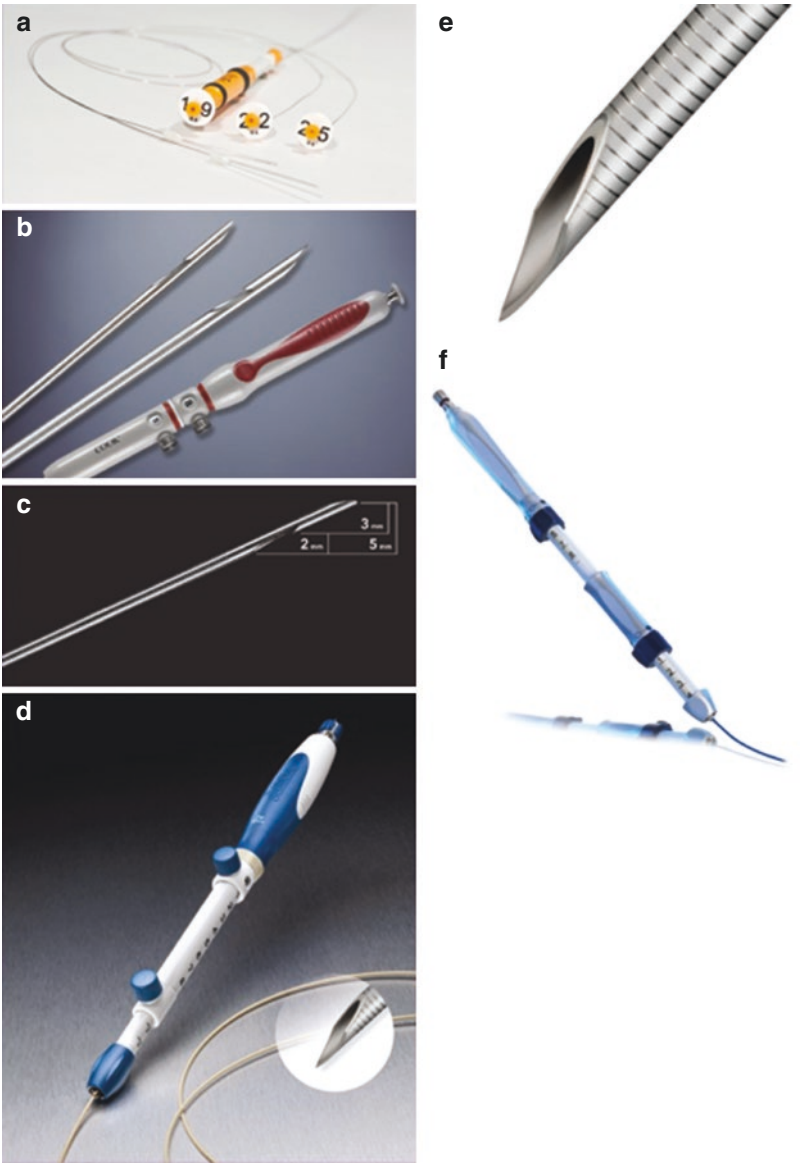

Fig. 9.2 Types of needles used for EUS-FNA and FNB. Used with permission from Weston BR, Bhutani MS. (2013) Gastroenterol Hepatol 9:352–363. (**a**) The BNX system with 19 gauge (G), 22G, and 25G needles allows multiple needle exchanges through the outer sheath. (Image courtesy of Beacon Endoscopic and used with permission.) (**b**) The EchoTip ProCore needle has a reverse bevel design for acquiring a tissue specimen. The 22G and 25G needles are shown. (**c**) A close-up view of the tip of the ProCore 25G needle. (Image courtesy of Cook Medical and used with permission.) (**d**) The nitinol-based Expect Flex 19G fine aspiration needle is more flexible than its stainless steel predecessors and appears more promising for use in the duodenum. (**e**) An extreme close-up view of the Expect 19G needle. (Image courtesy of Boston Scientific and used with permission.) (**f**) The ClearView endoscopic ultrasound-guided fine aspiration needle. The distal 2 cm of the needle are laser-etched to enhance visibility. (Image courtesy of ConMed Endoscopic Technologies and used with permission)

Table 9.1 Types of needles for fine needle aspiration and biopsy

Manufacturer	Type	Gauge
Beacon Endoscopic	Shark Core FNB	19,22,25
Beacon Endoscopic	BNX FNA	19,22,25
Boston Scientific	Expect	19,22,25
Boston Scientific	Expect Flex 19	19
Boston Scientific	Expect Slimline (SL)	19,22,25
Boston Scientific	Expect SL Flex	19
ConMed Corporation	ClearView	19,22,25
Cook Medical	EchoTip	22
Cook Medical	EchoTip Ultra	19,22,25
Cook Medical	EchoTip ProCore	19,22,25
Cook Medical	Quick-Core	19
Olympus	EZ Shot	22
Olympus	EZ Shot 2	19,22,25
Olympus	EZ Shot 2 with side port	22

duct, subepithelial, and other lesions. It provided samples for histological examination in only 40% of the cases, when the specimens were examined by two or three pathologists. The pooled sensitivity of that needle for neoplasia was 65% and specificity was 98%, with diagnostic accuracy of about 71% [5]. The number of passes needed for adequate tissue acquisition and diagnosis was assessed in a recent study of 117 pancreatic neoplasms. It was found that lesions smaller than 1.5 cm, located in the head of the pancreas, and pancreatic neuroendocrine tumors required two or more passes for adequate tissue sampling. It was concluded that the overall optimal number of passes in pancreatic lesions, without on-site cytopathologist, was between one and three [6]. A recent study found that needles are changed in 5% of the cases during a session of EUS-FNA of pancreatic, nodal, or other lesions, to improve sample cellularity or decrease bloodiness of the sample [7]. Overall the use of a 25 gauge needle is probably more appropriate for pancreatic masses and has been associated with higher diagnostic yield. For non-pancreatic lesions the use of high-definition FNB (19–22–25 gauge) should be considered in cases of inadequate samples obtained by an FNA needle and for lesions that need immunohistochemistry [8].

9.1.2 The Role of the Stylet

The role of the stylet has been studied extensively. Most of the studies have demonstrated that its use is not associated with inferior diagnostic yield compared to the non-stylet approach. However, stylet use has been occasionally shown to yield bloodier samples (75% vs. 52%, $p < 0.0001$) compared with FNA without stylet. It is therefore suggested that stylet use can be omitted without concern of compromising sample quality [9–14]. The use of air flush in tissue extraction from the FNA needle has been associated with cleaner, less bloodier specimen, compared to

pushing the stylet. Therefore, stylet use for this purpose should probably be used when there is difficulty in extracting the specimen from the needle. Caution must be applied when handling the stylet to avoid risk for stick injuries [15]. In our institution we do generally use stylet prior to tissue sampling and tissue extraction from the needle, as the stylet comes preloaded in all available needle devices.

9.1.3 The Role of Suction

The purpose of suction is to facilitate tissue acquisition through application of negative pressure during FNA. There are three techniques for suction during EUS-guided FNA: the use of dry and wet suction, a combination of those, or use of no suction at all [16]. In our institution we choose the type of suction based on immediate feedback from our in-room cytotechnician, depending on the quality of the aspirated material. Commonly, dry suction with 10 mL syringes is used. With wet suction, the needle is flushed with saline, and suction is applied in a syringe filled with 3 mL of saline [17]. Recent comparison of dry and wet techniques demonstrated superiority of wet technique in specimen cellularity and diagnostic yield [18]. However, frequently the application of more suction leads to more bloody aspirates. This effect may be more profound in FNA of LNs. From multiple studies it has been shown that it is associated with increased frequency of bloody aspirates, and therefore it should probably be avoided in LN sampling. However, in pancreatic lesions it may be more useful, as it has been shown to increase the cellularity, accuracy, and sensitivity of the FNA, although this observation has not been consistent among different studies [9, 15, 19, 20].

9.1.4 On-Site Cytopathology Evaluation

In EUS-FNA the goal is to obtain adequate tissue for cytopathological evaluation and diagnosis. From a number of retrospective studies, it has been suggested that rapid on-site cytopathology evaluation (ROSE) may be important for diagnosis. In a meta-analysis, the presence of on-site cytopathologist was associated with lower heterogeneity and improved, albeit not significant, sensitivity (88% vs. 80%) [21]. Another meta-analysis showed increased accuracy with on-site cytopathologist; however, it did not show statistically significant difference in the rate of inadequate sampling whether the cytopathologist was present or not, with a tendency toward inadequate sampling when a cytopathologist was not present [22]. Another meta-analysis found improved diagnostic accuracy in FNA of pancreatic lesions with ROSE, without impact on diagnostic yield [23]. A recent multicenter, prospective study focusing on the diagnostic yield of pancreatic specimens with and without ROSE demonstrated no difference in diagnostic yield of malignancy or adequacy of specimens between the two groups. However, less passes were required with

ROSE [24]. It is suggested that the use of ROSE does not have a major impact on the diagnostic yield of cancer and the number of inadequate specimens. It may be beneficial in centers with adequacy rate less than 90% [8].

9.2 Applications of Endoscopic Ultrasound-Guided Fine Needle Aspiration and Biopsy

9.2.1 Esophageal Cancer

EUS-FNA for staging of esophageal cancer should depend on clinical assessment and prospective of disease management. A retrospective study showed that FNA was associated with increased sensitivity of 93% compared to echo features alone [25]. In cases of esophageal strictures, EUS-FNA may be challenging or impossible due to inability to pass the echoendoscope beyond the stricture or manipulate it through the stenotic segment. Additionally, we do not perform FNA through the tumor due to contamination of the specimen. In such cases and when the LNs have malignant-appearing echo features (size more than 1 cm, round shape, well-demarcated borders, and hypoechogenicity), it is probably advisable to defer sampling, but sometimes this depends on specific institutional oncology policies [26, 27]. Lesions that invade the muscularis propria, the adventitia, or deeper are associated with poor outcomes, and therefore biopsy of associated LNs may not alter the prognosis. If decision is made to sample a LN, lesions that demonstrate avid FDG-PET uptake should be biopsied with priority [28].

9.2.2 Subepithelial Lesions

EUS-FNA is used in the diagnosis of subepithelial lesions of the gastrointestinal tract (Fig. 9.3). Multiple studies have evaluated the use of EUS-FNA and FNB in subepithelial masses with a sensitivity ranging from 46 to 93%. The diagnostic yield of FNB has been shown to be superior to FNA in these lesions. Two recent studies demonstrated the diagnostic yield of FNB to be 67 and 75% compared to 33 and 20% for FNA [29, 30]. Conventional cytology can differentiate between malignant and benign lesions; however in order to determine the type of benign lesion, additional assessment with immunohistochemistry may be necessary. The most common markers used in these cases are CD-117, CD-34, smooth muscle actin, and S-100 [31]. FNB with a 19 gauge needle has been shown to yield good results for subepithelial lesions, because it can provide histological examination and preservation of tissue architecture [32]. Gastrointestinal stromal tumors may have endosonographically malignant-appearing features (size over 3 cm, irregular extraluminal borders, cystic components, heterogeneous EUS appearance, and presence of malignant-appearing regional LNs). However, given that, independent of size, they

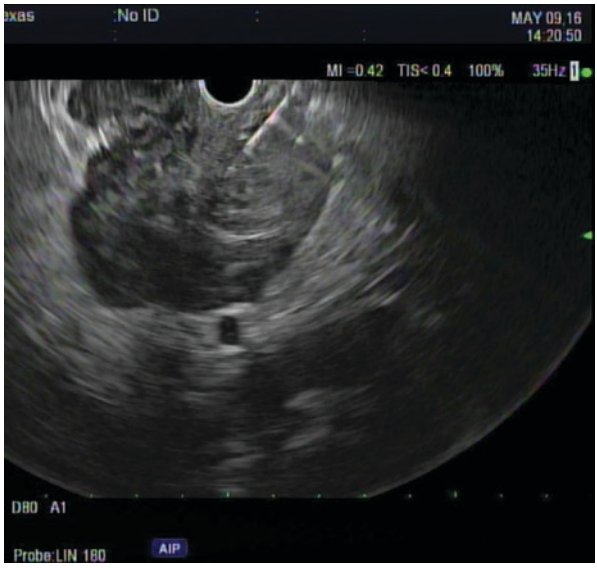

Fig. 9.3 FNB of gastrointestinal stromal tumor

may metastasize, FNB or FNA is useful in determining malignant potential. For gastric lymphomas FNA or FNB may be necessary for diagnosis, because frequently the lesion is subepithelial and cannot be diagnosed with endoscopic biopsies. EUS-guided FNA or FNB is used in these cases to obtain tissue for flow cytometry or assess regional LNs [33]. EUS-guided FNA has also been shown to be useful in the diagnosis of glomus tumors with cytological and immunohistochemical analysis and also granular cell tumors [34, 35].

9.2.3 Mediastinal Lymphadenopathy, Lung Cancer, and Pleural Fluid

EUS-FNA is considered a valuable method in the diagnosis of mediastinal adenopathy or metastatic disease (Fig. 9.4). In the setting of lung cancer, LNs are frequently metastatic, and EUS-FNA is useful in the diagnosis and staging of the disease. Isolated posterior mediastinal lesions are either lung cancer metastases, lymphoma, infectious, or cystic [36]. FNB is infrequently used in the mediastinum but may be useful in cases of lymphoma [37]. In cases of sarcoidosis, EUS-FNA has high accuracy in establishing the diagnosis by providing granulomatous tissue with sensitivity and specificity approaching 90% and 96%, respectively. Similarly, in cases of enlarged, irregular, calcified LNs or node clusters, fungal infections may be diagnosed after aspiration of granulomas in the appropriate clinical setting [38, 39]. Addition of polymerase chain reaction in FNA samples may assist in the diagnosis of tuberculosis [40]. Mediastinal cysts may be aspirated with EUS-FNA; however this approach has been associated with post-FNA cyst infection or mediastinitis, a

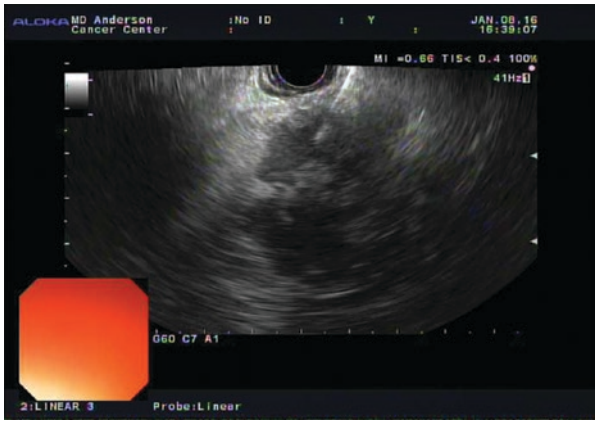

Fig. 9.4 FNA of metastatic periaortic melanoma

potentially fatal complication. When antibiotics are given at the time of FNA of a cyst, the risk of infection diminishes [41]. Aspiration of posterior mediastinal cysts is generally not recommended, but in cases when this is performed, complete aspiration of the fluid needs to be sought. Antibiotics at the time of the FNA, and for up to 5 days afterward, should be administered. EUS-FNA is frequently performed for the assessment of suspected mediastinal metastases of lung cancer, usually manifesting with subcarinal LNs or involvement of the posterior aortopulmonary window. Mediastinal metastases from other organs may also be diagnosed with EUS-FNA [42, 43]. Mediastinal lymphoma can also be diagnosed with EUS-FNA or FNB with sensitivity close to 90% when additional flow cytometry and immunohistochemistry are implemented [44]. Lung cancer diagnosis may also be facilitated with the use of EUS-FNA. Especially for lung lesions that exist in close proximity to the esophagus, EUS-FNA may be particularly useful. These lesions often present as hypoechoic, irregularly shaped masses, easily distinguishable from mediastinal LNs. In case of large lesions, attempt should be made to sample the periphery, where more viable tissue exists, and avoid sampling necrotic areas [36]. Potential complications of EUS-FNA of lung lesions are pneumothorax, hemoptysis, and infection [45]. In a small number of patients with non-small cell lung cancer, pleural effusions have been sampled by EUS-FNA using a 19 or 22 gauge needle. The procedure is technically feasible and safe and can help guide further management depending on positive or negative cytology results [46].

9.2.4 Pancreatic Lesions

9.2.4.1 Solid Pancreatic Lesions

EUS-FNA has evolved as a first-line procedure for the diagnosis of solid, benign, or malignant pancreatic lesions (Fig. 9.5). The procedure should be performed whenever the results are likely to affect further management, for example, for

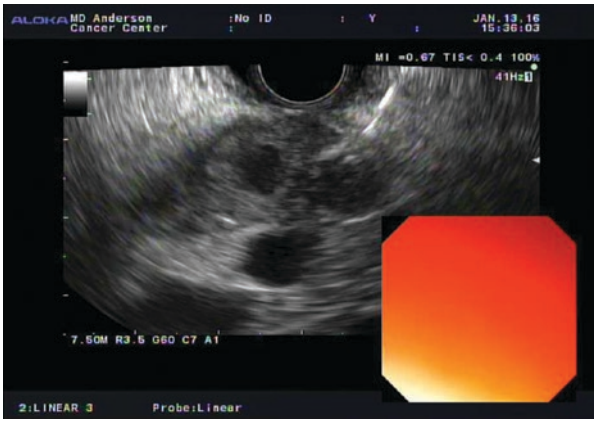

Fig. 9.5 FNA of pancreatic nodule in a patient with Whipple surgery (nodule seen adjacent to jejunal loop)

borderline resectable cases, unsuspected metastasis, or in cases such as pseudotumors to avoid unnecessary surgery. These lesions are usually hypoechoic compared to the pancreatic parenchyma [47, 48]. As demonstrated in a meta-analysis of almost 5000 patients, the pooled sensitivity, specificity, positive predictive value, and negative predictive value of this procedure was 85–91%, 94–98%, 98–99%, and 65–72%, respectively [21]. False-negative results occur up to 20–40% of the cases, and therefore repeated FNA is recommended in cases of strong clinical suspicion [49, 50]. EUS-FNA of solid pancreatic lesions is associated with a 1–2% risk of pancreatitis and very low risk of tumor seeding, only reported scarcely, mainly in cases of distal pancreatic body and tail lesions [51, 52]. Pancreatic lesions in the head and uncinate process are best approached from the duodenum whereas masses in the rest of the pancreas from the stomach [47]. Well-differentiated tumors, small in size or in the setting of chronic pancreatitis, may require more passes for adequate sampling or may render the malignancy not clearly visible by EUS. In cases of chronic pancreatitis, EUS-FNA has been shown to have low sensitivity, 54–74% in different studies. More passes may be needed in these cases to improve the diagnostic accuracy [47, 53, 54]. "Fanning" of the needle inside the lesion, targeting the periphery to avoid necrotic areas, and rapid back and forth movements may yield better cytology [47].

9.2.4.2 Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (PNET) can be diagnosed accurately with EUS-FNA. In one study EUS-FNA findings correlated in 83% with the surgical specimens [55]. Another study showed accuracy of EUS-FNA for PNET nearly 90% compared to surgery [56]. In a recent study, EUS-FNA demonstrated concordance rate with surgery of 87.5% and additionally was found to be effective for diagnosis and Ki-67 index grading for WHO 2010 classification, an important parameter for decision-making on unresectable PNET [57].

9.2.4.3 Pancreatic Cystic Lesions and Intraductal Papillary Mucinous Neoplasms (IPMN)

EUS-FNA plays a pivotal role in the diagnosis of pancreatic pseudocysts, cystic neoplasms, and IPMN [58]. In a recent study of 154 patients with pancreatic cysts who underwent EUS-FNA, 81% had adequate cellularity, and the FNA was diagnostic in 55% of the patients. In the same study, EUS, with or without FNA cytology, amylase, and carcinoembryonic antigen, showed higher sensitivity of 76% compared to CT or MRI (48% for CT and 34% for MRI) in differentiating neoplastic from nonneoplastic cysts [59]. Cysts that have concerning features on imaging, with size over 3 cm, dilated pancreatic duct, or solid components, should be considered for EUS with or without FNA [60]. EUS-guided aspiration of the cystic fluid is associated with rare incidence of bleeding, infection, or perforation of <2% [61]. Based on echo features alone, EUS cannot accurately distinguish mucinous from non-mucinous cystic lesions (sensitivity 63% and specificity 88%) [62]. EUS-FNA should be therefore utilized to differentiate these lesions, with the caveat that negative cytology has poor negative predictive value [63]. EUS-FNA has been shown to be superior to EUS alone for diagnosing malignant IPMN. Non-mucinous epithelium, severe atypia, single atypical cells, and irregular clusters are features that determine high probability for malignancy [64]. Histopathological analysis provides sensitivity of over 90% for IPMN with solid components [65]. Pseudocysts appear anechoic, frequently with hyperechoic rim, with high amylase and low CEA levels in the aspirate. EUS-FNA has been shown to accurately differentiate between pseudocysts and cystic neoplasms in about 90% of the cases [66]. Confocal laser endomicroscopy with a probe inserted through a 19 gauge needle has been used to diagnose pancreatic cystic neoplasms with 59% sensitivity and 100% specificity in one study [67]. Serous cystic neoplasms are vascular, and therefore FNA of these lesions may result in bloody aspirate and reduce cytology yield [68]. Solid pseudopapillary tumors usually demonstrate solid and cystic components, with low CEA levels. EUS-FNA of these lesions has been shown to be diagnostic in 65% of the cases, based on cytology and immunohistochemistry [69].

9.2.4.4 Autoimmune Pancreatitis (AIP)

EUS can enhance the diagnostic capabilities for AIP, a distinct type of pancreatic disease. According to the international consensus of diagnostic criteria for AIP (ICDC), only tissues obtained by EUS-FNB (Trucut) or resection are appropriate for histopathological diagnosis of AI [70]. Others have proposed that 22 gauge FNA needle is useful in the differentiation of AIP type 1 from type 2, particularly in seronegative cases. Histological diagnosis can be achieved in 80% of the case according to the ICDC. Rapid motion of the needle and proper handling of the tissue are emphasized to optimize the diagnostic yield [71, 72].

9.2.5 *Liver Lesions, Hepatocellular Carcinoma, and Cholangiocarcinoma*

For newly diagnosed liver lesions, EUS-FNA has been shown to have diagnostic accuracy of 98% in detecting hepatic metastases [73] (Fig. 9.6). For liver malignancies, EUS-FNA has a sensitivity of 94%, specificity of 100%, negative predictive value of 78%, and positive predictive value of 100% [74]. For the diagnosis of hepatocellular carcinoma (HCC), the EUS-FNA has been shown to have diagnostic accuracy of up to 94% [75]. Liver biopsy with a 19 gauge FNA needle was evaluated in a recent prospective study. With a mean of two passes, FNA yielded a histological diagnosis in 91% of the cases [76]. EUS-FNA has been studied in the management of hepatic cysts and abscesses. Hepatic cysts and abscesses can be drained with EUS-FNA with excellent results [77, 78]. When there is clinical suspicion for echinococcal cysts, FNA should probably be avoided due to risk of cyst rupture and anaphylactic shock [79]. The EUS plays an important role in the diagnosis of cholangiocarcinoma (CC), particularly in the setting of other nondiagnostic, noninvasive tests (MRI/MRCP/CT) [80]. A meta-analysis of EUS-FNA for the diagnosis of CC demonstrated pooled sensitivity and specificity of 66% and 100%, respectively. For those studies that had negative brush cytology, the sensitivity and specificity of EUS-FNA was 59% and 100%, respectively [81]. A retrospective study in patients with perihilar and distal CC demonstrated the superiority of EUS in diagnosing CC, compared to MRI or multiphase CT (tumor detected in 94% of the cases with EUS vs. 42% and 30% with MRI and CT, respectively). EUS sensitivity was shown to be significantly higher in distal than proximal CC (81%

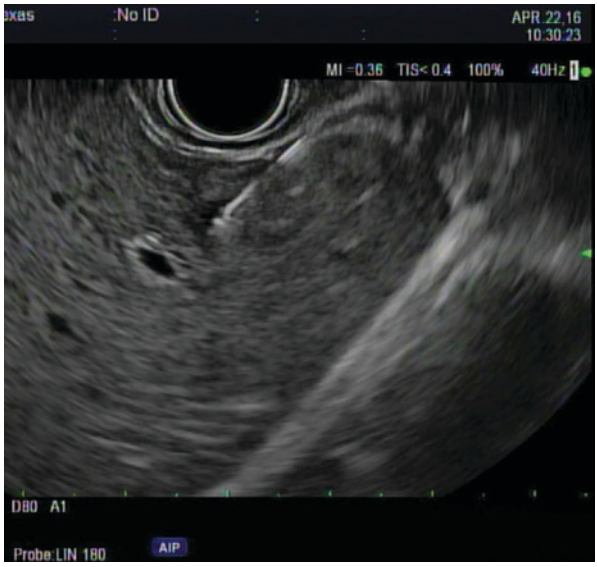

Fig. 9.6 FNA of metastatic pancreatic cancer in the left lobe of the liver

and 59%, respectively) [82]. Another study of EUS-FNA and FNB in patients with suspected perihilar malignant strictures demonstrated EUS sensitivity 79% and accuracy 82% [83]. It is suggested that EUS should not be used without FNA for the diagnosis of malignant LNs, since it has been shown that LNs in CC do not follow the typical imaging prognostic features of malignancy and non-FNA EUS is associated with low sensitivity for nodal metastases. EUS-FNA may detect malignant LNs despite negative CT or MRI and alter surgical management and potential for liver transplantation (LT) [82, 84]. The Mayo Clinic group has suggested that EUS or percutaneous FNA of perihilar CC is associated with significant risk of tumor seeding (83% vs. 8% in patients without FNA) and therefore should be avoided in cases of potentially curative resection or LT. The risk of seeding seems to be higher in transperitoneal FNA than after percutaneous transhepatic cholangiography (PTC) or FNA of HCC. The reason for this may be related to the distance of perihilar tumors from the abdominal wall, which allows more space for seeding during biopsy. Most patients in this study, however, underwent FNA using percutaneous approach rather than EUS-guided approach [85]. Therefore for suspected hilar cholangiocarcinoma, which is potentially resectable or curable with liver transplantation, a discussion with the surgical team is needed before attempting EUS-FNA of the hilar lesion to weigh in the risks and benefits. A recent prospective study compared EUS-FNA and ERCP with biopsy and demonstrated that both modalities have similar sensitivity and accuracy in evaluating proximal or distal malignant strictures (79% and 80%) and sensitivity of 80% and 67%, respectively, for proximal and distal indeterminate strictures [86].

9.2.6 Other Applications

9.2.6.1 Portal Vein Thrombosis, Peritoneal Metastases, Gallbladder, Ascitic Fluid Drainage, and Ampullary Lesions

EUS-FNA has also been utilized in the assessment of intra-abdominal and peritoneal metastatic disease (Fig. 9.7) and malignant portal vein thrombus [87]. Peritoneal metastatic lesions that appear hyperechoic compared to the ascitic fluid can be assessed with EUS-FNA [88, 89]. EUS-FNA, usually performed after administration of prophylactic antibiotics, has been also shown to be safe for paracentesis of ascitic fluid, with specificity of 100%, sensitivity of 80%, and diagnostic accuracy of 100%, as shown in a recent retrospective study [90]. EUS-FNA has been used for the diagnosis and staging of gallbladder masses, with accuracy of 100% for in situ tumors, and may be useful in cases when CT cannot detect the lesion [91, 92]. Endoscopic drainage of the gallbladder in cases of cholecystitis has also been described and is technically feasible and successful [93]. EUS-FNA has been excellent for diagnosis of tumors of the ampulla of Vater. As shown in a recent retrospective study, the EUS-FNA accuracy of high- and low-grade dysplasia and adenocarcinoma was 50%, 93%, and 100%, respectively [94].

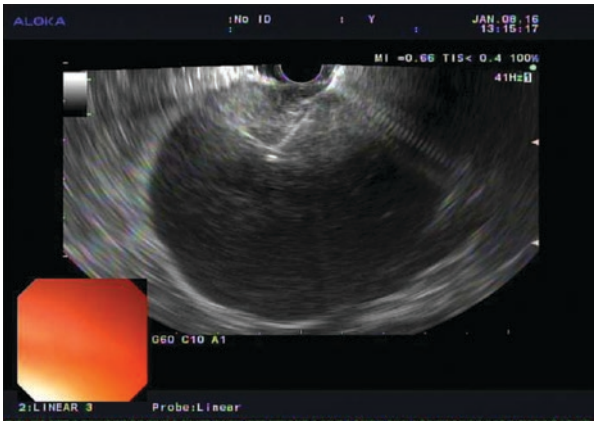

Fig. 9.7 FNA of peripancreatic germ cell tumor

9.2.6.2 Splenic Lesions

Splenic lesions mostly occur in infectious disease processes such as abscesses, leishmaniasis, tuberculosis, and malaria. EUS-FNA with a 22 gauge needle has been shown to be safe. In cases of FNA of vascular lesions, such as hemangiomas, the aspirate is bloody and diagnostic. Also, for splenic lymphomas a larger bore needle may be used; however this may be associated with higher rate of complications [95, 96]. However, a recent retrospective analysis showed that the procedure is safe and may assist in decision-making and avoidance of unnecessary splenectomy [97].

9.2.6.3 Adrenal Lesions

EUS-FNA is used to biopsy masses in the left adrenal gland. Approach of the left adrenal with FNA is technically feasible, because other organs are easily avoided [98]. The right adrenal gland, due to its deep position or adjacent to the inferior vena cava, makes FNA difficult. However, it can be seen occasionally with the echoendoscope positioned beyond the duodenal papilla. The left adrenal loses its typical appearance when it is infiltrated by a mass. A recent retrospective study using 19, 22, and 25 gauge needles demonstrated that the left adrenal FNA is safe and had sensitivity, specificity, positive predictive value, and negative predictive value of 86%, 97%, 96%, and 89%, respectively, for the diagnosis of malignancy [99].

9.2.6.4 Rectal and Perirectal Lesions

EUS is more specific than CT in the T and N regional staging of rectal carcinoma [100]. EUS-FNA for rectal and perirectal lesions has been evaluated in a limited number of studies. A recent retrospective study demonstrated sensitivity and specificity of

91% and 100%, respectively, in detecting benign or malignant lesions [101]. In another study, EUS-FNA was shown to be very useful in the diagnosis of primary metastatic colorectal lesions and improvement of staging of regional or distal nodal metastases. Using histology as a reference standard, the overall sensitivity, specificity, positive predictive value, and negative predictive value of EUS-FNA were 89% (74–100%), 79% (50–100%), 89% (74–100%), and 79% (51–100%), respectively [101].

9.2.6.5 Pelvic Lesions and Prostate

EUS-FNA of pelvic lesions is feasible when in reachable distance from the rectum. A retrospective study evaluated the use of EUS-FNA (with a 22 or 25 gauge needles) or Trucut biopsy (TCB) (with 19 gauge needle) in the diagnosis of pelvic masses. Compared with surgical pathology, EUS-FNA was 88% sensitive and 100% specific for malignancy. EUS-TCB had a sensitivity of 67% and specificity of 100% for malignancy, and the combination of both modalities had a sensitivity and specificity of 100%. Seven percent of the patients with FNA of cystic pelvic masses developed abscess, prompting the authors to recommend against biopsying cysts in that region [102]. Other authors have come to similar conclusions. In a recent retrospective study in benign and malignant pelvic lesions, the sensitivity and specificity of EUS-FNA with the use of a 22 gauge needle was 90% and 100%, respectively, positive predictive value was 100%, and negative predictive value was 90%. Contrary to other reports, there were no early or late complications in the sampling of cystic and noncystic lesions. Prophylactic antibiotics were given prior to sampling of cystic lesions [103]. Diagnosis of retroperitoneal endometriosis by EUS-FNA has been reported. The ectopic endometrial tissue appears hypoechoic and heterogeneous [104]. EUS-guided FNA has a utility in the diagnosis of local tumor recurrence and staging of pelvic urological malignancy. The examination should be performed with the patient in the left lateral decubitus position by an experienced endosonographer, with knowledge of the pelvic anatomy. The rectum should be cleaned prior to the procedure [105]. A retrospective study with the use of 22 gauge FNA and Trucut needles demonstrated EUS-guided biopsy sensitivity and specificity of almost 95% and 100%, respectively, and positive and negative predictive values of 100% and 50% (1–98), respectively. EUS-FNA of LNs, luminal wall, and perirectal space may increase the initial staging accuracy for urological cancers and may enhance detection of local tumor recurrence. Hematuria may develop as a complication of bladder EUS-guided FNA [106].

9.3 EUS-Guided FNA-Associated Morbidity and Mortality

A recent systematic review of EUS-FNA in almost 11,000 patients demonstrated EUS-FNA-specific morbidity of 0.98%. Pancreatitis was documented in 0.44% and post-procedural pain in 0.34% of the cases. The overall mortality rate was 0.02%.

For pancreatic mass, analysis of the prospective studies showed a morbidity rate of 2.44% compared to 0.35% in the retrospective studies. For pancreatic cysts, the morbidity rate was 2.33% in the prospective studies versus 5% in the retrospective ones. The most common documented complication was chest or abdominal pain (34.6% of the complications) and acute pancreatitis (33.6%). Most of the patients who developed post-FNA pancreatitis had mild presentation and only 0.04% severe. The overall bleeding rate was 0.1%, fever 0.08%, and infection 0.02%. For FNAs of mediastinal lesions, complications occurred in only 0.38% of the cases. For FNAs of hepatic lesions, 2.33% developed complications, and there was one mortality due to cholangitis. For perirectal lesions, the complication rate was 2.07% (abscess, limited bleeding, abdominal pain, transient fever). EUS-FNA of ascitic fluid was associated with 3.5% complication rate, mainly transient fever and bacterial peritonitis [107]. Bacteremia after EUS-FNA is rare. In a prospective study of 100 patients who underwent FNA of rectal or perirectal lesions, only two developed bacteremia. The authors concluded that prophylactic antibiotics are not warranted [108]. Another prospective study reached similar conclusions in EUS-FNA of upper GI tract lesions, with only 2 out of 50 patients developing bacteremia, albeit clinically insignificant [109]. The current ASGE guidelines advise against using prophylactic antibiotics for EUS-FNA of solid lesions. For pancreatic cystic lesions, it has been shown that the risk of infection is low; however, it seems to be a common practice to give prophylactic antibiotics prior to or during EUS-FNA and for 3–5 days after EUS-FNA [110, 111]. Complete aspiration of the punctured locule must be pursued to alleviate the risk of infection. Aspiration of mediastinal cysts is generally not recommended [51]. Generally, mediastinal cystic lesions should not be aspirated, unless the expected benefit clearly outweighs the risk, and always in consultation with the thoracic surgery colleagues.

References

1. Madhoun MF, Wani SB, Rastogi A, et al. The diagnostic accuracy of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided FNA of solid pancreatic lesions: a meta-analysis. Endoscopy. 2013;45:86–92.
2. Affolter KE, Schmidt RL, Matynia AP, et al. Needle size has only a limited effect on outcomes in EUS-guided fine needle aspiration: a systematic review and meta-analysis. Dig Dis Sci. 2013;58:1026–34.
3. Imazu H, Uchiyama Y, Kakutani H, et al. A prospective comparison of EUS-guided FNA using 25-gauge and 22-gauge needles. Gastroenterol Res Pract. 2009;2009:6. https://doi.org/10.1155/2009/546390.
4. Berzoza M, Villa N, El-Serag H, et al. Comparison of endoscopic ultrasound guided 22-gauge core needle with standard 25-gauage fine-needle aspiration for diagnosing solid pancreatic lesions. Endosc Ultrasound. 2015;4:28–33.
5. Attilli F, Petrone G, Abdulkader I, et al. Accuracy and inter-observer agreement of the Procore 25-gauge needle for endoscopic ultrasound-guided tissue core biopsy. Dig Liver Dis. 2015;47:943–9.
6. Uehara H, Sueyoshi H, Takada R, et al. Optimal number of needle passes in endoscopic ultrasound-guided fine needle aspiration for pancreatic lesions. Pancreatology. 2015;15:392–6.

7. Bang JY, Hebert-Magee S, Varadarajulu S. Objective assessment of reasons for needle change during endoscopic ultrasound-guided fine-needle aspiration. Dig Endosc. 2015;27(6):714. https://doi.org/10.1111/den.12500.
8. Wani S, Muthusamy R, Komanduri S. EUS-guided tissue acquisition: an evidence-based approach (with videos). Gastrointest Endosc. 2014;80:939–59.
9. Wani S. Basic techniques in endoscopic ultrasound-guided fine-needle aspiration: role of a stylet and suction. Endosc Ultrasound. 2014;3:17–21.
10. Wani S, Early D, Kunkel J, et al. Diagnostic yield of malignancy during EUS-guided FNA of solid lesions with and without a stylet: a prospective, single blind, randomized, controlled trial. Gastrointest Endosc. 2012;76:328–35.
11. Sahai AV, Paquin SC, Gariepy G. A prospective comparison of endoscopic ultrasound-guided fine needle aspiration results obtained in the same lesion, with and without the needle stylet. Endoscopy. 2010;42:900–3.
12. Wani S, Gupta N, Gaddam S, et al. A comparative study of endoscopic ultrasound guided fine needle aspiration with and without a stylet. Dig Dis Sci. 2011;56:2409–14.
13. Gimeno-Garcia AZ, Paquin SC, Gariepy G, et al. Comparison of endoscopic ultrasonography-guided fine-needle aspiration cytology results with and without the stylet in 3364 cases. Dig Endosc. 2013;25:303–7.
14. Rastogi A, Wani S, Gupta N, et al. A prospective, single-blind, randomized, controlled trial of EUS-guided FNA with and without a stylet. Gastrointest Endosc. 2011;74:58–64.
15. Lee JK, Choi JH, Lee KH, et al. A prospective, comparative trial to optimize sampling techniques in EUS-guided FNA of solid pancreatic masses. Gastrointest Endosc. 2013;77:745–51.
16. Bhutani MS. Endoscopic ultrasound comes of age: mature, established and here to stay! Endosc Ultrasound. 2014;3:143–51.
17. Villa NA, Berzosa M, Wallace MB, et al. Endoscopic ultrasound-guided fine needle aspiration: the wet suction technique. Endosc Ultrasound. 2016;5:17–20.
18. Attam R, Arain MA, Bloechl SJ, et al. "Wet suction technique (WEST)": a novel way to enhance the quality of EUS-FNA aspirate. Results of a prospective, single-blind, randomized, controlled trial using a 22-gauge needle for EUS-FNA of solid lesions. Gastrointest Endosc. 2015;81:1401–7.
19. Bhutani MS, Suryaprassad S, Moezzi J, et al. Improved technique for performing endoscopic ultrasound guided fine needle aspiration of lymph nodes. Endoscopy. 1999;31:550–3.
20. Puri R, Vilmann P, Saftoiou A, et al. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. Scand J Gastroenterol. 2009;44:499–504.
21. Hewitt MJ, McPhail MJ, Possamai L, et al. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75:319–31.
22. Hebert-Magee S, Bae S, Varadarajulu S, et al. The presence of a cytopathologist increases the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration cytology for pancreatic adenocarcinoma: a meta-analysis. Cytopathology. 2013;24:159–71.
23. Schmidt RL, Witt BL, Matynia AP, et al. Rapid on-site evaluation increases endoscopic ultrasound-guided fine-needle aspiration adequacy for pancreatic lesions. Dig Dis Sci. 2013;58:872–82.
24. Wani S, Mullady D, Early D, et al. The clinical impact of immediate on site cytopathology evaluation during endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of pancreatic mass: final results of a multicenter, prospective, randomized controlled trial. Gastrointest Endosc. 2014;79:AB192–3.
25. Vazquez-Sequeiros E, Norton ID, Clain J, et al. Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. Gastrointest Endosc. 2001;53:751–7.
26. Vazquez-Sequeiros E. Nodal staging: number or site of nodes? How to improve accuracy? Is FNA always necessary? Junctional tumors-what's N and what's M? Endoscopy. 2006;38(S1):s4–8.

27. Vazquez-Sequeiros E, Levy M, Clain JE, et al. Routine versus selective EUS-guided FNA approach for preoperative nodal staging of esophageal carcinoma. Gastrointest Endosc. 2006;63:204–11.
28. Santo E, Barkay O, Ross W, Bhutani MS. Advanced esophageal cancer. In: Bhutani MS, Deutsch JC, editors. EUS pathology with digital anatomy correlation. Textbook and atlas. Shelton: People's Medical Publishing House-USA; 2010. p. 25–32.
29. Kim GH, Cho YK, Kim EY, et al. Comparison of 22-gauge aspiration needle with 22-gauge biopsy needle in endoscopic ultrasonography-guided subepithelial tumor sampling. Scand J Gastroenterol. 2014;49:347–54.
30. Nagula SPK, Aslanian HR, Bucobo JC, et al. EUS-fine needle aspiration (FNA) vs. EUS-fine needle biopsy (FNB) for solid mass lesions: interim analysis of a large multicenter, randomized clinical trial. Gastrointest Endosc. 2013;77:AB357–8.
31. Weirsema MJ, Vilmann P, Gioavannini M, et al. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology. 1997;112:1087–95.
32. Hunt GC, Rader AE, Faigel DO. A comparison of EUS features between CD-117 positive GI stromal tumors and CD-117 negative GI spindle cell tumors. Gastrointest Endosc. 2003;57:469–74.
33. Hwang JH, Rulyak SJ. Subepithelial lesions of the upper GI tract. In: Bhutani MS, Deutsch JC, editors. EUS pathology with digital anatomy correlation. Textbook and atlas. Shelton: People's Medical Publishing House-USA; 2010. p. 79–94.
34. Debol SM, Stanley MW, MAllery S, et al. Glomus tumor of the stomach: cytologic diagnosis by endoscopic ultrasound-guided fine-needle aspiration. Diagn Cytopathol. 2003;28: 316–21.
35. Prematilleke IV, Piris J, Shah KA. Fine needle aspiration cytology of a granular cell tumor of the oesophagus. Cytopathology. 2004;15:120–1.
36. Savides TJ. EUS for mediastinal lymph nodes and masses. In: Bhutani MS, Deutsch JC, editors. EUS pathology with digital anatomy correlation. Textbook and atlas. Shelton: People's Medical Publishing House-USA; 2010. p. 117–28.
37. Levy MJ, Jondal ML, Clain J, et al. Preliminary experience with an EUS-guided Tru-Cut biopsy needle compared with EUS-guided FNA. Gastrointest Endosc. 2003;57:101–6.
38. Wildi SM, Judson MA, Fraig M, et al. Is endosonography guided fine needle aspiration (EUS-FNA) for sarcoidosis as good as we think? Thorax. 2004;59:794–9.
39. Savides TJ, Gress FG, Wheat LJ, et al. Dysphagia due to mediastinal granulomas: diagnosis with endoscopic ultrasonography. Gastroenterology. 2000;95:2278–84.
40. Kramer H, Nieuwenhuis JA, Groen HJ, et al. Pulmonary tuberculosis diagnosed by esophageal endoscopic ultrasound with fine-needle aspiration. Int J Tuberc Lung Dis. 2004;8:272–3.
41. Fazel A, Moezardalan K, Varadarajulu S, et al. The utility and safety of EUS-guided FNA in the evaluation of duplication cysts. Gastrointest Endosc. 2005;62:575–80.
42. Devereaux BM, LeBlanc JK, Yousif E, et al. Clinical utility of EUS-guided fine-needle aspiration of mediastinal masses in the absence of known pulmonary malignancy. Gastrointest Endosc. 2002;56:397–401.
43. Kramer H, Koeter GH, Sleijfer DT, et al. Endoscopic ultrasound-guided fine-needle aspiration in patients with mediastinal abnormalities and previous extrathoracic malignancy. Eur J Cancer. 2004;40:559–62.
44. Ribeiro A, Vazquez-Sequeiros E, Wiersema LM, et al. EUS-guided fine-needle aspiration combined with flow cytometry and immunohistochemistry in the diagnosis of lymphoma. Gastrointest Endosc. 2001;53:485–91.
45. Annema JT, Veselic M, Rabe KF. EUS-guided FNA of centrally located lung tumors following a non-diagnostic bronchoscopy. Lung Cancer. 2005;48:357–61.
46. Lococo P, Cesario A, Attili F, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration of pleural effusion for the staging of non-small cell lung cancer. Interact Cardiovasc Thorac Surg. 2013;17:237–41.

47. Weston BR, Bhutani MS. Optimizing diagnostic yield for EUS-guided sampling of solid pancreatic lesions: a technical review. Gastroenterol Hepatol. 2013;9:352–63.
48. Dumonceau JM, Polkowski M, Larghi A, et al. Indications, results, and clinical impact of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2011;43:897–912.
49. Dewitt J, McGreevy K, Sherman DS, et al. Utility of repeated EUS at a tertiary referral center. Gastrointest Endosc. 2008;67:610–9.
50. Eloubeidi MA, Varadarajulu S, Desai S, et al. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. J Gastroenterol Hepatol. 2008;23:567–70.
51. Adler DG, Jacobson BC, Davila RE, et al. ASGE guideline: complications of EUS. Gastrointest Endosc. 2005;61:8–12.
52. Katamuna A, Maguchi H, Hashigo S, et al. Tumor seeding after endoscopic ultrasound-guided fine needle aspiration of cancer in the body of the pancreas. Endoscopy. 2012;44:E160–1.
53. Fritscher-Ravens A, Brand L, Knofel WT, et al. Comparison of endoscopic ultrasound-guided fine needle aspiration for focal pancreatic lesions in patients with normal parenchyma and chronic pancreatitis. Am J Gastroenterol. 2002;97:2768–75.
54. Varadarajulu S, Tamhane A, Eloubeidi MA. Yield of EUS-guided FNA of pancreatic masses in the presence or the absence of chronic pancreatitis. Gastrointest Endosc. 2005;62: 728–36.
55. Larghi A, Capurso G, Carnuccio A, et al. Ki-67 grading of nonfunctioning pancreatic neuroendocrine tumors on histological samples obtained by EUS-guided fine-needle tissue acquisition: a prospective study. Gastrointest Endosc. 2012;76:570–7.
56. Unno J, Kanno A, Masamune A, et al. The usefulness of endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of pancreatic neuroendocrine tumors based on the World Health Organization classification. Scand J Gastroenterol. 2014;49:1367–74.
57. Sugimoto M, Takagi T, Hikichi T, et al. Efficacy of ultrasonography-guided fine needle aspiration for pancreatic neuroendocrine tumor grading. World J Gastroenterol. 2015;21:8118–24.
58. Brugge WR. Diagnosis and management of cystic lesions of the pancreas. J Gastrointest Oncol. 2015;6:3375–88.
59. Khashab MA, Kim K, Lennon AM, et al. Should we do EUS/FNA on patients with pancreatic cysts? The incremental diagnostic yield of EUS over CT/MRI for prediction of cystic neoplasms. Pancreas. 2013;42:717–21.
60. Levy MJ, Clain JE. Evaluation and management of cystic pancreatic tumors; emphasis on the role of EUS FNA. Clin Gastroenterol Hepatol. 2004;2:639–53.
61. Lee LS, Saltzman JR, Brounds BC, et al. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. Clin Gastroenterol Hepatol. 2005;3:231–6.
62. Thosani N, Thosani S, Qiao W, et al. Role of EUS-FNA-based cytology in the diagnosis of mucinous pancreatic cystic lesions: a systematic review and meta-analysis. Dig Dis Sci. 2010;55:2756–66.
63. Scheiman JM, Hwang JH, Moayyedi P. American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. Gastroenterology. 2015;148:824–848.e22.
64. Soweid AM, Skoury AM. Endoscopic ultrasonography in intraductal papillary mucinous tumors of the pancreas. In: Bhutani MS, Deutsch JC, editors. EUS pathology with digital anatomy correlation. Textbook and atlas. Shelton: People's Medical Publishing House-USA; 2010. p. 191–204.
65. Maire F, Couvelard A, Hammel P, et al. Intraductal papillary mucinous tumors of the pancreas: the preoperative value of cytological and histopathological diagnosis. Gastrointest Endosc. 2003;58:701–6.
66. Brugge WR. Approaches to the drainage of pancreatic pseudocysts. Curr Opin Gastroenterol. 2004;20:488–92.

67. Konda VJ, Meining A, Jamil LH, et al. A pilot study of in vivo identification of pancreatic cystic neoplasms with needle-based confocal laser endomicroscopy under endosonographic guidance. Endoscopy. 2013;45:1006–13.
68. Belsley NA, Pitman MB, Lauwers GY, et al. Serous cystadenoma of the pancreas: limitations and pitfalls of endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer. 2008;114:102–10.
69. Jani N, Dewitt J, Eloubeidi M, et al. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. Endoscopy. 2008;40:200–3.
70. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas. 2011;40:352–8.
71. Kanno A, Ishida K, Hamada S, et al. Diagnosis of autoimmune pancreatitis by EUS-FNA by using a 22-gauge needle based on the International Consensus Diagnostic Criteria. Gastrointest Endosc. 2012;76:594–602.
72. Ishikawa T, Itoh A, Kawashima H, et al. Endoscopic ultrasound-guided fine needle aspiration in the differentiation of type 1 and type 2 autoimmune pancreatitis. World J Gastroenterol. 2012;18:3883–8.
73. Singh P, Mukhopadhyay P, Bhatt B, et al. Endoscopic ultrasound versus CT scan for detection of the metastases to the liver. Results of a prospective comparative study. J Clin Gastroenterol. 2009;43:367–73.
74. Hollerbach S, Willert J, Topalidis T, et al. Endoscopic ultrasound-guided fine-needle aspiration biopsy of liver lesions: histological and cytological assessment. Endoscopy. 2003;35: 743–9.
75. Singh P, Erickson RA, Mukhopadhyay P, et al. EUS for detection of the hepatocellular carcinoma: results of a prospective study. Gastrointest Endosc. 2007;66:265–73.
76. Stavropoulos SN, Im GY, Jlayer Z, et al. High yield of same-session EUS-guided liver biopsy by 19-gauge FNA needle in patients undergoing EUS to exclude biliary obstruction. Gastrointest Endosc. 2012;75:310–8.
77. Lee S, Seo DW, Paik WH, et al. Ethanol lavage of huge hepatic cysts by using EUS guidance and a percutaneous approach. Gastrointest Endosc. 2014;80:1014–21.
78. Singhal S, Changela K, Lane D, et al. Endoscopic ultrasound-guided hepatic and perihilar abscess drainage: an evolving technique. Therap Adv Gastroenterol. 2014;7:93–8.
79. Wallace MB, Krishna M. Liver lesions. In: Bhutani MS, Deutsch JC, editors. EUS pathology with digital anatomy correlation. Textbook and atlas. Shelton: People's Medical Publishing House-USA; 2010. p. 287–98.
80. Anderson MA, Appalaneni V, Ben-Menachem T, et al. American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee. The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. Gastrointest Endosc. 2013;77: 167–74.
81. Navaneethan U, Njei B, Venkatesh PG, et al. Endoscopic ultrasound in the diagnosis of cholangiocarcinoma as the etiology of biliary strictures: a systematic review and meta-analysis. Gastroenterol Rep (Oxf). 2015;3:209–15.
82. Mohamadnejad M, DeWitt JM, Sherman S, et al. Role of EUS for preoperative evaluation of cholangiocarcinoma: a large single-center experience. Gastrointest Endosc. 2011;73:71–8.
83. Tellez FI, Bernal-Mendez AR, Guerrero-Vazquez CG, et al. Diagnostic yield of EUS-guided tissue acquisition as a first-line approach in patients with suspected hilar cholangiocarcinoma. Am J Gastroenterol. 2014;109:1294–6.
84. Gleeson FC, Rajan E, Levy MJ, et al. EUS-guided FNA of regional lymph nodes in patients with unresectable hilar cholangiocarcinoma. Gastrointest Endosc. 2008;67:438–43.
85. Heimbach JK, Sanchez W, Rosen CB, et al. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. HPB (Oxford). 2011;13:356–60.

86. Weilert F, Bhat YM, Binmoeller KF, et al. EUS-FNA is superior to ERCP-based tissue sampling in suspected malignant obstruction: results of a prospective, single-blind, comparative study. Gastrointest Endosc. 2014;80:197–4.
87. Storch I, Gomez C, Contreras F, et al. Hepatocellular carcinoma (HCC) with portal vein invasion, masquerading as pancreatic mass, diagnosed by endoscopic ultrasound fine-needle aspiration (EUS-FNA). Dig Dis Sci. 2007;52:789–91.
88. Hammoud GM, Almashhrawi A, Ibdah JA. Usefulness of endoscopic ultrasound-guided fine needle aspiration in the diagnosis of hepatic, gallbladder and biliary tract lesions. World J Gastrointest Oncol. 2015;6:420–9.
89. Rana SS, Bhasin DK, Srinivasan R. Endoscopic ultrasound-guided fine needle aspiration of peritoneal nodules in patients with ascites of unknown cause. Endoscopy. 2011;43:1010–3.
90. Wardeh R, Lee JG, Gu M. Endoscopic ultrasound-guided paracentesis of ascitic fluid: a morphologic study with ultrasonographic correlation. Cancer Cytopathol. 2011;119:27–36.
91. Sadamoto Y, Kubo H, Harada N, et al. Preoperative diagnosis and staging of gallbladder carcinoma by EUS. Gastrointest Endosc. 2003;58:536–41.
92. Varadarajulu S, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration in the evaluation of gallbladder masses. Endoscopy. 2005;37:751–4.
93. Choi JH, Lee SS, Choi JH, et al. Long-term outcomes after endoscopic ultrasonography-guided gallbladder drainage for acute cholecystitis. Endoscopy. 2014;46:656–61.
94. Roberts KJ, McCulloch N, Sutcliffe R, et al. Endoscopic ultrasound assessment of lesions of the ampulla of Vater is of particular value in low-grade dysplasia. HPB (Oxford). 2013;15:18–23.
95. Fritscher-Ravens A, Topalidis T. Splenic lesions. In: Bhutani MS, Deutsch JC, editors. EUS pathology with digital anatomy correlation. Textbook and atlas. Shelton: People's Medical Publishing House-USA; 2010. p. 299–311.
96. Fritscher-Ravens A, Mylonaki M, Pates A, et al. Endoscopic ultrasound-guided biopsy for the diagnosis of focal lesions of the spleen. Am J Gastroenterol. 2003;98:1022–7.
97. Handa U, Tiwari A, Singhal N, et al. Utility of ultrasound-guided fine needle aspiration in splenic lesions. Diagn Cytopathol. 2013;41:1038–42.
98. Eloubeidi MA, Black RK, Tamhane A, et al. A large single-center experience of EUS-guided FNA of the left and right adrenal glands: diagnostic utility and impact on patient management. Gastrointest Endosc. 2010;71:745–53.
99. Martinez M, LeBlanc J, Al-Haddad M, et al. Role of endoscopic ultrasound fine-needle aspiration evaluation adrenal gland enlargement or mass. World J Nephrol. 2014;3:92–100.
100. Knight CS, Eloubeidi MA, Crowe R, et al. Utility of endoscopic ultrasound-guided fine-needle aspiration in the diagnosis and staging of colorectal carcinoma. Diagn Cytopathol. 2013;41:1031–7.
101. Amin K, Olyaee M, Tawfik O, et al. Endoscopic ultrasound guided fine needle aspiration as a diagnostic and staging tool for rectal and perirectal lesions-an institute experience. Ann Diagn Pathol. 2013;17:493–7.
102. Mohamadnejad M, Al-Haddad MA, Sherman S, et al. Utility of EUS-guided biopsy of extramural pelvic masses. Gastrointest Endosc. 2012;75:146–51.
103. Rzouq F, Brown J, Fan F, et al. The utility of lower endoscopic ultrasound fine-needle aspiration for the diagnosis of benign and malignant pelvic lesions. J Clin Gastroenterol. 2014;48:127–30.
104. Artifon ELA, Franzini TAP, Kumar A, et al. EUS-guided FNA facilitates the diagnosis of retroperitoneal endometriosis. Gastrointest Endosc. 2007;66:620–2.
105. Artifon ELA, Sakai P, Bhutani MS. Prostate lesions. In: Bhutani MS, Deutsch JC, editors. EUS pathology with digital anatomy correlation. Textbook and atlas. Shelton: People's Medical Publishing House-USA; 2010. p. 387–96.
106. Gleeson FC, Clain JE, Karnes RJ, et al. Endoscopic-ultrasound-guided tissue sampling facilitates the detection of local recurrence and extra pelvic metastasis in pelvic urologic malignancy. Diagn Ther Endosc. 2012;2012:6. https://doi.org/10.1155/2012/219521.

107. Wang KX, Ben QW, Jin ZD, et al. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. Gastrointest Endosc. 2011;73:283–90.
108. Levy MJ, Norton ID, Clain JE, et al. Prospective study of bacteremia and complications with EUS FNA of rectal and perirectal lesions. Clin Gastroenterol Hepatol. 2007;5:684–9.
109. Janssen J, Konig K, Knop-Hammad V, et al. Frequency of bacteremia after linear EUS of the upper GI tract with and without FNA. Gastrointest Endosc. 2004;59:339–44.
110. Guarner-Argente C, Shah P, Buchner A, et al. Use of antimicrobials for EUS-guided FNA of pancreatic cysts: a retrospective, comparative analysis. Gastrointest Endosc. 2011;74:81–6.
111. Khashab MA, Chithadi KV, Acosta RD, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc. 2015;81:81–9.

Chapter 10
Present Status and Future Perspectives of Endoscopic Ultrasonography-Guided Fine Needle Aspiration (EUS-FNA)

Mitsuhiro Kida, Tomohisa Iwai, and Hiroshi Imaizumi

Abstract The first report of pancreatic cancer diagnosing by EUS-FNA has been reported by Peter Vilmann in 1992. Then EUS-FNA has widened its application such as submucosal tumor, mediastinal lesions, liver lesions, adrenal lesions, biliary lesions, etc. Furthermore, EUS-FNA widened not only diagnostic but also therapeutic procedure such as pseudocyst drainage, necrosectomy, EUS-BD, EUS-PD, EUS-CPN/CGN, injection treatment, and gastrojejunostomy.

The application of EUS-FNA seems to be widened year by year in the future.

Keywords EUS • FNA • FNI • FNT • Future perspectives

10.1 History of EUS

After endoscopic ultrasonography (EUS) for gastroenterological diseases was firstly reported by Strohm and DiMagno in 1980, EUS had widened its indications, in which EUS had been employed not only for the evaluation of biliopancreatic diseases but also diagnosis of gastrointestinal diseases and mediastinal lesions, etc. And finally, EUS had become an indispensable examination in the clinical fields until the late 1980s. However, clinical demand for EUS had been widened year by year. For example, characteristics of metastatic lymph node had been reported as hypoechoic, well demarcated, round shape, more than 10 mm, without central hyperecho, etc.; using these findings, the diagnostic accuracy varied still from 70 to 80%. Concerning about submucosal tumors, the diagnostic accuracy of EUS had been also 80–90%, and especially differentiation of malignant GIST from benign leiomyoma and schwannoma, etc. had been 50–70%. There is no imaging diagnostic examination, which was more accurate than histology and cytology. In order to

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improve its accuracy, it had become necessary to obtain cytology or histology because of unsatisfactory EUS diagnostic accuracy. Then, the first report of EUS-FNA (fine needle aspiration) was made by Vilmann in 1992. After its introduction, EUS-FNA has widened its indication with high accuracy and low complication rate in the clinical fields. And EUS-FNA technique has been improved on the size of needle, stroke, number of passes, and negative aspiration pressure.

10.2 EUS-FNA Indication Spreading

Vilmann et al. performed the first case of EUS-guided fine needle aspiration (EUS-FNA) for pancreatic cancer in 1992 [1]. And at the same time, two Japanese doctors, Nagakawa et al. and Harada et al., also performed EUS-FNA in gastric submucosal tumor [2, 3]. After these reports, Wiersema et al. reported a cohort study of EUS-FNA comprised of 26 patients including seven cases of mediastinal lymph node in 1994 [4]. Chang et al. reported EUS-FNA of pleural effusion and ascites [5], and Pedersen et al. performed EUS-FNA in mediastinal lesions in 1995 [6]. Silvestri et al. did the first report of EUS-FNA comprised of 27 patients in the diagnosis and staging of lung cancer in 1996 [7]. Nguyen et al. performed EUS-FNA in 14 (2.4%) liver lesions out of 574 consecutive patients in 1999 [8]. Erickson did the first report of EUS-FNA in 18 (1.6%) retroperitoneum neoplasms out of 1120 patients in 2000 [9]. Gerk performed EUS-FNA for pleural effusion [10]. Jacobson et al. performed

Table 10.1 Spreading indication of EUS-FNA

Author	Year	Target of EUS-FNA
Harada	1991	Basic study of EUS-FNA
Vilmann	1992	Pancreatic cancer
Nagakawa	1993	Gastric submucosal tumor
Harada	1993	Gastric submucosal tumor
Wiersema	1994	Lymph node
Chang	1995	Pleural effusion, ascites
Pedersen	1995	Mediastinal lesions
Silvestri	1996	Lung cancer
Nguyen	1999	Liver lesions
Erickson	2000	Retroperitoneal tumor
Gerke	2001	Pleural effusion, ascites
Jacobson	2002	Bile juice in the gallbladder
Farrell	2002	Kidney
Hernandez	2002	Pancreatic cyst
Bounds	2002	IPMN
Lai	2002	Pancreatic duct
Fritscher-Ravens	2003	Spleen
Matsumoto	2003	AIP
Shami	2004	Rectum
Varadarajulu	2005	Gallbladder tumor

bile aspiration of the gallbladder with a 22-guage needle in three patients and concluded that transduodenal EUS-guided FNA of the gallbladder bile carries a significant risk of bile peritonitis [11].

Lai et al. reported the first EUS-guided pancreatic duct aspiration of 12 patients with 75% diagnostic yield in 2002 [12].

Varadarajulu et al. performed the first EUS-FNA of gallbladder mass lesions which diagnosed five malignant and one benign in 2005 (Table 10.1) [13].

10.3 Recent Application of Therapeutic EUS

Basic study of EUS-FNA was done by Harada et al. in 1991 [14]. First therapeutic EUS of pseudocyst drainage was performed by Grimm et al. [15] in 1992. They punctured a needle into the pseudocyst with endoscopic ultrasound guidance, kept a guidewire, changed echoendoscope to duodenoscope, and then inserted a drainage tube. In the same time, Koito et al. performed EUS-guided sclerotherapy for esophageal varices [2]. Harada et al. also reported a first case of endoscopic ultrasound-guided pancreatography in 1995 [16]. Wiersema M. J. et al. performed transgastric injection of the celiac plexus with bupivacaine and 98% dehydrated absolute ethanol (EUS-CPN) in 25 patients in 1996 [17]. Then 79–88% of patients had persistent improvement in their pain score. Wiersema et al. also reported endosonography-guided cholangiopancreatography with ten patients who failed pancreatico-ductography by ERCP. Hoffmann et al. reported treatment of achalasia by injection of botulinum toxin under endoscopic ultrasound guidance in 1997 [18]. After Sahai et al. reported experimental EUS-BD (hepatico-gastrostomy) in pigs in 1998 [19], Giovannini et al. performed EUS-BD (choledochoduodenostomy) in a 56-year-old man with obstructive jaundice in 2001 [20]. Concerning about EUS-PD, Francois et al. performed the first case of EUS-PD (pancreaticogastrostomy), and Bateile et al. did EUS-PD (rendezvous) in 2002 [21, 22]. In 2000, Seifert et al. went out through the gastric wall into pancreatic abscess and removed the necrotic tissue, so-called necrosectomy, which has been frequently employed as a first step of treatment of pancreatic abscess [23]. After Chang et al. reported phase 1 clinical trial of allogenic mixed lymphocyte culture (cytoimplant) injection in patients with advanced pancreatic carcinoma, many agents such as ONYX-015 (E1B-55kD gene-deleted replication-selective adenovirus) for pancreatic cancer by Hecht [24], ethanol for GIST by Gunter [25], dendritic cell for pancreatic cancer by Irisawa [26], ethanol for pancreatic cyst by Gan [27], TNFα for pancreatic cancer by Senzer [28], ethanol for pancreatic insulinoma, etc. [29] have been tried in the clinical fields. In 2008 Levy et al. reported that the celiac ganglia can be visualized by EUS and performed direct injection into the celiac ganglia for neurolysis (CGN) and block (CGB) with 33 patients [30]. After Fritscher-Ravens et al. reported experimental gastrojejunostomy and cholecystogastric anastomosis in pigs, Itoi et al. performed gastrojejunostomy in humans with a new double-balloon enteric tube in 2013 [31, 32].

Table 10.2 Spreading indication of therapeutic EUS

Author	Year	Therapeutic procedure
Grimm	1992	Pseudocyst drainage
Nobuta, Koito	1992	Injection to the esophageal varix
Harada	1995	Pancreatography
Wiersema	1996	Celiac plexus neurolysis
Wiersema	1996	Choledochography
Hoffmann	1997	Botulinus toxin injection to the esophagus of achalasia
Sahai	1998	EUS-BD (hepatico-gastrostomy) in pig
Chang K	2000	Injection therapy (cytoimplant) for pancreatic cancer
Giovannini	2001	EUS-BD (choledochoduodenostomy)
Seifert	2000	Endoscopic necrosectomy for pancreatic abscess
Francois	2002	EUS-PD (pancreaticogastrostomy)
Bataile	2002	EUS-PD (rendezvous)
Fritscher-Ravens	2003	Gastrojejunostomy and cholecystogastric anastomosis in pigs
Hecht	2003	Injection therapy (ONYX-015) for pancreatic cancer
Gunter	2003	Injection therapy (ethanol) for GIST
Irisawa	2004	Injection therapy (dendritic cell) for pancreatic cancer
Gan	2004	Injection therapy (ethanol) for pancreatic cyst
Ashida	2004	Ethanol injection to the pancreas in pig
Senzer	2004	Injection therapy (TNFα) for pancreatic cancer
Sun	2005	Brachytherapy for pancreatic cancer
Jurgensen C	2006	Injection therapy (ethanol) for pancreatic insulinoma
Levy	2008	Celiac ganglion neurolysis
Itoi	2013	Gastrojejunostomy

Nowadays EUS-FNA technique has introduced many possibilities such as injection of agents, anastomosis, etc. Then we have to collaborate with basic science and are waiting for new agents in order to treat diseases (Table 10.2).

References

1. Vilmann P, Jacobsen GK, Henriksen FW, et al. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreas disease. Gastrointest Endosc. 1992;38(2):172–3.
2. Koito K, Murashima Y. The usefulness of endoscopic color Doppler ultrasonography for digestive diseases. Dig Endosc. 1993;3:306.
3. Harada N, Kouzu T, Isono K. Fine-needle aspiration biopsy of a submucosal tumor of the stomach using ultrasonography. Dig Endosc. 1993;5:417–20.
4. Wiersema MJ, Kochman ML, Cramer HM, et al. Endosonography-guided real-time fine-needle aspiration biopsy. Gastrointest Endosc. 1994;40:700–7.
5. Chang KJ, Albers CG, Nguyen P. Endoscopic ultrasound-guided fine needle aspiration of pleural and ascetic fluid. Am J Gastroenterol. 1995;90:148–50.

6. Pedersen BH, Vilmann P, Milman N, et al. Endoscopic ultrasonography with guided fine needle aspiration biopsy of a mediastinal mass lesion. Acta Radiol. 1995;36(3):326–8.
7. Silvestri GA, Hoffman BJ, Bhutani MS, et al. Endoscopic ultrasound with fine needle aspiration in the diagnosis and staging of lung cancer. Ann Thorac Surg. 1996;61:1441–6.
8. Nguyen P, Feng JC, Chang KJ. Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration (FNA) of liver lesions. Gastrointest Endosc. 1999;50(3):357–61.
9. Erickson RA, Tretjak Z. Clinical utility of endoscopic ultrasound and endoscopic ultrasound-guided fine needle aspiration in retroperitoneal neoplasms. Am J Gastroenterol. 2000;95:1188–94.
10. Gerke H, Bittinger F, Galle PR. Diagnosis of a pleural mesothelioma by endosonography-guide transgastric fine needle aspiration. Endoscopy. 2001;33:906.
11. Jacobson BC, Waxman I, Parmar K, et al. Endoscopic ultrasound-guided gallbladder bile aspiration in idiopathic pancreatitis carries a significant risk of bile peritonitis. Pancreatology. 2002;2(1):26–9.
12. Lai R, Stanley MW, Bardaleo R, et al. Endoscopic ultrasound-guided pancreatic duct aspiration. Endoscopy. 2002;34:715–20.
13. Varadarajulu S, Eloubeidi MA. Endoscopic ultrasound-guided fine needle aspiration in the evaluation of gallbladder masses. Endoscopy. 2005;37:751–4.
14. Harada N, Kouzu T, Ohshima I, et al. A trial of endoscopic ultrasound-guided picture technique. Gastro Enterol Endosc. 1991;33:1657–63.
15. Grimm H, Binmoeller K, Soehendra N. Endosonography-guided drainage of a pancreas pseudocyst. Gastrointest Endosc. 1992;38(2):170.
16. Harada N, Kouzu T, Arima M, et al. Endoscopic ultrasound-guided pancreatography. Endoscopy. 1995;27:612–3.
17. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc. 1996;44:656–62.
18. Hoffman BJ, Knapple WL, Bhutani MS, et al. Treatment of achalasia by injection of botulinum toxin under endoscopic ultrasound guidance. Gastrointest Endosc. 1997;45:77–9.
19. Sahai AV, Hoffman BJ, Hawes RH. Endoscopic ultrasoundguided hepaticogastrostomy to palliate obstructive jaundice: preliminary results in pigs [abstract] Gastrointest Endosc 1998;47:AB37.
20. Giovannini M, Moutardier V, Pesenti C, et al. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy. 2001;33:898–900.
21. Francois E, Kahaleh M, Giovannini M, et al. EUS-guided pancreaticogastrostomy. Gastrointest Endosc. 2002;56:128–33.
22. Bataille L, Deprez P. A new application for therapeutic EUS: main pancreatic duct drainage with a “pancreatic rendezvous technique”. Gastrointest Endosc. 2002;55:740–3.
23. Seifert H, Wehrmann T, Schmitt T, et al. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. Lancet. 2000;356:653–5.
24. Hecht JR, Bedford R, Abbruzzese JL, et al. A phase I/II trial of intratumoral endoscopic ultrasound injection of ONYX-015 with intravenous gemcitabine in unresectable pancreatic carcinoma. Clin Cancer Res. 2003;9:555–61.
25. Gunter E, Lingenfelser T, Eitelbach F, et al. EUS-guided ethanol injection for treatment of a GI stromal tumor. Gastrointest Endosc. 2003;57:113–5.
26. Irisawa A, Takagi T, Kanazawa M, et al. Endoscopic ultrasound-guided fine-needle injection of immature dendritic cells into advanced pancreatic cancer refractory to gemcitabine: a pilot study. Pancreas. 2007;35:189–90.
27. Gan SI, Thompson CC, Lauwers GY, et al. Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc. 2005;61:746–52.
28. Senzer N, Mani S, Rosemurgy A, et al. TNFerade biologic, an adenovector with a radiation-inducible promoter, carrying the human tumor necrosis factor alpha gene: a phase I study in patients with solid tumors. J Clin Oncol. 2004;22:592–601.

29. Jungensen C, Schuppan D, Neser F, et al. EUS-guided alcohol ablation of an insulinoma. Gastrointest Endosc. 2006;63:1059–62.
30. Levy MJ, Topazian MD, Wiersema MJ, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct ganglia neurolysis and block. Am J Gastroenterol. 2008;103:98–103.
31. Fritscher-Ravens A, Mosse CA, Mukherjee D, et al. Transluminal endosurgery: single lumen access anastomotic device for flexible endoscopy. Gastrointest Endosc. 2003;58:585–91.
32. Itoi T, Itokawa F, Uraoka T, et al. Novel EUS-guided gastrojejunostomy technique using a new double-balloon enteric tube and lumen-apposing metal stent. Gastrointest Endosc. 2013;78:934–9.
33. Farrell JJ, Bruggen WR. EUS-guided fine-needle aspiration of a renal mass: an alternative method for diagnosis of malignancy. Gastrointest Endosc. 2002;56:450–2.
34. Hernandez LV, Mishra G, Forsmark C, et al. Role of endoscopic ultrasound (EUS) and EUS-guided fine needle aspiration in the diagnosis and treatment of cystic lesions of the pancreas. Pancreas. 2002;25:222–8.
35. Bounds BC. Diagnosis and fine needle aspiration of intraductal papillary mucinous tumor by endoscopic ultrasound. Gastrointest Endosc Clin N Am. 2002;12:735–45.
36. Fritscher-Ravens A, Mylonaki M, Pantes A, et al. Endoscopic ultrasound-guided biopsy for the diagnosis of focal lesions of the spleen. Am J Gastroenterol. 2003;98:1022–7.
37. Matsumoto G, Yamao K, Yokoi T, et al. Role of endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) in the evaluation of duct-narrowing pancreatitis. In: Japanese with English abstracts Suizo. Vol. 18. 2003. p. 473–8.
38. Shami VM, Parmar KS, Waxman I. Clinical impact of endoscopic ultrasound and endoscopic ultrasound-guided fine-needle aspiration in the management of rectal carcinoma. Dis Colon Rectum. 2004;47:59–65.
39. Chang KJ, Nguyen PT, Thompson et al. Phase I clinical trial of allogeneic mixed lymphocyte culture (cytoimplant) delivered by endoscopic ultrasound-guided fine-needle injection in patients with advanced pancreatic carcinoma. Cancer. 2000;88(6):1325–35.
40. Ashida R, Yamao K, Matsumoto K, et al. Experimental study of endoscopic ultrasound guided ethanol injection in the pancreas: novel strategy for pancreatic lesion. Gastrointest Endosc. 2004;59:AB212.
41. Sun S, Xu H, Xin J, et al. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. Endoscopy. 2006;38:399–403.

Chapter 11
EUS-BD and EUS-GBD

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Abstract Endoscopic retrograde cholangiopancreatography (ERCP) has become the standard tool for diagnosis and treatment of patients with biliary obstruction. However, ERCP occasionally fails owing to anatomical or technical problems, despite high reported success rates. Endoscopic ultrasound-guided biliary drainage (EUS-BD) has recently emerged as an effective alternative biliary drainage method over percutaneous transhepatic biliary drainage (PTBD) after unsuccessful ERCP. EUS-BD includes EUS-rendezvous technique, EUS-guided transluminal biliary drainage including choledochoduodenostomy and hepaticogastrostomy, and EUS-guided gallbladder drainage (EUS-GBD).

This section describes the techniques and current status of EUS-BD procedures.

Keywords EUS-BD • EUS-CDS • EUS-RV • EUS-HGS • EUS-GBD

11.1 Introduction

Endoscopic biliary drainage (EBD) is an established means of providing biliary decompression in patients with bile duct obstruction. However, EBD sometimes fails due to failed biliary cannulation or inaccessible papilla due to duodenal stenosis caused by tumor invasion. Percutaneous transhepatic biliary drainage (PTBD) or surgical intervention is required in such situations, and both methods are associated with higher morbidity and mortality rates. Since 1996, endoscopic ultrasound (EUS)-guided biliary drainage (EUS-BD) has served as an alternative technique to PTBD when endoscopic retrograde cholangiopancreatography (ERCP) fails.

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Multiple approaches to EUS-BD have been described. Transluminal stenting (EUS-TL) includes EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS), EUS-guided hepaticoenterostomy (EUS-HES), and EUS-guided rendezvous (EUS-RV) via transesophageal, transgastric (TG), and transduodenal (TD) routes [1, 2]. The indications, techniques, and complications of EUS-HGS/EUS-HES and CDS are quite different. A guide wire inserted into an extrahepatic or intrahepatic bile duct for EUS-RV is then advanced via the papilla and retrieved using an endoscope for interventions such as stent placement. Many published reports including reviews have described the techniques, indications, safety, and effectiveness of EUS-BD [3–18]. This section describes the techniques and current status of EUS-BD procedures.

11.2 EUS-BD

Wiersema et al. [19] originally described EUS-guided cholangiopancreatography in 1996 as a diagnostic alternative in two patients with failed ERCP. EUS-BD comprises mainly the rendezvous technique (EUS-RV) and transluminal stenting (EUS-TL). The latter uses transgastric (TG) and transduodenal (TD) approaches. The intrahepatic biliary radical is punctured using a needle from the left lobe of the liver (EUS-HGS) in the TG approach, whereas the common bile duct is punctured from the duodenum (EUS-CDS) in the TD approach. The findings of several systematic and meta-analyses of EUS-BD have been published [11, 12, 16, 18].

A systematic review of 42 studies [18] found rates of 94.71%, 91.66%, and 23.32% of cumulative technical success (TSR), functional success (FSR), and adverse events, respectively. Some articles [12, 16, 20] describe comparative evaluations of EUS-BD and PTCD among patients with distal malignant biliary obstruction. In these reports, the technical success rate was higher, but the clinical success and stent patency were the same, and the adverse event rate (70.6% vs. 18.2%, $P < 0.001$) and total charges were higher in the PTCD group ($P = 0.003$).Therefore, it concluded that EUS-BD should be selected if the procedure can be performed by experienced endoscopists [6].

A recent systematic analysis of 1192 patients who underwent EUS-BD revealed a cumulative adverse event rate of 23.32%.

11.3 EUS-Guided Biliary Drainage with the Rendezvous Technique

EUS-guided bile duct drainage with the rendezvous technique was originally described in 2004 by Mallery et al. [21], who used EUS-RV to drain obstructed biliary duct in patients with ERCP failure. Many reports followed [22–28], which caused the procedure to become widely recognized.

11.3.1 Patient Selection

EUS-RV is actually indicated for patients who have difficulties with biliary cannulation defined as unachievable even via advanced techniques such as a double guide wire, pancreatic sphincter, or needle knife precuts or judged as difficult by operators due to conditions such as tumor invasion of the papilla or the location of the papilla.

11.3.2 EUS-RV Puncture Route

The puncture sites are the stomach, duodenal bulb, and descending duodenum (Fig. 11.1). The first route is transmural puncture of the intrahepatic bile duct (IHBD) as the IHBD route (Fig. 11.1a). Transesophageal puncture of B2 and TG puncture of B2 or B3 can be the puncture routes for IHBD. In addition, transjejunal puncture is a possibility for patients who have undergone reconstruction after total gastrectomy. However, the TG puncture route, especially B2, is a popular choice in many patients. The extrahepatic bile duct (EHBD) can be punctured via the proximal duodenum (D1) and via the second portion of the duodenum (D2). The scope is in the long (push) and short position when the EHBD is punctured via D1 (Fig. 11.1b) and D2 (Fig. 11.1c), respectively.

11.3.3 EUS-BD with Rendezvous Technique

After positioning the echoendoscope in the esophagus, stomach, or duodenum and the bile duct is visualized by endosonography, the bile ducts are punctured primarily with a 19-G needle (Fig. 11.2a). Contrast is injected through the EUS needle to visualize the bile ducts. After bile duct puncture is deemed successful by confirmation on

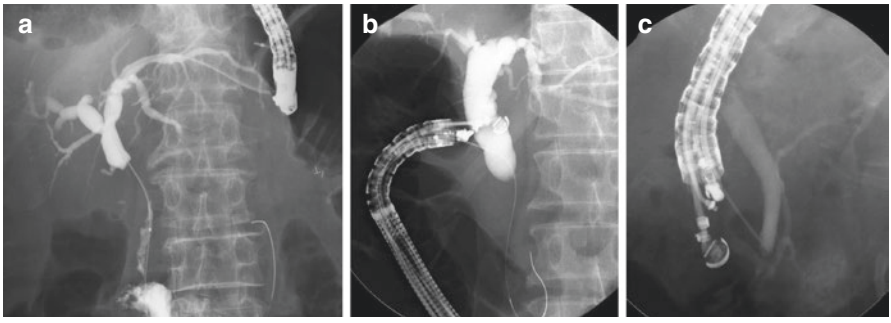

Fig. 11.1 Three puncture sites in EUS-RV. (**a**) Transgastric puncture of intrahepatic bile duct (B2). (**b**) Transduodenal bulb approach via long position. (**c**) Transduodenal (descending duodenum) approach via short position

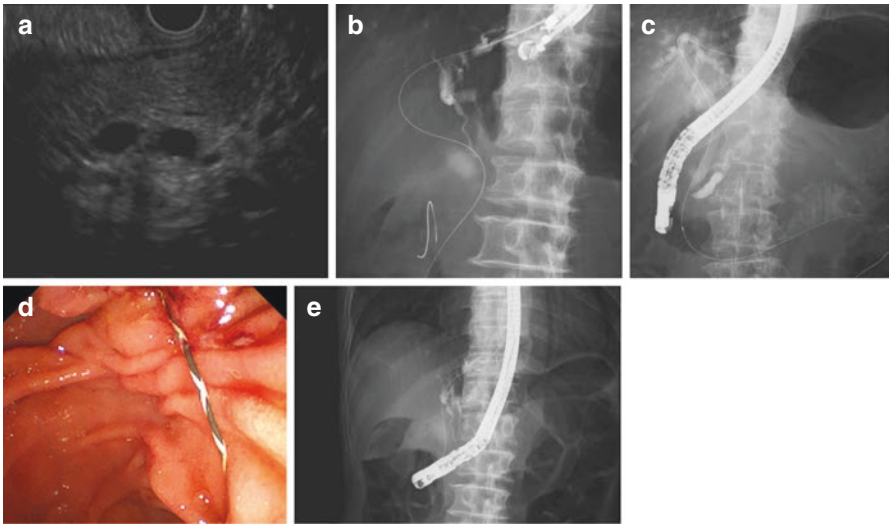

Fig. 11.2 Endoscopic ultrasound-guided rendezvous technique. (**a**) Intrahepatic bile duct is punctured with 19-G needle under endoscopic ultrasound guidance. (**b**) Contrast is injected, and then 0.025-in. guide wire is inserted through the needle and manipulated across the papilla into the duodenum. (**c**) Needle and echoendoscope are exchanged for duodenoscope. (**d**) Guide wire from the papilla is grasped with loop cutter and pulled out through working channel of duodenoscope. (**e**) Deep biliary cannulation achieved over guide wire

endosonographic and fluoroscopic images, a guide wire (0.025 in.) is advanced distally through any stricture and across the papilla using fluoroscopic guidance (Fig. 11.2b). Although a 0.018- or 0.021-in. guide wire with a 22-G needle can be used if a bile duct is insufficiently dilated, it is prone to kinking. Therefore, re-puncture with a 19-G needle achieved by fully dilating the bile duct using contrast imaging can be useful. After the guide wire has passed through the papilla into the duodenum, making several loops of wire in the duodenum or stabilizing the wire by introducing it over the Treitz during subsequent endoscope exchange is advisable (Fig. 11.2c). The EUS scope is then removed leaving the guide wire in place. A duodenoscope is passed by the side of the guide wire placed by EUS up to the papilla. The papillary end of the guide wire is grasped with a snare, forceps, or loop cutter and pulled back out of the working channel of the duodenoscope for subsequent over-the-wire cannulation (Fig. 11.2d). Finally, the common bile duct is accessed, and standard endoscopic retrograde cholangiography (ERC) with stent placement can proceed (Fig. 11.2e).

11.3.4 Success Rate

A recent review of 15 publications including 383 patients who underwent EUS-RV [26] found that the overall success rate of EUS-RV is 81% with a complication rate of 10%. The success rates for the IHBD and EHBD puncture routes were 65% and

87%, respectively. The major complications were bleeding, bile leakage, peritonitis, pneumoperitoneum, and pancreatitis. The incidences of procedural accidents were 17% and 8%, respectively, when using the IHBD and EHBD puncture routes.

11.4 EUS-Guided Choledochoduodenostomy (EUS-CDS)

Giovannini et al. first described EUS-CDS in 2001 [29], and this was subsequently followed by many studies [4, 6, 30–47]. The technique is similar to EUS-guided drainage of pancreatic pseudocysts.

11.4.1 Patient Selection

Patients with failed EBS who have been excluded from prospective clinical trials usually undergo EUS-CDS [35, 48, 49]. This procedure is applicable when the middle and lower areas of the bile duct are obstructed. However, it is contraindicated for patients with surgically altered anatomy, such as a Roux-en-Y anastomosis or duodenal obstruction caused by invasion by a tumor, which is impenetrable by an endoscope. In such circumstances, EUS-guided hepaticogastrostomy might be indicated. However, if the duodenal bulb is not involved, EUS-CDS can be combined with duodenal stenting (Fig. 11.3). The indications for EUS-CDS vs. ERCP for benign conditions are not established. Hence, the following are indications for EUS-CDS: failed EBS, inaccessible ampulla of Vater caused by situations such as tumor invasion of the duodenum, contraindications for percutaneous transhepatic biliary drainage (PTBD), and middle or lower bile duct obstruction.

11.4.2 EUS-CDS Technique

The EUS scope is advanced into the duodenal bulb via the long position to visualize the CBD on EUS (Fig. 11.4a). Doppler visualization of the route is confirmed to avoid any intervening vessels, and then the CBD is punctured using a 19-G needle (Fig. 11.4b). Bile juice is aspirated and a small amount of contrast medium is injected. A guide wire is then placed deep in the intrahepatic bile duct. When the CBD is aligned parallel to the FNA needle EUS images, the guide wire can be easily advanced toward the hepatic hilum to the IHBD (Fig. 11.4c). A 0.025-in. guide wire with a highly flexible tip, sufficient rigidity, and easy-seeking ability is preferable. When the guide wire is inserted along with other devices, then all devices should be visualized under EUS and fluoroscopic guidance to ensure that they fit the axis. Various devices have been described to dilate the fistula after puncturing the CBD. The newer Cysto Gastro Set diathermic dilator (Endoflex GmbH, Voerde,

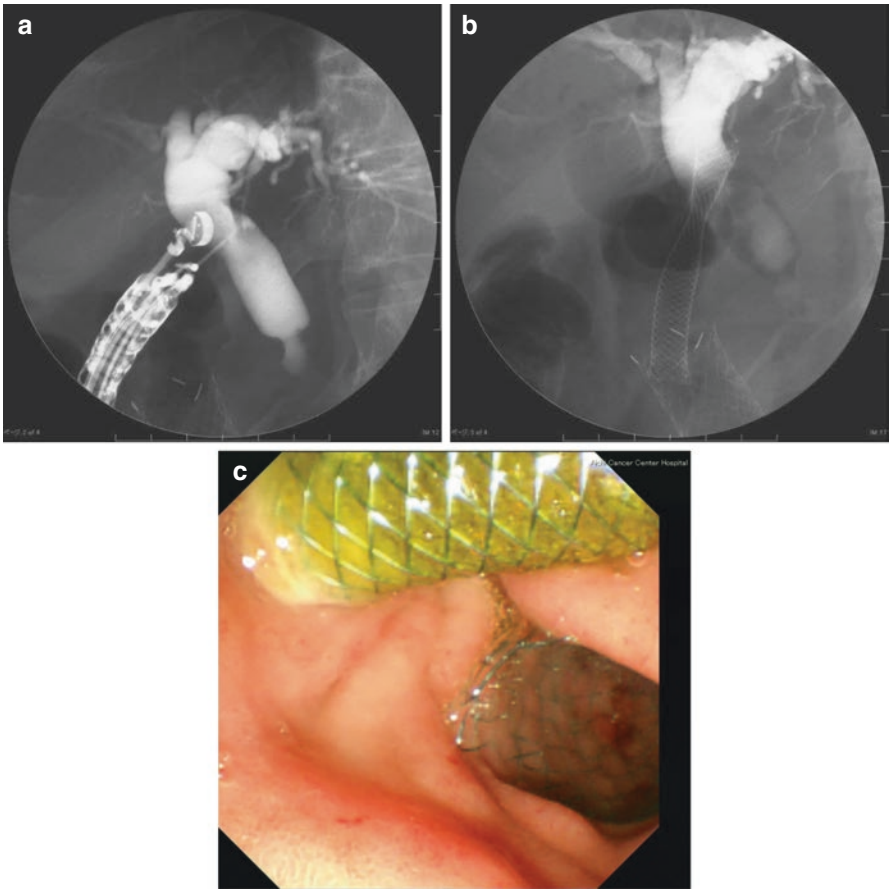

Fig. 11.3 EUS-CDS with duodenal stent. (**a**) Needle puncture from duodenal bulb under duodenum stent up to descending portion. (**b**) Fully covered self-expandable metal stent deployed apart from duodenum stent. (**c**) Endoscopic view of SEMS via transduodenal fistula with distal duodenum stent from duodenum descending portion to horizontal portion

Germany) is coaxial with the guide wire, and thus it might reduce the incidence of EUS-BD-related adverse events when applied to fistula dilation.

11.4.3 Stent Selection

Although both plastic and metallic stents have been deployed during EUS-CDS, the latter should offer some clinical benefits. Plastic stents require a tract with a diameter that is at least equal to or larger than their own, which might associate such stents with bile leakage into the peritoneal space. By contrast, metallic stents can effectively seal the gap between the stent and the fistula tract, thus reducing the risk of bile leakage. Furthermore, the larger diameter of metallic stents results in patency for longer periods.

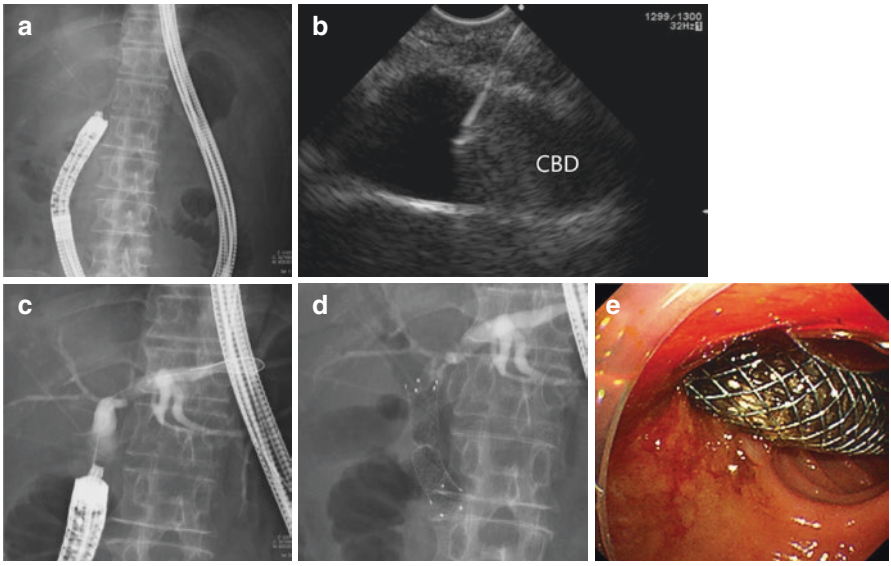

Fig. 11.4 EUS-CDS technique. (**a**) EUS scope is advanced into duodenal bulb via long position. (**b**) Doppler visualization is confirmed and CBD is punctured using 19-G needle. (**c**) Guide wire is advanced toward the hepatic hilum to the IHBD. (**d**) Fully covered self-expandable metal stent deployed. (**e**) Endoscopic view of SEMS via transduodenal fistula

Thus, partially or fully covered self-expandable metal stents (SEMS) should be deployed (Fig. 11.4d, e). However, they have the disadvantage of potentially occluding the side branch of the bile duct. This suggests that a partially covered SEMS should be selected to prevent occlusion of the intrahepatic bile duct if the distance between the puncture site and the hepatic hilar portion is short.

Stent migration is another complication of EUS-BD. A double-pigtail, plastic stent can be placed inside a standard metal stent, with the pigtail functioning as an anchor [14].

11.5 EUS-Guided Hepaticogastrostomy (EUS-HGS)

After the first report of EUS-guided hepaticogastrostomy by Burmester et al. [50] in 2003, many studies of EUS-CDS were published [13, 32, 33, 43, 44, 51].

11.5.1 Patient Selection

When ERCP fails due to surgical anatomy and/or an inaccessible ampulla of Vater, EUS-HGS should be indicated. Although EUS-CDS is contraindicated in patients with surgically altered anatomy, such as a Roux-en-Y anastomosis or duodenal bulb

obstruction caused by tumor invasion, EUS-HGS is an option because it is implemented via the stomach. With respect to biliary stricture, EUS-HGS might be contraindicated if the hepatic hilum is obstructed, because the right hepatic bile duct cannot drain when a stent is deployed in the left intrahepatic bile duct. In fact, EUS-BD has been reported as an expanding indication for right hepatic biliary obstruction [52, 53]. Hence, the indications for EUS-HGS comprise failed ERCP, inaccessible ampulla of Vater including that due to surgical anatomy and tumor invasion, and contraindications for PTCD such as ascites and possibility self-tube removal. The contraindications for EUS-HGS comprise massive ascites between the stomach and the liver, as well as unresectable gastric cancer.

11.5.2 EUS-HGS Technique

The EUS should be advanced into the stomach to visualize the left intrahepatic bile duct, and then the left hepatic lobe can be visualized using a slight counterclockwise rotation. A more rigid guide wire can be inserted through the FNA needle, because a dilated fistula is needed to insert the stent delivery system more than with EUS-CDS. Because each device is passed through the mediastinum when puncturing via the esophagus, extreme adverse events such as mediastinitis or pneumomediastinum might arise if segment 2 (B2) is punctured. Therefore, segment 3 (B3) should be initially selected as the puncture site for EUS-HGS (Fig. 11.5a). After the guide wire is inserted up to the common bile duct, contrast is injected to confirm the obstructed site and the left bile duct (Fig. 11.5b). While inserting devices along with the guide wire, the other devices must be continuously visualized by EUS imaging to ensure that they fit the axis during various EUS-guided procedures. The bile duct and stomach wall must be dilated to insert a stent delivery system. Among various devices for fistula dilation, Soehendra 6–10 Fr biliary dilation catheter (Cook Medical, Bloomington, IN, USA), balloon catheters, and Cysto Gastro Set diathermic dilators (Endoflex GmbH) are the most popular.

11.5.3 Stent Selection

Fully covered self-expandable metallic stents (FCSEMS) seem to be the most popular choice for EUS-HGS (Fig. 11.5c), perhaps because bile is less likely to leak from the gap between the stent and a large fistula created to insert the stent delivery system, stent patency might last longer, and a tamponade effect of the FCSEMS itself will occur if the stomach wall bleeds. Of course, FCSEMS also has the disadvantages of being expensive, having to consider shortening (especially in the luminal portion to prevent stent migration), and possibly obstructing side branches of the left hepatic biliary tract. On the other hand, Umeda et al. [54] performed EUS-HGS using a novel, 8-Fr, 20-cm-long single-pigtail plastic stent with an effective length of 15 cm with four flanges. The proximal end has a pigtail stricture, and the distal end is tapered.

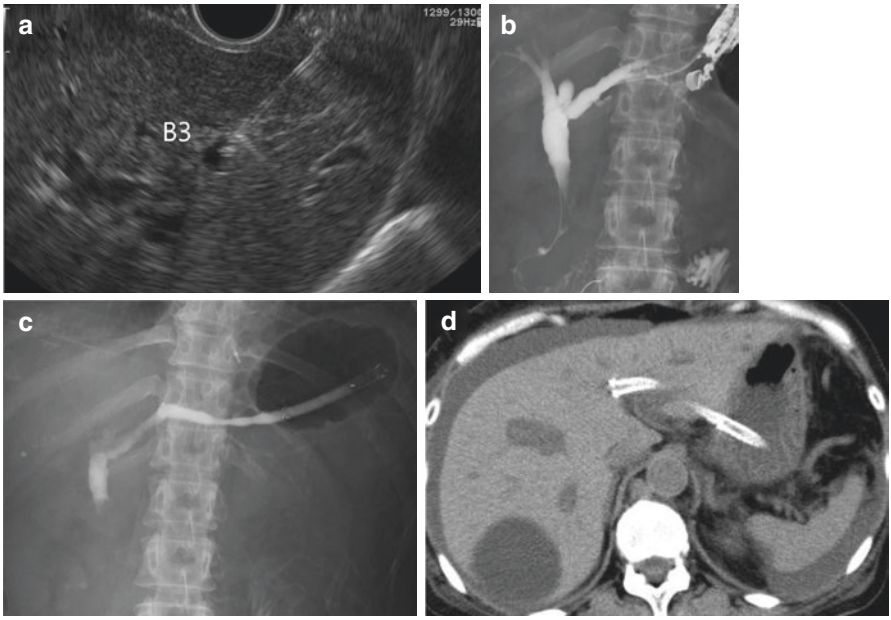

Fig. 11.5 EUS-HGS technique. (**a**) Segment 3 (B3) should be initially selected as puncture site. (**b**) Guide wire is inserted up to common bile duct, and then obstruction site and left bile duct are confirmed using contrast. (**c**) After deployment of metallic stent. (**d**) CT image

11.5.4 Success Rates

The reported technical and clinical success rates of EUS-HGS range from 65% to 100% and from 87% to 100%, respectively [55].

11.6 EUS-Guided Gallbladder Drainage (EUS-GBD)

Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) has recently been reported as an alternative to PTGBD [56–70].

11.6.1 EUS-GBD Technique

The gallbladder is visualized under EUS from the distal gastric antrum or the duodenal bulb. The gallbladder is then punctured with a 19-G needle, avoiding intervening vessels. Punctures from the duodenum usually access the gallbladder

at the neck or infundibulum, whereas those from the distal antrum access the gallbladder fundus or body [67]. Transduodenal access might interfere with subsequent cholecystectomy after interval EUS-GBD. On the other hand, TG EUS-GBD might be more prone to stent dislocation or migration, since the stomach is more mobile than the duodenum [67]. After gallbladder puncture, a 0.025-in. guide wire is introduced and coiled into the gallbladder. The tract is then dilated before stent placement. Consensus about the optimal dilation technique has not been reached. As described above for EUS-HGS, tracts have been dilated using various cautery and non-cautery devices either alone or serially. After gallbladder puncture and tract dilation, a stent is deployed in the gallbladder under combined EUS and fluoroscopic guidance. Various types of stents can be deployed for EUS-GBD (Fig. 11.6).

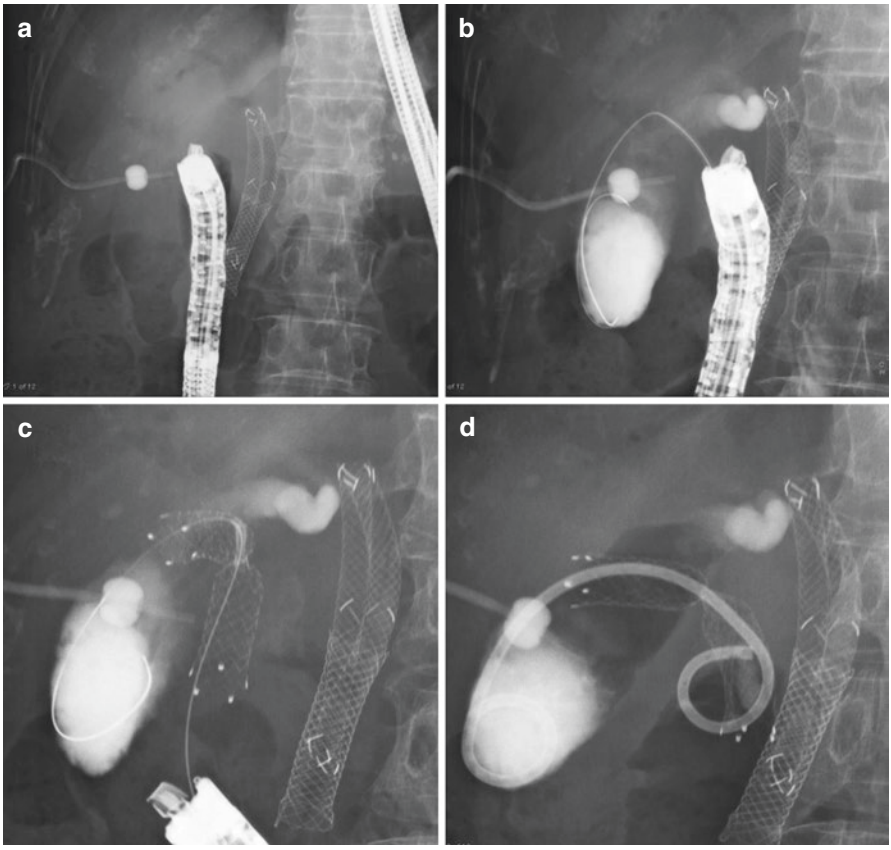

Fig. 11.6 EUS-GBD technique. (**a**) EUS is advanced to duodenal bulb via long position. (**b**) The gallbladder is punctured with 19-G needle, and then tract is dilated using non-cautery device. (**c**) Tubular metallic stent is deployed. (**d**) Pigtail stent inserted through SEMS serves as anchor and safeguard against migration

11.6.2 Stent Selection

Plastic stents were initially deployed for EUS-GBD. Double-pigtail stents are the most popular types of plastic stents used for EUS-GBD because tubular stents can migrate. The pigtail inside the gallbladder is thought to offer protection against the risk of outward migration [67].

However, the patency of plastic stents is shorter, and bile is more likely to leak compared with large-diameter metallic stents. Regarding SEMS, tubular metal stents are not specifically designed for EUS-guided drainage procedures and have several limitations when applied to transluminal drainage [71]. They do not provide lumen anchorage, which increases the risk of adverse events such as bile leakage or pneumoperitoneum. Despite modifications in tubular SEMS design or adjunct techniques such as pigtail-in-SEMS, tubular stent migration remains a distinct risk. Beyond tubular SEMS modifications, novel lumen-apposing metal stents (LAMS) such as the AXIOS stent (Xlumena, Mountain View, CA, USA) have been developed [71]. Such stents provide robust anchorage between nonadherent luminal structures and overcome that specific limitation of tubular stents. The bilateral flanges of LAMS are wider than the saddle section to provide anchorage and prevent migration. Some authors recommend placing a pigtail stent through a tubular standard SEMS when used for EUS-GBD to serve as an anchor or safeguard against migration [67, 69].

11.7 Conclusion

Although EUS-BD is an effective alternative procedure for relieving biliary obstruction, it is safe and appropriate only when performed by experts.

References

1. Savides TJ, Varadarajulu S, Palazzo L. EUS 2008 Working Group document: evaluation of EUS-guided hepaticogastrostomy. Gastrointest Endosc. 2009;69(2 Suppl):S3–7.
2. Itoi T, Yamao K. EUS 2008 Working Group document: evaluation of EUS-guided choledochoduodenostomy (with video). Gastrointest Endosc. 2009;69(2 Suppl):S8–12.
3. Alvarez-Sanchez MV, Jenssen C, Faiss S, Napoleon B. Interventional endoscopic ultrasonography: an overview of safety and complications. Surg Endosc. 2014;28(3):712–34.
4. Chan SM, Teoh AY. Endoscopic ultrasound-guided biliary drainage: a review. Curr Treat Options Gastroenterol. 2015;13(2):171–84.
5. Gupta K, Perez-Miranda M, Kahaleh M, Artifon EL, Itoi T, Freeman ML, et al. Endoscopic ultrasound-assisted bile duct access and drainage: multicenter, long-term analysis of approach, outcomes, and complications of a technique in evolution. J Clin Gastroenterol. 2014;48(1):80–7.
6. Hara K, Yamao K, Mizuno N, Hijioka S, Imaoka H, Tajika M, et al. Endoscopic ultrasonography-guided biliary drainage: who, when, which, and how? World J Gastroenterol. 2016;22(3):1297–303.

7. Itoi T, Isayama H, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, et al. Stent selection and tips on placement technique of EUS-guided biliary drainage: transduodenal and transgastric stenting. J Hepatobiliary Pancreat Sci. 2011;18(5):664–72.
8. Itoi T, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, Ishii K, et al. Endoscopic ultrasonography-guided biliary drainage. J Hepatobiliary Pancreat Sci. 2010;17(5):611–6.
9. Iwashita T, Doi S, Yasuda I. Endoscopic ultrasound-guided biliary drainage: a review. Clin J Gastroenterol. 2014;7(2):94–102.
10. Kedia P, Gaidhane M, Kahaleh M. Endoscopic guided biliary drainage: how can we achieve efficient biliary drainage? Clin Endosc. 2013;46(5):543–51.
11. Khan MA, Akbar A, Baron TH, Khan S, Kocak M, Alastal Y, et al. Endoscopic ultrasound-guided biliary drainage: a systematic review and meta-analysis. Dig Dis Sci. 2016;61(3):684–703.
12. Moole H, Bechtold ML, Forcione D, Puli SR. A meta-analysis and systematic review: success of endoscopic ultrasound guided biliary stenting in patients with inoperable malignant biliary strictures and a failed ERCP. Medicine. 2017;96(3):e5154.
13. Ogura T, Higuchi K. Does endoscopic ultrasound-guided biliary drainage really have clinical impact? World J Gastroenterol. 2015;21(4):1049–52.
14. Sarkaria S, Lee HS, Gaidhane M, Kahaleh M. Advances in endoscopic ultrasound-guided biliary drainage: a comprehensive review. Gut Liver. 2013;7(2):129–36.
15. Sarkaria S, Sundararajan S, Kahaleh M. Endoscopic ultrasonographic access and drainage of the common bile duct. Gastrointest Endosc Clin N Am. 2013;23(2):435–52.
16. Sharaiha RZ, Khan MA, Kamal F, Tyberg A, Tombazzi CR, Ali B, et al. Efficacy and safety of EUS-guided biliary drainage in comparison with percutaneous biliary drainage when ERCP fails: a systematic review and meta-analysis. Gastrointest Endosc. 2017;85(5):904–14.
17. Sharaiha RZ, Kumta NA, Desai AP, DeFilippis EM, Gabr M, Sarkisian AM, et al. Endoscopic ultrasound-guided biliary drainage versus percutaneous transhepatic biliary drainage: predictors of successful outcome in patients who fail endoscopic retrograde cholangiopancreatography. Surg Endosc. 2016;30(12):5500–5.
18. Wang K, Zhu J, Xing L, Wang Y, Jin Z, Li Z. Assessment of efficacy and safety of EUS-guided biliary drainage: a systematic review. Gastrointest Endosc. 2016;83(6):1218–27.
19. Wiersema MJ, Sandusky D, Carr R, Wiersema LM, Erdel WC, Frederick PK. Endosonography-guided cholangiopancreatography. Gastrointest Endosc. 1996;43(2 Pt 1):102–6.
20. Khashab MA, Valeshabad AK, Afghani E, Singh VK, Kumbhari V, Messallam A, et al. A comparative evaluation of EUS-guided biliary drainage and percutaneous drainage in patients with distal malignant biliary obstruction and failed ERCP. Dig Dis Sci. 2015;60(2):557–65.
21. Mallery S, Matlock J, Freeman ML. EUS-guided rendezvous drainage of obstructed biliary and pancreatic ducts: report of 6 cases. Gastrointest Endosc. 2004;59(1):100–7.
22. Isayama H, Nakai Y, Kawakubo K, Kawakami H, Itoi T, Yamamoto N, et al. The endoscopic ultrasonography-guided rendezvous technique for biliary cannulation: a technical review. J Hepatobiliary Pancreat Sci. 2013;20(4):413–20.
23. Iwashita T, Lee JG. Endoscopic ultrasonography-guided biliary drainage: rendezvous technique. Gastrointest Endosc Clin N Am. 2012;22(2):249–58, viii–ix.
24. Jirapinyo P, Lee LS. Endoscopic ultrasound-guided pancreatobiliary endoscopy in surgically altered anatomy. Clin Endosc. 2016;49(6):515–29.
25. Shami VM, Kahaleh M. Endoscopic ultrasound-guided cholangiopancreatography and rendezvous techniques. Dig Liver Dis. 2010;42(6):419–24.
26. Tsuchiya T, Itoi T, Sofuni A, Tonozuka R, Mukai S. Endoscopic ultrasonography-guided rendezvous technique. Dig Endosc. 2016;28(Suppl 1):96–101.
27. Yasuda I, Isayama H, Bhatia V. Current situation of endoscopic biliary cannulation and salvage techniques for difficult cases: current strategies in Japan. Dig Endosc. 2016;28(Suppl 1):62–9.
28. Iwashita T, Yasuda I, Mukai T, Iwata K, Ando N, Doi S, et al. EUS-guided rendezvous for difficult biliary cannulation using a standardized algorithm: a multicenter prospective pilot study (with videos). Gastrointest Endosc. 2016;83(2):394–400.

29. Giovannini M, Moutardier V, Pesenti C, Bories E, Lelong B, Delpero JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. Endoscopy. 2001;33(10):898–900.
30. Video of the month: a novel technique for treating cholangitis following EUS-CDS. Am J Gastroenterol. 2014;109(10):1527.
31. Akiyama D, Hamada T, Nakai Y, Isayama H, Takagi K, Mizuno S, et al. Placement of multiple metal stents for malignant intrahepatic biliary obstruction via an endoscopic ultrasound-guided choledochoduodenostomy fistula. Arab J Gastroenterol. 2015;16(3–4):145–7.
32. Amano M, Ogura T, Onda S, Takagi W, Sano T, Okuda A, et al. Prospective clinical study of EUS-guided biliary drainage using novel balloon catheter (with video). J Gastroenterol Hepatol. 2017;32(3):716–20.
33. Cho DH, Lee SS, Oh D, Song TJ, Park DH, Seo DW, et al. Long-term outcomes of a newly developed hybrid metal stent for EUS-guided biliary drainage (with videos). Gastrointest Endosc. 2017;85(5):1067–75.
34. Dhir V, Itoi T, Khashab MA, Park DH, Yuen Bun Teoh A, Attam R, et al. Multicenter comparative evaluation of endoscopic placement of expandable metal stents for malignant distal common bile duct obstruction by ERCP or EUS-guided approach. Gastrointest Endosc. 2015;81(4):913–23.
35. Hara K, Yamao K, Hijioka S, Mizuno N, Imaoka H, Tajika M, et al. Prospective clinical study of endoscopic ultrasound-guided choledochoduodenostomy with direct metallic stent placement using a forward-viewing echoendoscope. Endoscopy. 2013;45(5):392–6.
36. Kawakubo K, Isayama H, Kato H, Itoi T, Kawakami H, Hanada K, et al. Multicenter retrospective study of endoscopic ultrasound-guided biliary drainage for malignant biliary obstruction in Japan. J Hepatobiliary Pancreat Sci. 2014;21(5):328–34.
37. Kawakubo K, Isayama H, Nakai Y, Sasahira N, Kogure H, Sasaki T, et al. Simultaneous duodenal metal stent placement and EUS-Guided choledochoduodenostomy for unresectable pancreatic cancer. Gut Liver. 2012;6(3):399–402.
38. Kawakubo K, Kawakami H, Kuwatani M, Kubota Y, Kawahata S, Kubo K, et al. Endoscopic ultrasound-guided choledochoduodenostomy vs. transpapillary stenting for distal biliary obstruction. Endoscopy. 2016;48(2):164–9.
39. Khashab MA, Messallam AA, Penas I, Nakai Y, Modayil RJ, De la Serna C, et al. International multicenter comparative trial of transluminal EUS-guided biliary drainage via hepatogastrostomy vs. choledochoduodenostomy approaches. Endosc Int Open. 2016;4(2):E175–81.
40. Minaga K, Kitano M, Gon C, Yamao K, Imai H, Miyata T, et al. Endoscopic ultrasonography-guided choledochoduodenostomy using a newly designed laser-cut metal stent: feasibility study in a porcine model. Dig Endosc. 2017;29(2):211–7.
41. Minaga K, Kitano M, Imai H, Yamao K, Kamata K, Miyata T, et al. Urgent endoscopic ultrasound-guided choledochoduodenostomy for acute obstructive suppurative cholangitis-induced sepsis. World J Gastroenterol. 2016;22(16):4264–9.
42. Nicholson JA, Johnstone M, Raraty MG, Evans JC. Endoscopic ultrasound-guided choledocho-duodenostomy as an alternative to percutaneous trans-hepatic cholangiography. HPB. 2012;14(7):483–6.
43. Ogura T, Chiba Y, Masuda D, Kitano M, Sano T, Saori O, et al. Comparison of the clinical impact of endoscopic ultrasound-guided choledochoduodenostomy and hepaticogastrostomy for bile duct obstruction with duodenal obstruction. Endoscopy. 2016;48(2):156–63.
44. Ogura T, Higuchi K. Technical tips of endoscopic ultrasound-guided choledochoduodenostomy. World J Gastroenterol. 2015;21(3):820–8.
45. Song TJ, Hyun YS, Lee SS, Park DH, Seo DW, Lee SK, et al. Endoscopic ultrasound-guided choledochoduodenostomies with fully covered self-expandable metallic stents. World J Gastroenterol. 2012;18(32):4435–40.
46. Thotakura RV, Thotakura S, Sofi A, Bawany MZ, Nawras A. Synchronous EUS-guided choledochoduodenostomy with metallic biliary and duodenal stents placement in a patient with malignant papillary tumor. J Interv Gastroenterol. 2012;2(2):88–90.

47. Yamao K, Hara K, Mizuno N, Hijioka S, Imaoka H, Bhatia V, et al. Endoscopic ultrasound-guided choledochoduodenostomy for malignant lower biliary tract obstruction. Gastrointest Endosc Clin N Am. 2012;22(2):259–69, ix.
48. Hara K, Yamao K, Niwa Y, Sawaki A, Mizuno N, Hijioka S, et al. Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction. Am J Gastroenterol. 2011;106(7):1239–45.
49. Itoi T, Itokawa F, Tsuchiya T, Tsuji S, Tonozuka R. Endoscopic ultrasound-guided choledochoantrostomy as an alternative extrahepatic bile duct drainage method in pancreatic cancer with duodenal invasion. Dig Endosc. 2013;25(Suppl 2):142–5.
50. Burmester E, Niehaus J, Leineweber T, Huetteroth T. EUS-cholangio-drainage of the bile duct: report of 4 cases. Gastrointest Endosc. 2003;57(2):246–51.
51. Nakai Y, Isayama H, Yamamoto N, Matsubara S, Ito Y, Sasahira N, et al. Safety and effectiveness of a long, partially covered metal stent for endoscopic ultrasound-guided hepaticogastrostomy in patients with malignant biliary obstruction. Endoscopy. 2016;48(12):1125–8.
52. Park SJ, Choi JH, Park DH, Choi JH, Lee SS, Seo DW, et al. Expanding indication: EUS-guided hepaticoduodenostomy for isolated right intrahepatic duct obstruction (with video). Gastrointest Endosc. 2013;78(2):374–80.
53. Ogura T, Sano T, Onda S, Imoto A, Masuda D, Yamamoto K, et al. Endoscopic ultrasound-guided biliary drainage for right hepatic bile duct obstruction: novel technical tips. Endoscopy. 2015;47(1):72–5.
54. Umeda J, Itoi T, Tsuchiya T, Sofuni A, Itokawa F, Ishii K, et al. A newly designed plastic stent for EUS-guided hepaticogastrostomy: a prospective preliminary feasibility study (with videos). Gastrointest Endosc. 2015;82(2):390–6.e2.
55. Ogura T, Higuchi K. Technical tips for endoscopic ultrasound-guided hepaticogastrostomy. World J Gastroenterol. 2016;22(15):3945–51.
56. Anderloni A, Buda A, Vieceli F, Khashab MA, Hassan C, Repici A. Endoscopic ultrasound-guided transmural stenting for gallbladder drainage in high-risk patients with acute cholecystitis: a systematic review and pooled analysis. Surg Endosc. 2016;30(12):5200–8.
57. Choi JH, Kim HW, Lee JC, Paik KH, Seong NJ, Yoon CJ, et al. Percutaneous transhepatic versus EUS-guided gallbladder drainage for malignant cystic duct obstruction. Gastrointest Endosc. 2017;85(2):357–64.
58. Choi JH, Lee SS. Endoscopic ultrasonography-guided gallbladder drainage for acute cholecystitis: from evidence to practice. Dig Endosc. 2015;27(1):1–7.
59. Choi JH, Lee SS, Choi JH, Park DH, Seo DW, Lee SK, et al. Long-term outcomes after endoscopic ultrasonography-guided gallbladder drainage for acute cholecystitis. Endoscopy. 2014;46(8):656–61.
60. Imai H, Kitano M, Omoto S, Kadosaka K, Kamata K, Miyata T, et al. EUS-guided gallbladder drainage for rescue treatment of malignant distal biliary obstruction after unsuccessful ERCP. Gastrointest Endosc. 2016;84(1):147–51.
61. Irani S, Baron TH, Grimm IS, Khashab MA. EUS-guided gallbladder drainage with a lumen-apposing metal stent (with video). Gastrointest Endosc. 2015;82(6):1110–5.
62. Irani S, Ngamruengphong S, Teoh A, Will U, Nieto J, Abu Dayyeh BK, et al. Similar efficacies of endoscopic ultrasound gallbladder drainage with a lumen-apposing metal stent vs. percutaneous transhepatic gallbladder drainage for acute cholecystitis. Clin Gastroenterol Hepatol. 2017;15(5):738–45.
63. Isayama H, Nakai Y, Kawakubo K, Koike K. Recent progress in endoscopic ultrasonography guided biliary intervention. Clin J Gastroenterol. 2012;5(2):93–100.
64. Itoi T, Itokawa F, Kurihara T. Endoscopic ultrasonography-guided gallbladder drainage: actual technical presentations and review of the literature (with videos). J Hepatobiliary Pancreat Sci. 2011;18(2):282–6.
65. Jang JW, Lee SS, Song TJ, Hyun YS, Park DY, Seo DW, et al. Endoscopic ultrasound-guided transmural and percutaneous transhepatic gallbladder drainage are comparable for acute cholecystitis. Gastroenterology. 2012;142(4):805–11.

66. Kahaleh M, Perez-Miranda M, Artifon EL, Sharaiha RZ, Kedia P, Penas I, et al. International collaborative study on EUS-guided gallbladder drainage: are we ready for prime time? Dig Liver Dis. 2016;48(9):1054–7.
67. Penas-Herrero I, de la Serna-Higuera C, Perez-Miranda M. Endoscopic ultrasound-guided gallbladder drainage for the management of acute cholecystitis (with video). J Hepatobiliary Pancreat Sci. 2015;22(1):35–43.
68. Takagi W, Ogura T, Sano T, Onda S, Okuda A, Masuda D, et al. EUS-guided cholecystoduodenostomy for acute cholecystitis with an anti-stent migration and anti-food impaction system; a pilot study. Therap Adv Gastroenterol. 2016;9(1):19–25.
69. Widmer J, Alvarez P, Gaidhane M, Paddu N, Umrania H, Sharaiha R, et al. Endoscopic ultrasonography-guided cholecystogastrostomy in patients with unresectable pancreatic cancer using anti-migratory metal stents: a new approach. Dig Endosc. 2014;26(4):599–602.
70. Widmer J, Singhal S, Gaidhane M, Kahaleh M. Endoscopic ultrasound-guided endoluminal drainage of the gallbladder. Dig Endosc. 2014;26(4):525–31.
71. Binmoeller KF, Shah J. A novel lumen-apposing stent for transluminal drainage of nonadherent extraintestinal fluid collections. Endoscopy. 2011;43(4):337–42.

Chapter 12
New Insight of EUS-Guided Transluminal Drainage for Pancreatic and Peripancreatic Fluid Collections

Atsushi Irisawa, Akane Yamabe, Ai Sato, and Goro Shibukawa

Abstract Endoscopic ultrasound (EUS)-guided drainage, in which accumulated pancreatic and peripancreatic fluid collections are approached directly through the digestive tract, has been widely performed. This therapy is a procedure that allows for simple, reliable, and effective drainage without putting any burden on the pancreatic parenchyma. In addition, for cases in which elimination or remission of the lesions cannot be achieved with EUS-guided transgastric drainage alone, endoscopic necrosectomy is also carried out. However, these therapies are associated with a relatively high incidence of adverse events, and therefore, the indications must be fully considered, and the procedure must be mastered before it is performed.

Keywords Walled-off necrosis • Pancreatic pseudocyst • EUS-guided drainage Endoscopic necrosectomy

12.1 Introduction

Drainage under endoscopic ultrasound (EUS), in which accumulated pancreatic and peripancreatic fluid collections are approached directly through the digestive tract, has been widely used in recent years. The method described in this treatment is a procedure that allows for simple, reliable, and effective drainage without putting any burden on the pancreatic parenchyma. In addition, for cases in which elimination or remission of the lesions cannot be achieved with EUS-guided transgastric drainage alone, endoscopic necrosectomy is also carried out. However, these therapeutic procedures are associated with a relatively high incidence of adverse events,

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and therefore, the indications must be fully considered, and the procedure must be mastered before it is performed. In this article, we describe the therapeutic procedures using EUS for the treatment of pancreatic and peripancreatic fluid collections associated with pancreatitis, as well as perspectives on the indications for treatment, and the actual execution of treatment.

12.2 Concept of Pancreatic and Peripancreatic Fluid Collections Associated with Acute Pancreatitis and Changes in the Concept

Based on concepts understood thus far, pancreatic pseudocysts (PPCs) are defined as "an accumulation of pancreatic juice encapsulated in a wall of fibrous or granulation tissue, due to acute pancreatitis, traumatic injuries, or chronic pancreatitis," as proposed at the 1992 International Symposium on Acute Pancreatitis [1], which was held in Atlanta, GA, USA.

Due to recent advances in endoscopic equipment, the endoscopic treatment of pancreatic and peripancreatic fluid collections associated with pancreatitis has developed extensively. Thus, treatment outcomes have been reported to differ depending on the presence or absence of infection, and unlike pseudocysts, which are composed of only liquid components, pancreatic and peripancreatic fluid collections may contain necrotic tissue, and in such cases, treatment efficacy has been reported to vary even when the same therapeutic method was performed [2–4]. These findings show that the condition can no longer be explained on the basis of the aforementioned Atlanta classification alone. Thus, a revised version of the Atlanta classification [5] based on an international consensus was published in 2013. In this classification, the concept of PPCs developing after acute pancreatitis has changed drastically, and the processes of formation of pancreatic and peripancreatic fluid collections caused by other diseases such as interstitial edematous pancreatitis and necrotizing pancreatitis (cystic lesions caused by inflammation) were newly considered in the interpretation of pathological conditions, which had thus far been included among acute pseudocysts (Table 12.1).

In the case of interstitial edematous pancreatitis, PPCs were defined as acute peripancreatic fluid collections (APFCs) that develop first as a result of inflammation, and which become encapsulated over time in order to become a cyst, without including pancreatic or peripancreatic necrotic tissue. Their formation often involves a collapse of the main pancreatic duct, as well as pancreatic duct branches, and the cyst's liquid content often shows extremely high levels of pancreatic enzymes. Diagnostic imaging usually shows that the cyst has a relatively uniform internal structure (often unilocular), because no necrotic tissue is contained inside (Fig. 12.1). Such a condition is believed to rarely lead to the development of fluid collections

Table 12.1 Processes of formation of pancreatic and peripancreatic fluid collections caused by acute pancreatitis

Within the first 4 weeks after onset of		More than the first 4 weeks
Interstitial edematous pancreatitis		
Acute peripancreatic fluid collection (sterile/infected)	→	Pancreatic pseudocyst (sterile/infected)
Necrotizing pancreatitis		
Acute necrotic collection (sterile/infected)	→	Walled-off necrosis (WON) (sterile/infected)

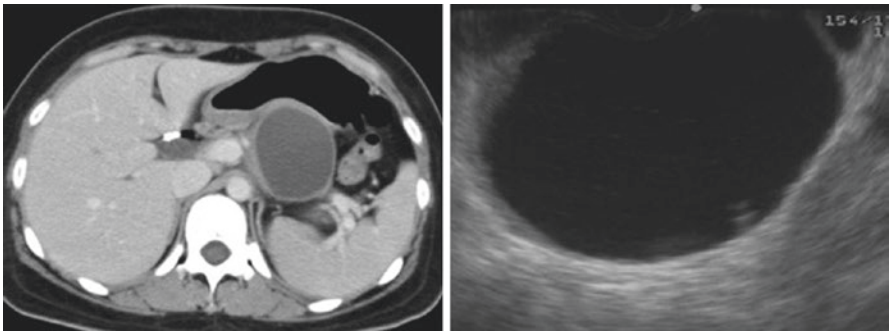

Fig. 12.1 Pancreatic pseudocyst. CT and EUS images show that an encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with no necrosis

after acute pancreatitis, and the cyst is highly likely to be resorbed during the clinical course and to heal spontaneously.

Meanwhile, the accumulation of exudate associated with necrotizing pancreatitis is called "acute necrotic collection" in its initial stages; later, pancreatic and peripancreatic necrosis reaches a peak, and liquefaction starts to develop. Usually, a border becomes clearly visible between the necrotic focus and the adjacent tissue after 4 or more weeks, leading to a condition known as "walled-off necrosis (WON)," in which the necrosis is encapsulated. Each of the above has been proposed to be considered an independent pathological condition. In most cases, WON is multilocular and contains necrotic tissue inside (Fig. 12.2). However, pseudocysts associated with chronic pancreatitis (chronic pseudocysts) have a frequency of approximately 30% [6]; they are often unilocular and have a morphology that is apparently different from that of WON. In most cases, such pseudocysts communicate with the pancreatic duct.

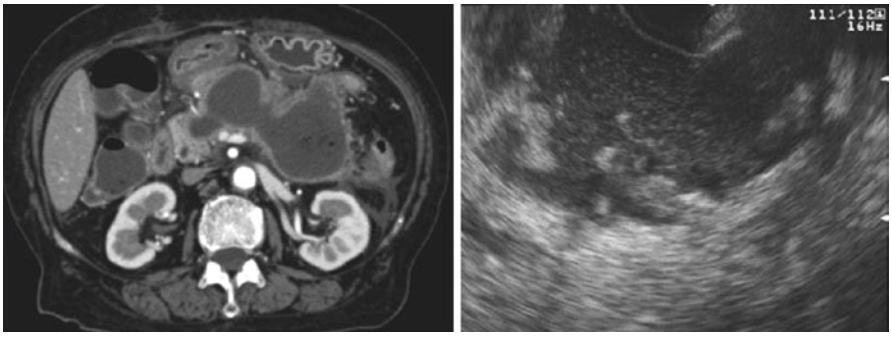

Fig. 12.2 Walled-off necrosis (WON). CT and EUS images show a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON is multilocular and contains necrotic tissue inside

12.3 Indications of Treatment Under EUS (Drainage, Necrosectomy)

12.3.1 Overview of the EUS Treatment of Pancreatic and Peripancreatic Fluid Collections

EUS-guided transgastric drainage is an endoscopic treatment aimed at forming an artificial fistula by puncturing the cyst cavity directly from the gastrointestinal tract. Using a convex EUS allows for performing the procedure while confirming in real time the puncture route, as well as the blood vessels on the route; as a result, decompression and drainage of the inner cavities of pseudocysts and WON can be performed easily, conveniently, and safely. The purpose of an endoscopic necrosectomy is to create, under EUS guidance, a relatively large fistula between the gastric wall and the WON, to insert the endoscope directly into the cavity, to control infection in the WON cavity, and to remove necrotic materials involved in the production of chemical mediators and cytokines. Puncture through the digestive tract is performed under EUS guidance, and if the WON is drainable, the same route can be used to perform an endoscopic necrosectomy through the digestive tract.

12.3.2 Understanding the Mechanism of the Formation of WON/PPCs and Treatment Options

12.3.2.1 WON

This section describes current considerations regarding the mechanism of formation of WONs. When inflammation spreads outside the pancreas as a result of acute necrotizing pancreatitis, an exudate accumulates in the cavity of the omental bursa

between the pancreas and the stomach. Intense inflammation inside the cavity of the omental bursa causes a closure of Winslow's hiatus; thus, the exudate, as well as pancreatic and peripancreatic necrotic materials, is encapsulated mainly in the cavity of the omental bursa, leading to the formation of cystic lesions. In such cases, inflammation inside the cavity of the omental bursa causes adhesions between the gastric serosa and the omental bursa. As a result, the gastric wall itself is integrated in the wall of the WON [7]. Because of this mechanism of formation of WON, the risk of leakage of the contained liquid into the abdominal cavity is low, and performing drainage is relatively safe, even if the procedure includes performing a transgastric puncture.

12.3.2.2 PPCs

Pseudocysts following an acute pancreatitis are due to the encapsulation of APFCs as a result of the spread of inflammation to the peripancreatic region. In other words, the process of formation of a cyst is similar to that of the aforementioned WON, and cysts can also be treated with transgastric drainage.

Meanwhile, chronic pseudocysts due to pancreatic duct stricture or pancreatic calculi are basically intrapancreatic cysts, and because the cavity of the omental bursa is present between the pseudocyst and the stomach, the gastric wall and the cyst wall are disconnected from each other. Therefore, in principle, transpapillary drainage needs to be performed in the case of such cysts. However, in many cases, even when a chronic pseudocyst is clearly present inside the pancreas, repeated inflammation leads to adhesion between the gastrointestinal wall and the cyst wall, and in such cases, treatment can be conducted through the digestive tract [7].

12.3.2.3 Indications and Timing of Treatment

Understanding the natural history of cystic lesions after pancreatitis is important for estimating and determining the indications and timing of the treatment [8, 9]. In 1979, Bradley et al. [10] reported that if a PPC has a diameter less than 6 cm, it has a 40% chance to regress spontaneously within 6 weeks after its development. In addition, in 1985, O'Malley VP et al. [11] reported that if a cyst was small with a diameter of approximately 4 cm, it was highly likely to regress spontaneously; however, if the cyst's diameter exceeded 6 cm, spontaneous regression was less likely, and the risks of complications such as internal hemorrhage inside the cyst, infection, or rupture were elevated. Considering all of the above, spontaneous regression is unlikely, and treatment is indicated when a cyst has a diameter of 6 cm or more, regardless of the presence or absence of symptoms. Treatment is also indicated if 6 weeks have elapsed since the development of the cyst. Meanwhile, if the cyst increases in size during the follow-up period, if it bleeds or gets infected, or if the patient has abdominal pain or a disorder of gastrointestinal transit time, treatment is indicated, regardless of the size or timing mentioned earlier [10]. In the natural

history of WON, the cavity may communicate with the gastric or intestinal lumen in some cases; its size may also decrease naturally, and in other cases, the infection may also resolve spontaneously [12].

Even in cases of acute necrotic pancreatic/peripancreatic collections, which are conditions that precede the aforementioned WON, infection control through drainage should be carried out if the fluid collection is complicated by infection and also if no improvement is achieved after administration of conservative antimicrobial therapy. However, as often as possible, conservative treatment alone should be carried out during this period. If the patient's general condition is relatively stable, elective treatment should be considered in order to have a lower incidence of complications and a lower mortality rate [13, 14]. In addition, since retention cysts developing as a complication of chronic pancreatitis are less likely to regress spontaneously [15], treatment should be actively considered in patients with clinical symptoms.

12.3.2.4 Judgment of the Value of EUS-Guided Transgastric Drainage and that of Endoscopic Necrosectomy

Previous reports have shown that the treatment outcomes of EUS-guided transgastric drainage were very good in roughly 95% of cases, and previously reported recovery rates were approximately 90%, also showing a favorable outcome [16, 17]. The procedural success rate (94–100%) has been reported to be higher than that of drainage performed under direct visualization by using an endoscope [18, 19]. The incidence of procedural accidents is believed to be approximately 11% [7].

Although endoscopic necrosectomy has often been reported as highly effective, its high incidence of procedural accidents has been considered problematic. Earlier reports [20], which could be considered from the dawn of the development of the method described in this study, have shown that endoscopic necrosectomy was more advantageous for the treatment of WON (a high treatment success rate and an incidence of procedural accidents similar to that associated with the method using drainage). In addition, a report based on a comparative controlled study of endoscopic necrosectomy and surgical necrosectomy [21] showed that in patients treated with endoscopic necrosectomy, the postoperative serum levels of IL-6 were significantly lower, and the frequency of occurrence of procedural accidents was also significantly lower, indicating that endoscopic necrosectomy was less invasive and therapeutically superior. However, at a time when reports on endoscopic necrosectomy became more common, a systematic review [22] reported that while 76% of patients showed improvements after being treated with endoscopic necrosectomy alone, the incidence of procedural accidents was 27%, and the mortality rate was 5%. In other reviews [23] as well, although the rate of effectiveness of endoscopic necrosectomy for treating WON has been reported to be as high as 84%, the occurrence of procedural accidents has been reported to be 24%, and the mortality rate was 3.4%; therefore, the method cannot actually be said to be safe in all cases.

Based on this information, the step-up approach has recently been recommended. In other words, patients are initially treated by using an EUS-guided transgastric drainage, and endoscopic necrosectomy is performed only in uncontrollable cases. In 2010, van Santvoort et al. [24] conducted a randomized controlled trial that included a group of participants treated by surgical necrosectomy from the beginning and a step-up group in which the participants were first treated by percutaneous or endoscopic drainage and secondarily treated by necrosectomy if necessary. The findings showed that although there was no significant difference in the mortality rate between the two groups (19 vs. 16%), the incidence of severe cases of procedural accidents, including surgery-related deaths, was 69% in the surgical necrosectomy-treated group and significantly lower (40%) in the step-up group. In addition, the incidence of newly developed multiple organ failure was also significantly lower in the step-up group (12%) than in the surgical necrosectomy-treated group (40%). They also reported that 60% of patients with WON were treatable by drainage alone, and necrosectomy therefore did not need to be performed [14].

12.4 Therapeutic Procedures and Results

12.4.1 EUS-Guided Transgastric Drainage

12.4.1.1 Therapeutic Procedure and Its Efficacy

The method described in this study applies to procedures used in EUS-guided fine needle aspiration biopsy and percutaneous biliary drainage. First, the targeted lesion is visualized, the absence of blood flow in the lesion and the puncture line is confirmed by color Doppler, and the puncture route is determined. Next, the puncturing device is fixed to the accessory channel of the endoscope, and the targeted lesion is punctured (Fig. 12.3a). The stylet is pulled out, and a guide wire is inserted (Fig. 12.3b). The puncture needle is removed, and later, a dilator is inserted, and the puncture site is dilated; then a drainage tube is inserted. In the case of an infected cyst, an external fistula method is carried out, in which an indwelling nasotracheal tube is put in place and the properties of the drainage fluid confirmed; performing a lavage should be considered if necessary (Fig. 12.3c). Reports from previous studies have shown that a recovery rate of 90% or higher has been achieved even when the internal fistula method alone was used [16, 25]; however, for cases in which infection develops inside the cyst, the external fistula method is recommended, to allow for lavage inside the cystic cavity. In addition, in cases with infected cysts, infection control has been pointed out as likely to be difficult with the external fistula method alone [26]. Therefore, in recent years, starting with a combination of internal and external fistulas from the initial phases of treatment has been considered a better option [27, 28]. Particularly, in the case of WON, the method using an external fistula for lavage of the cystic cavity has also been actively carried out.

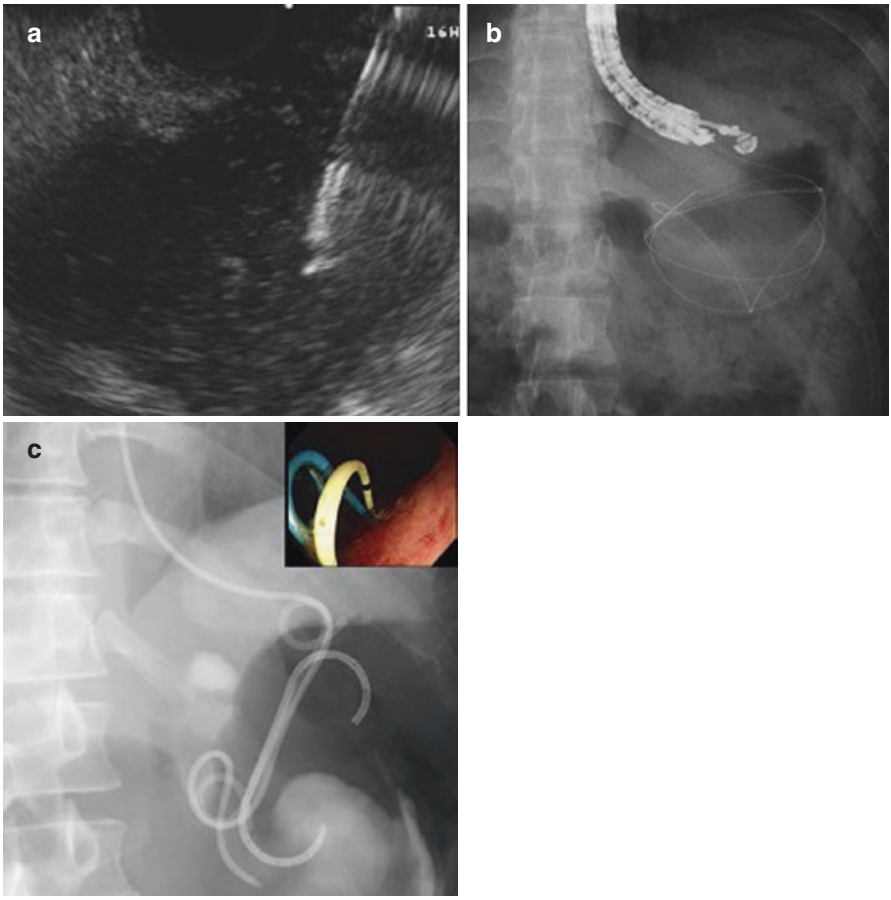

Fig. 12.3 Procedure of EUS-guided drainage for WON. (**a**) The targeted lesion is punctured using 19-gauge needle device. (**b**) A guide wire (0.025 in.) is inserted into the cavity of WON. (**c**) Multiple stents are indwelled into the cavity of WON (one external and two internal stents, single transluminal gateway transcystic multiple drainages)

In recent years, various efforts have been carried out to improve the performance of drainage. In particular, in WON, the cavity encapsulated inside the cyst is often multilocular, and therefore, the therapeutic effect may not be fully achieved if drainage is conducted only on a partial portion of the cavity. Suzuki et al. [29] previously reported a case of multilocular WON in which overall improvement could not be achieved by only drainage from the stomach into an adjacent site. To deal with the case, they inserted a small-diameter endoscope transgastrically and placed an indwelling transnasal drainage tube in the cavity of the WON, which was located at a site distant from the stomach where the drainage effect could not be achieved. Later, healing was achieved after they performed a lavage of the inner cavity by using approximately 500 mL of physiological saline for several consecutive days. In addition, Varadarajulu et al. [30] reported having achieved favorable outcomes after treating a multilocular WON by using a multiple transluminal gateway technique

consisting of carrying out a puncture drainage from various sites. Further, Mukai et al. [31] reported the usefulness of single transluminal gateway transcystic multiple drainages. The technique consisted of placing several indwelling stents in multiple directions (inside each cavity with a multilocular structure) by inserting them from one puncture cavity in the same way as the multiple transluminal gateway technique (Fig. 12.3c). This has been shown to have favorable therapeutic effects.

In addition, in an increasing number of reports, metallic indwelling stents with larger diameters have been put in place instead of plastic stents, to achieve favorable therapeutic effects, as well as the early formation of a fistula [32–37]. The outcomes have been generally favorable, with a procedural success rate and recovery rate of approximately 90%. Among such cases, Saxena et al. [37] reported that by placing exclusively an indwelling metallic stent only once (without needing additional treatments such as necrosectomy), they achieved a high recovery rate and an extremely short duration of hospitalization (mean duration of hospital stay, 1 day). Walter et al. [38] (in a study conducted on 61 patients) reported that the procedural success rate was 98%, and the disappearance of clinical symptoms and the reduction in the size of the lesions to 2 cm or less accounted for 93% (including 95% of pseudocysts and 81% of WON); the mean duration of placement of indwelling stents was 32 days, and removal was achievable in 82% of the cases. However, relatively severe procedural accidents (cyst cavity infection, perforation) occurred in 9% of the patients, whereas 6.5% of the patients needed additional treatment requiring surgery.

Recently, Itoi et al. [39, 40], Yamamoto et al. [41], and Bapaye et al. [42] have reported the usefulness of dumbbell-shaped metallic stents using both ends as anchors. Their major advantages consist of their large aperture diameter and high drainage effect, as well as the fact that they allow for endoscopic necrosectomy to be performed easily through the stent lumen.

12.4.1.2 Procedural Accidents

Numerous reports have also shown that procedural accidents occurred with a frequency of approximately 10% and mainly included bleeding, cyst infection, perforation, and stent migration/deviation. Rare cases of accidental punctures of the gallbladder have also been reported [43]. Bleeding during puncture is the most frequently encountered procedural accident, and bleeding associated with electric needles has been reported to account for 15.7% of cases, whereas that associated with non-electric needles accounted for 4.6% [44].

12.4.2 Endoscopic Necrosectomy

The basic target lesions are WON. The basic procedure is as follows:

1. By using a direct-view endoscope and an EUS-guided transgastric drainage, an indwelling guide wire is inserted into the WON cavity from the site where an indwelling stent has been placed.

2. The site of the fistula is forcibly expanded by using a balloon for dilating the digestive tract (diameter, approximately 18 mm) (Fig. 12.4a).
3. The endoscope itself is inserted into the WON cavity while the balloon is left inflated.
4. The balloon catheter is removed, and then an endoscope is inserted into the WON, and a lavage of the cavity is carried out, as well as a removal of necrotic materials (Fig. 12.4b).

This procedure is performed approximately twice a week, and the purpose is to cause the WON cavity to shrink and disappear. Although rare, procedural accidents consisting of air embolisms have been reported, and therefore, using CO_2 gas is recommended for air insufflation during the procedure [45, 46].

Lavage of the cavity with a physiological saline solution during the necrosectomy procedure, as well as that of the cavity by using an indwelling transnasal drainage tube placed after the necrosectomy procedure, is widely performed [47–51]. Meanwhile, Jurgensen et al. [52] reported having achieved full therapeutic effects without adding perfusion and lavage to endoscopic necrosectomy, and no clear evidence of the utility of lavage has yet been established.

In general, most reports have shown good therapeutic effects. In a report from a multicenter study conducted in Japan, Germany, and the United States (the studies were conducted on 57, 93, and 104 cases, respectively) [37, 38, 53], the treatment success rates were 75%, 80%, and 91.3%, respectively.

12.4.3 Procedural Accidents

In the aforementioned multicenter study conducted in Japan, Germany, and the United States, the incidence of procedural accidents and mortality rate were reportedly high in all cases (33% and 11%, 26% and 7.5%, and 14% and 6.7% incidence

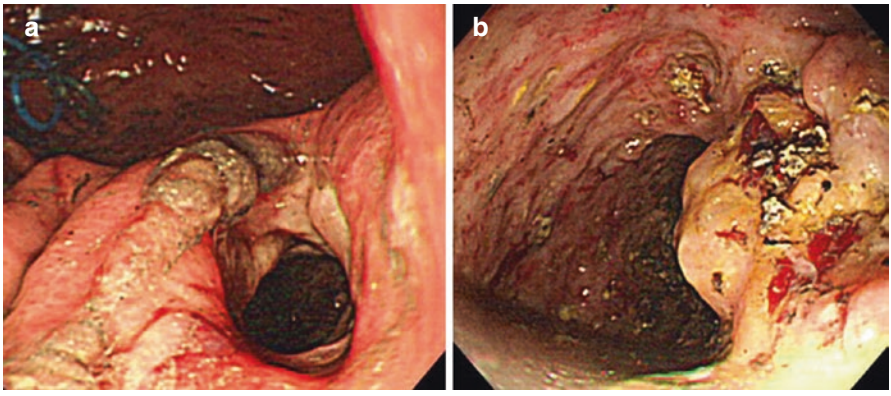

Fig. 12.4 Endoscopic necrosectomy. (**a**) The huge fistula between the stomach and WON is made using a large balloon. (**b**) An endoscope is inserted into the cavity of WON to perform necrosectomy

of procedural accidents and mortality rate, respectively). In detail, the procedural accidents included bleeding from the puncture site, shock, splenic aneurysm rupture, necrotic cavity wall perforation (retroperitoneal perforation), pneumoperitoneum, and air embolism. The most frequent procedural accident was bleeding. In addition, the reported causes of death include bleeding, sepsis, air embolism, multiple organ failure, and thrombosis of the superior mesenteric artery.

12.5 Conclusions

EUS-guided treatment has recently been widely used for the management of pancreatic and peripancreatic fluid collections; however, unless the most appropriate treatment for each case is selected and carried out after having firmly understood each patient's clinical condition, the usefulness of this therapeutic method may not be fully achieved. Fully understanding the information conveyed by this article is needed before conducting treatment by using the method described herein.

References

1. Bradley EL III. A clinically based classification system for acute pancreatitis. Summary of the international symposium on acute pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg. 1993;128:586–90.
2. Baron TH, Thaggard WG, Morgan DE, et al. Endoscopic therapy for organized pancreatic necrosis. Gastroenterology. 1996;111:755–64.
3. Baron TH, Morgan DE. Current concepts: acute necrotizing pancreatitis. N Engl J Med. 1999;340:1412–7.
4. Klöppel G. Pseudocysts and other non-neoplastic cyst of the pancreas. Semin Diagn Pathol. 2000;17:7–15.
5. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS, Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
6. Miyake H, Harada H, Kunichika K, et al. Clinical course and prognosis of chronic pancreatitis. Pancreas. 1987;2:378–85.
7. Irisawa A, Shibukawa G, Hikichi T, et al. Interventional EUS for pancreatic pseudocyst and walled-off necrosis. Nihon Shokakibyo Gakkai Zasshi. 2013;110:575–84. (in Japanese)
8. Vitas GJ, Sarr MG. Selected management of pancreatic pseudocysts: operative versus expectant management. Surgery. 1992;111:123–30.
9. Yeo CJ, Bastidas JA, Lynch-Nyhan A, et al. The natural history of pancreatic pseudocysts documented by computed tomography. Surg Gynecol Obstet. 1990;170:411–7.
10. Bradley EL, Clements JL Jr, Gonzalez AC. The natural history of pancreatic pseudocysts: a unified concept of management. Am J Surg. 1979;137:135–41.
11. O'Malley VP, Cannon JP, Postier RG. Pancreatic pseudocysts: cause, therapy, and results. Am J Surg. 1985;150:680–2.
12. Imamura H, Irisawa A, Takagi T, et al. Two cases of pancreatic abscess associated with penetration to the gastrointestinal tract during treatment using endoscopic ultrasound-guided drainage. Fukushima J Med Sci. 2007;53:39–49.

13. Besselink MG, Verwer TJ, Schoenmaeckers EJ, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg. 2007;142:1194–201.
14. Van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011;141: 1254–63.
15. Munn JS, Aranha GV, Greenlee HB, et al. Simultaneous treatment of chronic pancreatitis and pancreatic pseudocyst. Arch Surg. 1987;122:662–7.
16. Will U, Wanzar C, Gerlach R, et al. Interventional ultrasound-guided procedures in pancreatic pseudocysts, abscesses and infected necrosis treatment algorithm in a large single-center study. Ultraschall Med. 2011;32:176–83.
17. Seewald S, Ang TL, Kida M, Teng KY, Soehendra N, EUS 2008 Working Group. Evaluation of EUS-guided drainage of pancreatic-fluid collections (with video). Gastrointest Endosc. 2009;69:S13–21.
18. Varadarajulu S, Christein JD, Tamhane A, et al. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). Gastrointest Endosc. 2008;68:1102–11.
19. Park DH, Lee SS, Moon SH, et al. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. Endoscopy. 2009;41:842–8.
20. Gardner TB, Chahal P, Papachristou GI, et al. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. Gastrointest Endosc. 2009;69:1085–94.
21. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307: 1053–61.
22. Haghshenasskashani A, Laurence JM, Kwan V, et al. Endoscopic necrosectomy of pancreatic necrosis: a systematic review. Surg Endosc. 2011;25:3724–30.
23. Fogel EL. Endoscopic pancreatic necrosectomy. J Gastrointest Surg. 2011;15:1098–100.
24. Van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362:1491–502.
25. Giovannini M. What is the best endoscopic treatment for pancreatic pseudocysts? Gastrointest Endosc. 2007;65:620–3.
26. Yasuda I, Iwata K, Mukai T, et al. EUS-guided pancreatic pseudocyst drainage. Dig Endosc. 2009;21:S82–6.
27. Itoi T, Itokawa F, Tsuchiya T, et al. EUS-guided pancreatic pseudocyst drainage: simultaneous placement of stents and nasocystic catheter using double-guidewire technique. Dig Endosc. 2009;21:S53–6.
28. Siddiqui AA, Dewitt JM, Strongin A, et al. Outcomes of EUS-guided drainage of debris-containing pancreatic pseudocysts by using combined endoprosthesis and a nasocystic drain. Gastrointest Endosc. 2013;78:589–95.
29. Suzuki R, Irisawa A, Bhutani MS, et al. Ultrathin endoscope-guided trangastric nasocystic irrigation tube placement to manage paracolic gutter extension of pancreatic necrosis. Gastrointest Endosc. 2012;76:457–9.
30. Varadarajulu S, Phadnis M, Christein J, et al. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic wall-off pancreatic necrosis. Gastrointest Endosc. 2011;74:74–80.
31. Mukai S, Itoi T, Sofuni A, et al. Novel single transluminal gateway transcystic multiple drainages after EUS-guided drainage for complicated multilocular walled-off necrosis (with videos). Gastrointest Endosc. 2014;79:531–5.
32. Talreja JP, Shami VM, Ku J, et al. Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stents. Gastrointest Endosc. 2008;68: 1199–203.
33. Penn DE, Draganov PV, Wagh MS, et al. Prospective evaluation of the use of fully covered self-expanding metal stents for EUS-guided transmural drainage of pancreatic pseudocysts. Gastrointest Endosc. 2012;76:679–84.

34. Fabbri C, Luigiano C, Cennamo V, et al. Endoscopic ultrasound-guided transmural drainage of infected Pancreatic fluid collections with placement of covered self-expanding metal stents: a case series. Endoscopy. 2012;44:429–33.
35. Weilert F, Binmoeller KF, Shah JN, et al. Endoscopic ultrasound-guided drainage of pancreatic fluid collections with indeterminate adherence using temporary covered metal stents. Endoscopy. 2012;44:780–3.
36. Shah RJ, Shah JN, Waxman I, et al. Safety and efficacy of endoscopic ultrasound-guided drainage of pancreatic fluid collections with lumen-apposing covered self-expanding metal stents. Clin Gastroenterol Hepatol. 2015;13:747–52.
37. Saxena P, Singh VK, Messallam A, et al. Resolution of walled-off pancreatic necrosis by EUS-guided drainage when using a fully covered through-the-scope self-expandable metal stent in a single procedure (with video). Gastrointest Endosc. 2014;80:319–24.
38. Walter D, Will U, Sanchez-Yague A, et al. A novel lumen-apposing metal stent for endoscopic ultrasound-guided drainage of pancreatic fluid collections: a prospective cohort study. Endoscopy. 2015;47:63–7.
39. Itoi T, Binmoeller KF, Shah J, et al. Clinical evaluation of a novel lumen-apposing metal stent for endosonography guided pancreatic pseudocyst and gallbladder drainage (with video). Gastrointest Endosc. 2012;75:870–6.
40. Itoi T, Reddy DN, Yasuda I. New fully-covered self-expandable metal stent for EUS-guided intervention in infectious walled-off pancreatic necrosis (with video). J Hepatobiliary Pancreat Sci. 2013;20:403–6.
41. Yamamoto N, Isayama H, Kawakami H, et al. Preliminary report on a new, fully covered, metal stent designed for the treatment of pancreatic fluid collections. Gastrointest Endosc. 2013;77:809–14.
42. Bapaye A, Itoi T, Kongkam P, et al. New fully covered large-bore wide-flare removable metal stent for drainage of pancreatic fluid collections: results of a multicenter study. Dig Endosc. 2015;27:499–504.
43. Hikichi T, Irisawa A, Takagi T, et al. A case of transgastric gallbladder puncture as a complication during endoscopic ultrasound-guided drainage of a pancreatic pseudocyst. Fukushima J Med Sci. 2007;53:11–8.
44. Monkemuller KE, Baron TH, Morgan DE. Transmural drainage of pancreatic fluid collections without electrocautery using the Seldinger technique. Gastrointest Endosc. 1998;48:195–200.
45. Yasuda I, Nakashima M, Iwai T, et al. Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis (The JENIPaN study). Endoscopy. 2013;45:627–34.
46. Seifert H, Biermer M, Schmitt W, et al. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicenter study with long-term follow-up (the GEPARD study). Gut. 2009;58:1260–6.
47. Seewald S, Groth S, Omar S, et al. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm (videos). Gastrointest Endosc. 2005;62:92–100.
48. Charnley RM, Lochan R, Gray H, et al. Endoscopic necrosectomy as primary therapy in the management of infected pancreatic necrosis. Endoscopy. 2006;38:925–8.
49. Escourrou J, Shehab H, Buscail L, et al. Peroral transgastric/transduodenal necrosectomy: success in the treatment of infected pancreatic necrosis. Ann Surg. 2008;248:1074–80.
50. Coelho D, Ardengh JC, Eulalio JM, et al. Management of infected and sterile pancreatic necrosis by programmed endoscopic necrosectomy. Dig Dis. 2008;26:64–9.
51. Raczynski S, Teich N, Borte G, et al. Percutaneous transgastric irrigation drainage in combination with endoscopic necrosectomy in necrotizing pancreatitis (with videos). Gastrointest Endosc. 2006;64:420–4.
52. Jürgensen C, Neser F, Boese-Landgraf J, et al. Endoscopic ultrasound-guided endoscopic necrosectomy of the pancreas: is irrigation necessary? Surg Endosc. 2012;26:1359–63.
53. Gardner TB, Coelho-Prabhu N, Gordon SR, et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. Gastrointest Endosc. 2011;73:718–26.

Chapter 13
Ablation of Tumor Using EUS

Hyoung-Chul Oh, Woo Hyun Paik, Tae Jun Song, and Dong Wan Seo

Abstract EUS started as an imaging tool for deeply seated organ and pathology. After introduction of EUS-guided fine needle aspiration (FNA), EUS became an important tool for histologic diagnosis of pancreatic, peripancreatic, mediastinal, retroperitoneal, and gastrointestinal tract lesions. Therapeutic and interventional EUS started by modification of EUS-FNA technology and EUS-guided pseudocyst drainage is increasingly used for the management of pancreatic pseudocyst. EUS-guided ablation of pancreatic solid mass is also tried by ethanol injection. Radiofrequency ablation has long been used to ablate hepatic tumors via percutaneous route. Recently, EUS-guided RFA probe was introduced and is cautiously applied for the ablation of pancreatic solid tumors. EUS-guided pancreatic cyst ablation has been investigated in a variety of clinical studies. EUS-guided pancreatic cyst ablation is safe and feasible and shows potential to become an alternative to surgery. In this chapter, EUS-guided ablation of pancreatic cysts, EUS-guided injection therapy of benign solid mass, and EUS-guided RFA will be discussed.

Keywords Endoscopic ultrasonography • Pancreatic cyst • Ablation

13.1 EUS-Guided Pancreatic Cyst Ablation

13.1.1 Introduction

Pancreatic cyst becomes a surprisingly common finding in clinical practice because of widespread use of cross-sectional imaging. Although most pancreatic cysts are incidentally detected, pancreatic cysts represent a wide spectrum of

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histopathology, and neoplastic cysts are more prevalent than previously estimated. Some histologic types including mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs) have malignant potential [1, 2]. Discrimination of pancreatic cysts with malignant potential from those with benign behavior is an essential step in formulating a management strategy. High-resolution imaging and cyst fluid analysis improved the diagnostic accuracy. However, a substantial portion of pancreatic cysts remains indeterminate even after extensive evaluation [3]. Surgical resection of a pancreatic cystic neoplasm is associated with a perioperative morbidity of 20–40% and a mortality rate of 2% [4, 5]. This clinical dilemma has raised the need to develop a safe, effective, and minimally invasive approach for the treatment of pancreatic cysts. Based on the accumulated experience with EUS-guided fine needle aspiration (FNA) and pancreatic tissue ablation by EUS-guided injection of ethanol or other ablative agents [6–8], EUS-guided pancreatic cyst ablation has been investigated in a variety of clinical studies. In this section, procedural basics and special considerations of cyst ablation, as well as associated clinical outcomes, are summarized. Briefly, the terms used for cyst ablation may be defined as follows: ablation is related to the destruction of cyst epithelium; injection refers to forceful placement of an ablative agent into a cyst; and lavage is the act of repeated injections and aspiration.

13.1.2 EUS-Guided Cyst Ablation Technique

Imaging evaluation of pancreatic cystic lesion by EUS is an important first step to determine the internal structure in terms of septation, wall thickness, and the presence of a mural nodule or mass. Using a curvilinear-array echoendoscope, the cyst may be punctured via a transgastric or transduodenal route with a 22-gauge needle. The collection of cyst fluid provides important diagnostic material, as well as space for the ablative agent in the cyst cavity. After subtotal evacuation of the cyst, a bolus of ethanol is injected, equal in volume to the fluid initially aspirated, and the cyst is lavaged for 3–5 min, with alternate filling and emptying of the cavity. Alternatively, simple retention of injected ethanol for 3–5 min may be performed instead of lavage. During lavage, fresh ethanol may be injected after each reaspiration of injected ethanol. Following the lavage process, the injected ethanol is evacuated, leaving just enough fluid to outline the cyst cavity. A second ablative agent (a chemotherapeutic agent such as paclitaxel) may then be injected into and left in the cyst cavity; the total injection volume should not exceed the volume of aspirated fluid. During the procedure, the needle tip is carefully maintained within the cyst to avoid parenchymal injury or a leak in the cyst wall. After completion of the injection or lavage, the needle is removed from the cyst cavity (Fig. 13.1) [3, 9–12].

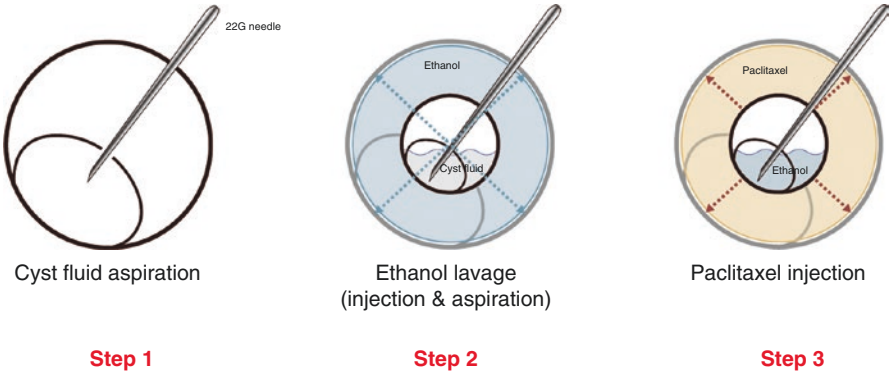

Fig. 13.1 Stepwise EUS-guided pancreatic cyst ablation therapy. Step 1: FNA within a septated cyst (*heavy black line*). Step 2: 5-min ethanol lavage of the cyst, followed by aspiration of the ethanol. Step 3: injection of paclitaxel into the cyst, resulting in the expansion of the cyst to its original diameter (Reprinted from Gastrointestinal Endoscopy, Volume 77 (4), Hyoung-Chul Oh and William R Brugge, EUS-guided pancreatic cyst ablation: a critical review (with video), 526–533, 2015, with permission from Elsevier)

13.1.2.1 Ablative Agents

Ethanol is an inexpensive, widely available, low-viscosity agent that is easy to inject through a small-gauge needle. Ethanol injected into hepatic cysts induces cell membrane lysis, protein denaturation, and vascular occlusion within 10 min but penetrates the fibrous capsule slowly [13, 14].

Paclitaxel, a widely used chemotherapeutic agent, inhibits cell processes that are dependent on microtubules. It is hydrophobic and viscous in nature and hence can exert a durable effect on the epithelium within the cyst cavity with a low risk of leakage [15]. Because of the high viscosity of its cosolvent, Cremophor (castor oil), the paclitaxel solution, needs to be diluted 1:1 in 0.9% normal saline solution (a final dose concentration of 3 mg/mL paclitaxel) for injection. However, a new formula of paclitaxel with a less viscous delivery vehicle (polymeric micelle) can be used without dilution (a dose concentration of 6 mg/mL) [3].

13.1.3 Clinical Trial Outcomes

To date, four clinical trials of cyst injection therapy [3, 9, 12, 16], three preliminary case series [17–19], one long-term follow-up report [10], and two case reports [20, 21] have been reported. These reports were summarized in Table 13.1.

In the initial pilot study [9], 25 patients underwent ethanol lavage and were followed for 6–12 months. Eight of twenty-three patients (35%) with complete follow-

Table 13.1 Summary of previous reports of EUS-guided cyst ablations

Authors	Patients, *n*	Ablative agent	Follow-up period	Complete resolution
Gan et al. [9]	25	5–80% ethanol	6–12 months	35% (8/23)
Oh et al. [17]	14	80/99% ethanol with paclitaxel	Median 9 months (6–23 months)	79% (11/14)
Oh et al. [18][a]	10	99% ethanol with paclitaxel	Median 8.5 months (6–18 months)	60% (6/10)
DeWitt et al. [16]	42	80% ethanol	3–4 months after second lavage	33% (12/36)
Oh et al. [3][b]	47	99% ethanol with paclitaxel	Median 20 months (12–44)	62% (29/27) ≥ (29/47)
Gomez et al. [12]	23	80% ethanol	Median 37 months (7–82)	9% (2/23)

[a]Included only patients with septated cyst
[b]Included study population of two preliminary reports [18, 19]

up had complete resolution. All septated cysts persisted despite ethanol ablation therapy. Five patients underwent surgical resection. All five patients had a diagnosis of MCN, and a variable degree of epithelial ablation (up to complete) was observed on surgical pathology.

To increase the ablative effect, a chemotherapeutic agent (paclitaxel) has been combined with ethanol ablation therapy [17]. It was hypothesized that the epithelial distortion by ethanol could allow the diffusion of paclitaxel in the injured epithelium. In a pilot feasibility study with ethanol and paclitaxel, 14 patients were followed for more than 6 months after injection therapy, and complete resolution was achieved in 11 patients. The cyst resolution rate (79%) was greater than the previously observed rate with ethanol alone (33%), suggesting a synergistic effect between ethanol and paclitaxel.

A randomized, double-blind trial of 42 patients comparing ethanol with saline solution lavage demonstrated further evidence of cyst ablation [16]. Ethanol lavage resulted in a significant decrease in cyst size at 3 months after initial ablation compared with saline solution alone. Thirty-three of 42 patients enrolled for the initial randomization underwent a second unblinded ethanol lavage. There was no significant difference in cyst size of subjects exposed to one or two injections of ethanol. Complete resolution as shown by CT scan was achieved in 33%.

The durable effect of cyst ablation is an important concern because cyst resolution achieved for a short-term period may not ensure the long-term ablative effect and ultimately the prevention of malignant transformation. In a clinical trial of 47 patients who underwent ethanol lavage and paclitaxel injection [3], 29 patients (62%) showed complete resolution of the cyst over a median follow-up of 22 months (range 12–44 months). The histopathologic extent of epithelial ablation among four resected cases ranged from 0 to 100%, and a spectrum of histopathologic changes including epithelial denudation with fibrosis and an atrophied epithelium was observed (Fig. 13.2). In another follow-up report [10], nine patients who had com-

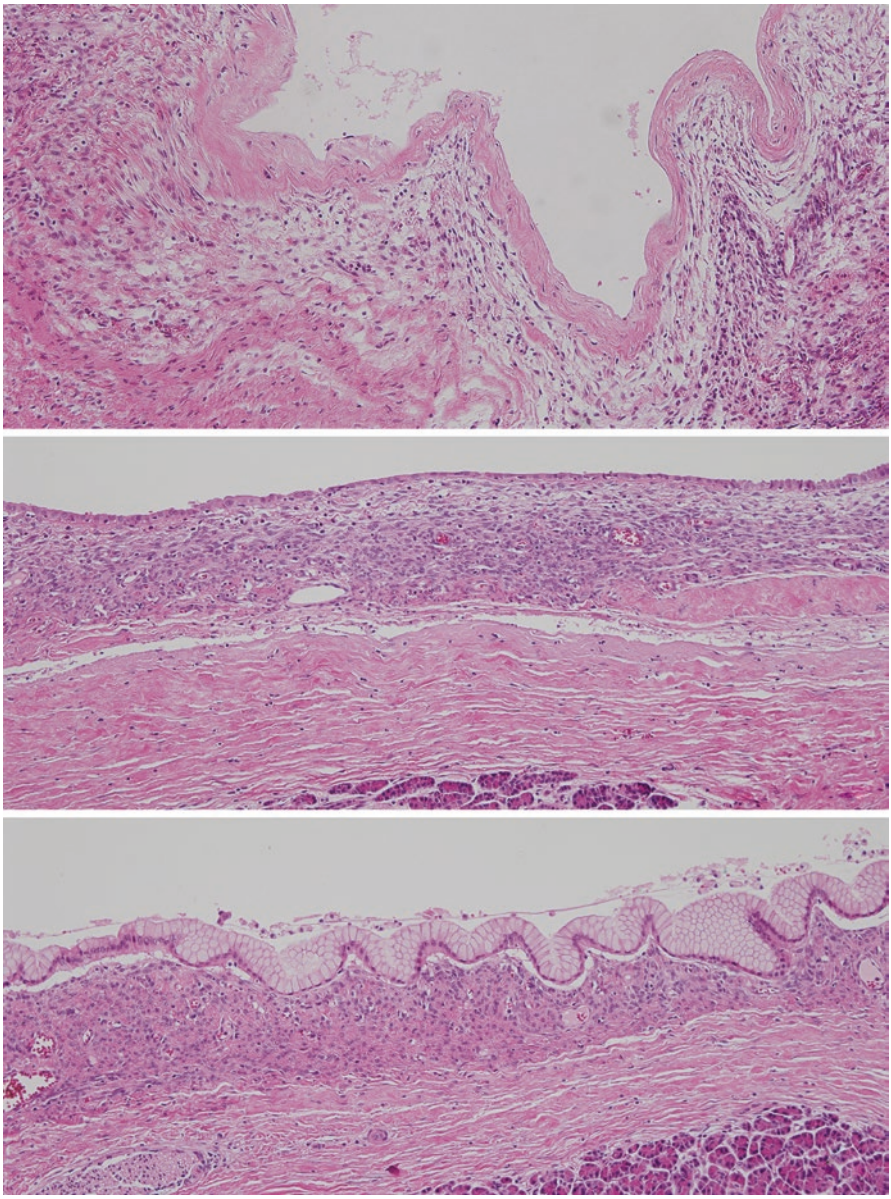

Fig. 13.2 The resected specimen showed variable degrees of histopathologic ablation in the cyst epithelial linings of mucinous cystadenoma with an ovarian-like stroma; epithelial linings were denuded and replaced by secondary fibrosis (D), were atrophied (A), or were mucinous (M) (Reprinted from Gastroenterology, Volume 140, Hyoung-Chul Oh et al. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cyst, 172–179, 2011, with permission from Elsevier)

plete resolution as shown on a CT scan after 1 or 2 ethanol lavages were followed over a median of 26 months (range 13–39 months). Cyst recurrence on CT scan was not observed in any patient. Imaging evidence of cyst resolution includes complete disappearance of cyst, small low-density focus, or residual calcification (Fig. 13.3). Imaging-based resolution may not correlate, however, with histologic ablation. Close monitoring should be continued even after complete disappearance, but surveillance policy may be modified based on risk analysis.

To improve the ablative effect of cyst ablation therapy, procedural techniques including a second needle pass at a different angle and booster ablation have been tried. In one case series of 13 patients with branch-duct IPMN [19], multiple sessions of cyst lavage were performed. Although cyst diameter and surface area showed no significant decrease after one ethanol lavage session, these parameters decreased after two ethanol lavage sessions. Complete resolution was achieved in 38% (5/13) only after two lavage sessions.

A study evaluated genomic in pancreatic cyst fluid following cyst ablation with ethanol and paclitaxel [22]. Analysis of postablation cyst fluid revealed elimination

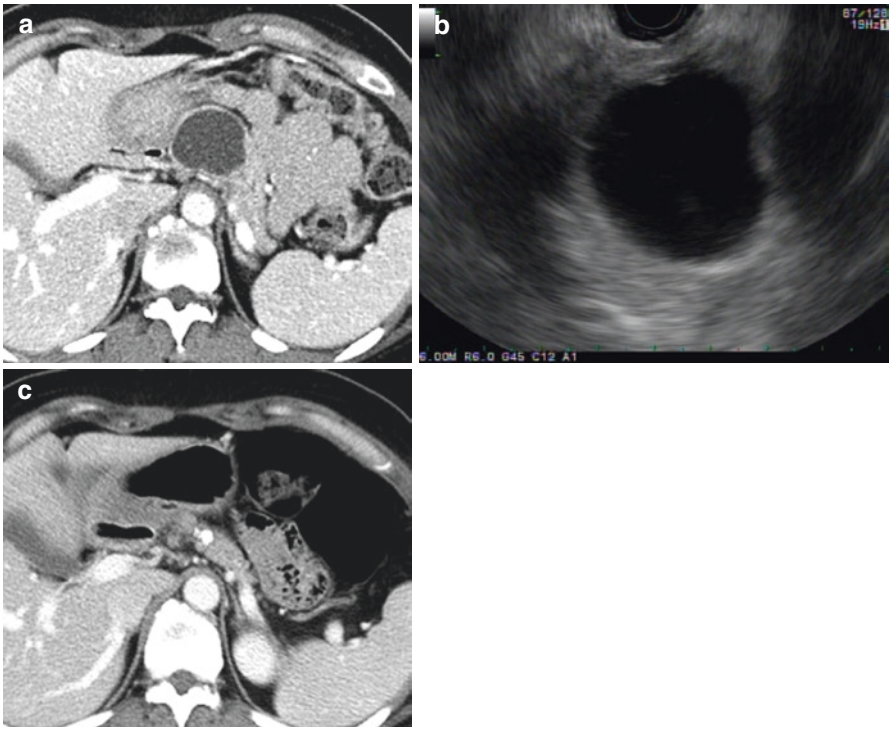

Fig. 13.3 (**a**, **b**) A 36-mm unilocular cyst in the body of the pancreas. (**c**) Dense calcification replaced the original cyst on follow-up CT scan at 30 months after cyst ablation (Reprinted from Gastrointestinal Endoscopy, Volume 77 (4), Hyoung-Chul Oh and William R Brugge, EUS-guided pancreatic cyst ablation: a critical review (with video), 526–533, 2015, with permission from Elsevier)

of all baseline mutations in 8 of 11 patients. Complete resolution was achieved in 10 out of 20 patients (50%) overall and in 5 of the 9 patients with postablation loss of all cyst fluid DNA mutations.

13.1.4 Safety of Cyst Ablation

Procedure-related adverse events reported in the four representative clinical trials are summarized in Table 13.2. Most adverse events were mild and self-limited. Abdominal pain just after cyst ablation was the most common acute complication. Contrary to initial concerns, the frequency of ablation-related pancreatitis was low (2.2%, 4/175). The risk of pancreatitis was increased if there was inadvertent injection of an ablative agent into the pancreatic parenchyma.

Venous obliteration and thrombosis in the venous system adjacent to the cyst have been reported in two patients who underwent ethanol lavage and paclitaxel injection [3, 21]. Extensive inflammation within and around the cyst induced by the injection itself or pericystic leak of the ablative agent may result in local extension of inflammation into the adjacent vessels. These adverse events may become serious because portal hypertension and collateral formation may develop. In addition, substantial difficulty may be encountered in subsequent surgical resection for the persistent cyst.

For prevention of procedure-related adverse events, it is important to maintain the needle in the visual plane and within the cyst cavity during the entire procedure. The optimal volume of ablative agent needs to be cautiously titrated, and an aggressive lavage procedure should be avoided, especially when a cyst is in close proximity to the portosplenic venous system.

13.1.5 Proposed Indications

EUS-guided pancreatic cyst ablation is still an investigational modality and should be judiciously used in select patients based on strict inclusion criteria that may predict high treatment efficacy while minimizing procedure-related risks. The ideal

Table 13.2 Cyst ablation-related complications

	Gan et al. [9] (n = 25)	DeWitt et al. [16] (n = 75)	Oh et al. [3] (n = 52)	Gomez et al. [12] (n = 23)	Overall (n = 175)
Complications, n (%)					
Abdominal pain	0	11	1	1	13 (7.4)
Acute pancreatitis	0	2	1	1	4 (2.2)
Fever	0	0	1	0	1 (0.6)
Pericystic spillage	0	0	1	0	1 (0.6)
Splenic vein obliteration	0	0	1	0	1 (0.6)

n total number of cases who underwent one session of EUS-guided cyst ablation

cyst candidate for ablation should have (1) a benign appearance without any malignant feature, (2) a diameter between 2 and 4 cm, (3) a unilocular or oligolocular morphology, and (4) no communication with the main pancreatic duct.

Patient selection should be based on the specific type of cyst. MCN is the ideal target for EUS-guided cyst ablation because it has malignant potential and is often unilocular. Cyst ablation should be considered only when the viscous mucinous cyst fluid can be effectively aspirated. There are some concerns about the treatment of a benign cyst such as serous cystadenoma (SCA). Because SCAs may exhibit significant growth, they may ultimately lead to cyst-related symptom [23, 24]. Cyst ablation may be considered for macrocystic SCAs that demonstrate a size increase during follow-up.

13.1.6 Future Perspectives

EUS-guided cyst ablation is a promising modality that may become an alternative to surgical resection. For this paradigm shift, some limitations associated with cyst ablation need to be overcome. Procedural modifications may improve the treatment efficacy by (1) a second needle pass in septated cysts, (2) a booster ablation for a large cyst that demonstrates a plateau in response after initial ablation, and (3) maintenance ethanol concentration in the cyst during ethanol lavage [25]. Discovery and development of novel ablative agents that may exert durable activity by using slow-releasing formula may provide improved ablation effect [8].

13.2 EUS-Guided Pancreatic Solid Mass Ablation

13.2.1 Introduction

There are various types of pancreatic solid tumors other than ductal adenocarcinoma, including neuroendocrine tumor and solid pseudopapillary neoplasm. The pancreatic solid tumors other than adenocarcinoma are rare and show heterogeneous behavior. The strategy for treating small pancreatic tumor is surgical resection. However, despite advances in surgery, the perioperative morbidity of pancreatic surgery is still high, even in large-volume centers.

EUS is a well-established modality for the diagnosis of pancreatobiliary disease. Recently, EUS is used as a treatment modality for pancreatic tumors or biliary drainage as well. EUS-guided pancreatic cyst ablation has been investigated in a variety of clinical studies and now used as an alternative treatment option in some institutions. However, only a few attempts using ethanol ablation to treat pancreatic solid tumors have been reported. The safety and efficacy of EUS-guided ethanol ablation therapy for pancreatic solid tumors still remain unclear.

13.2.2 Detection and Ablation of Pancreatic Solid Tumors Under EUS Guidance

EUS is one of the most sensitive imaging techniques for identifying small pancreatic lesions, though the sensitivity is operator-dependent [26]. EUS plays an important role in localizing small pancreatic tumors, especially insulinoma, and the detection rate is reported to be approximately 90% [27]. There has been the development of complementary techniques with EUS, and contrast-enhanced harmonic EUS (CEH-EUS) is helpful for the detection and characterization of solid pancreatic tumors [28]. Before ablation therapy, EUS-guided fine needle aspiration and biopsy is also possible for the histological confirmation of pancreatic solid tumor.

The technique of EUS-guided pancreatic solid tumor ablation is similar to that of pancreatic cyst. Briefly, under real-time imaging obtained by curvilinear-array echoendoscope, puncture of pancreatic tumor is performed using 22- or 19-gauge conventional needle. Then, ethanol is injected as the needle was gently withdrawn from deep within the tumor. The injection was finished when hyperechoic blush was seen inside the whole tumor (Fig. 13.4). To minimize procedure-related adverse events, injection of small amount of ethanol with multiple repeated sessions is recommended [29].

13.2.3 Clinical Study Outcomes

To date, several case reports and only three preliminary case series have been reported (Table 13.3) [29–31]. In 2006, Jurgensen et al. reported an insulinoma case that was treated successfully by using EUS-guided ethanol ablation for the first time. After that, several case reports about EUS-guided ethanol ablation of insulinoma have been documented. Most of the cases reported mild acute pancreatitis after the procedure, and one case reported a life-threatening complication, the occurrence of hematoma, and ulceration of the duodenal wall [32].

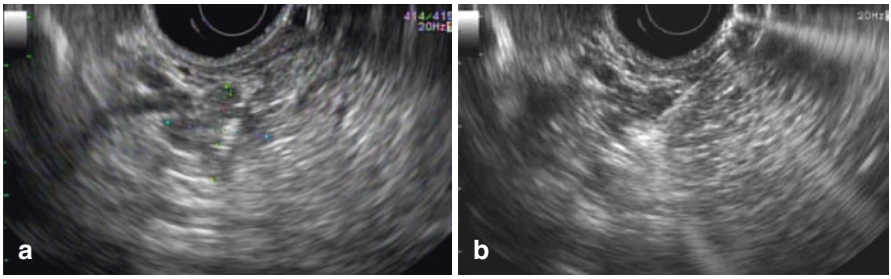

Fig. 13.4 (**a**) EUS-guided puncture of a nonfunctioning neuroendocrine tumor. (**b**) During the injection of ethanol, the hyperechoic blush was seen inside the tumor

Table 13.3 Summary of EUS-guided ethanol ablation for pancreatic solid tumor

Reference	*n*	Diagnosis	Size (mm)	Follow-up period	Response	Early adverse events	Late adverse events
Levy et al. [29]	5	5 insulinomas	8–21	Median 13 months (range, 5–38 months)	Symptomatic improvement in all patients[a]	–	–
Park et al. [30]	11 (14 lesions)	10 nonfunctioning NETs and 4 insulinomas	6–19	Median 370 days (range, 152–730 days)	62% (8/13)[b]	36% (4/11; 3 mild pancreatitis and 1 abdominal pain)	9% (1/11; pancreatic duct stricture)
Paik et al. [31]	8	2 SPNs, 3 insulinomas, 1 gastrinoma, and 2 nonfunctioning NETs	7–29	Median 16.5 months (range, 5.4–55.3 months)	75% (6/8)	50% (4/8; 2 abdominal pain, 1 fever, and 1 severe acute pancreatitis)	13% (1/8, local recurrence)

[a]Image follow-up was not performed
[b]One patient was excluded due to follow-up loss

In 2012, Levy et al. [29] reported the feasibility of EUS-guided ethanol ablation of insulinoma in symptomatic patients considered to be poor surgical candidates or after incomplete surgical resection. All five patients who underwent ethanol injection under EUS guidance experienced complete absence of hypoglycemia-related symptoms or marked clinical improvement after the procedure. They experienced no procedure-related adverse events since they used lower volumes of alcohol and repeated treatment sessions, aiming for symptom relief rather than complete ablation of the tumor.

In 2015, Park et al. [31] reported a pilot study about EUS-guided ethanol ablation for small pancreatic neuroendocrine tumors including nonfunctioning neuroendocrine tumors. They included 11 patients with 14 tumors: 10 nonfunctioning neuroendocrine tumors and 4 insulinomas. At 3 months after the intervention, treatment response was assessed according to the enhanced residual tumor areas based on contrast-enhanced computed tomography and/or CEH-EUS 3 months later the intervention. If there is still an enhanced lesion within the tumor, repeated session of ethanol ablation was performed. Finally, the complete response rate was 62% (8/13), and none of enrolled patients developed progressive disease during follow-up. There were four adverse events after the procedure, three mild pancreatitis and one abdominal pain. One patient, who had been previously treated for mild pancreatitis, developed pancreatic duct stricture requiring stent placement 1 month after the ablation.

13.2.4 Special Considerations

The assessment of treatment outcome is an important issue. In case of functioning neuroendocrine tumors, treatment outcome can be assessed by hormonal assay and symptomatic improvement. Nonfunctioning tumor or other pancreatic solid tumors

are mainly assessed by using radiologic or EUS imaging. In these circumstances, evaluation of treatment outcome with imaging only seems to be inappropriate, and the main problem is whether imaging findings guarantees actual complete remission of the tumor. The adjunctive use of CEH-EUS to facilitate the detection of necrotic area would be helpful (Fig. 13.5).

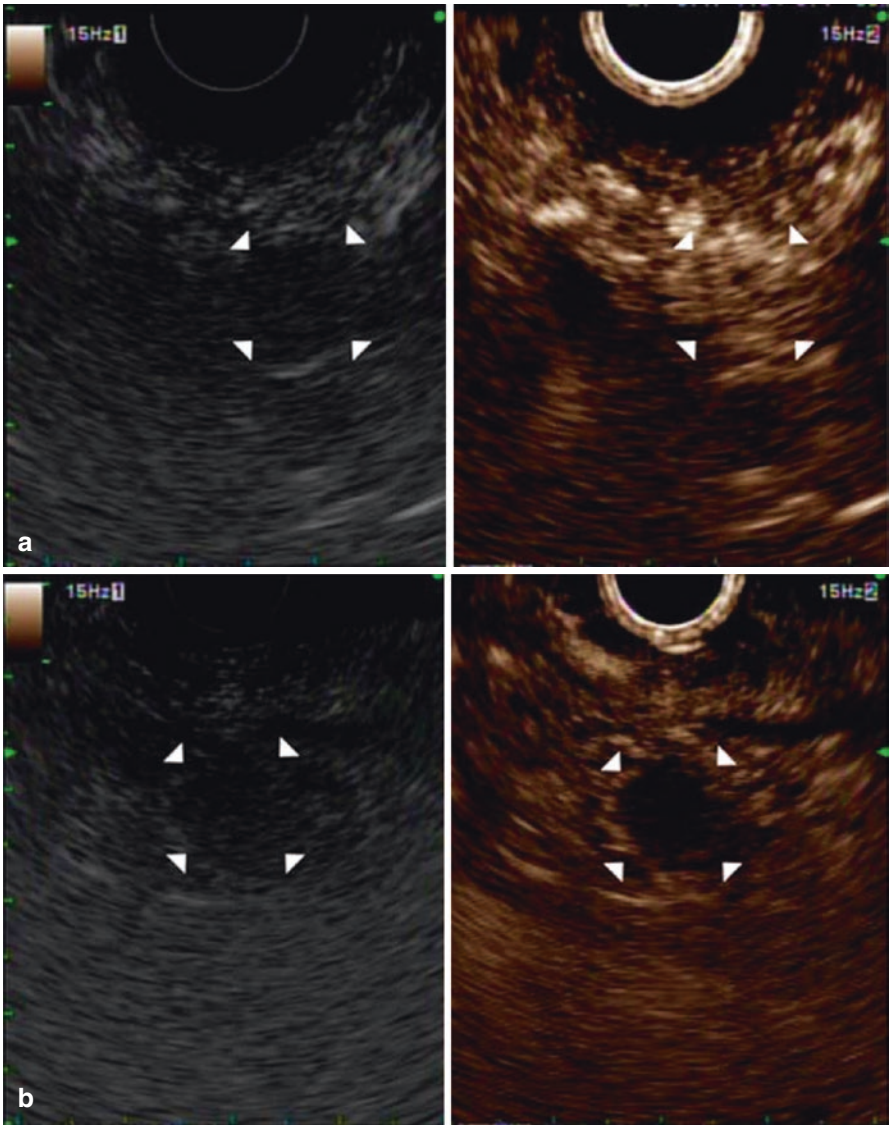

Fig. 13.5 (**a**) An early homogenous enhancing insulinoma on contrast-enhanced harmonic EUS (CEH-EUS) before ethanol ablation therapy. (**b**) After treatment, no enhancement inside the tumor could be observed on CEH-EUS (Reprinted from Paik et al. [31])

The main concern of ethanol ablation therapy is the risk of acute pancreatitis. Because severe acute pancreatitis can occur during EUS-guided ethanol ablation therapy, indiscriminate treatment should be avoided and the procedure must be carefully performed. As mentioned above, using small aliquots of ethanol at each session, careful intratumoral injection of optimal volume of ethanol under real-time EUS guidance, and accurate targeting of the tumor would be important.

13.2.5 Future Perspectives

EUS-guided ablation of pancreatic solid tumor is still under investigation. In case of functioning neuroendocrine tumors, it can be a good treatment option. Since functioning neuroendocrine tumors are usually small and sometimes demonstrate as multiple lesions [33], EUS-guided ablation therapy can show a complementary role with surgical treatment. However, in case of other pancreatic solid tumors such as nonfunctioning tumor or solid pseudopapillary neoplasm, EUS-guided ablation therapy carries some issues. The major concerns of local ablation therapy are local recurrence and distant metastasis of the tumor. Since pancreatic solid tumors are rare and the natural history of these tumors is protean, selection of the patients must be based on strict criteria.

In conclusion, EUS-guided ethanol ablation therapy seems to be a promising option for patients with small solid pancreatic tumors and could be used to complement radical resection. However, safety-related issues such as acute pancreatitis and tumor recurrence should be considered.

13.3 EUS-Guided Radiofrequency Ablation

13.3.1 Introduction

Endoscopic ultrasound (EUS) is a useful method for the diagnosis of lesions within and adjacent to the pancreas. EUS-guided procedures have been used for treating the various types of pancreatic diseases including pancreatic cancers [3]. Therapeutic EUS rapidly gained a role for a variety of therapeutic applications in the treatment of cancers. Particularly, therapeutic EUS has an evolving role in the field of pancreatic tumor therapy.

Percutaneous radiofrequency ablation (RFA) has been commonly used to treat in liver, thyroid, and kidney cancer. In recent times, EUS devices are revolutionized with the ability to treat the lesions such as pancreatic cancer using RFA which is the similar method of doing EUS-guided fine needle aspiration procedure [34]. The RFA electrode is advanced through the EUS scope's working chan-

nel. It is described as a new technique to demonstrate clinical trials, safety, as well as new indications.

13.3.2 Principles of RFA System

RFA is physically based on radiofrequency current about 350 KHz (electromagnetic wave) and a high-frequency alternating current which causes vibration of local ions, thereby producing controlled frictional heat to destroy the tissue. It is transmitted between an active electrode and a reference electrode, establishing lines of electrical field that produces ionic oscillation, which creates thermal heat around the tip of the electrode. Eventually, it will destroy the tumor. The thermal heat around the electrode is generated and induces coagulation necrosis. The temperature at a certain distance from the RFA electrode will be decreased because of heat transfer by convection or conduction. The delivery of RF energy is directly proportional to the amplitude of oscillations, and the volume of coagulation necrosis will be evaluated according to the temperature and time.

With regard to needle-type electrode, R (radius around electrode) is correlated with T (temperature). Based on T $1/r4$ formulation, RF ablation effectively causes thermal damage around the tip of the electrode.

The "heat sink" effect of RFA may occur in treating tumors adjacent to large vessels. The inflow of cold blood at body temperature may impair the heating of the tumor cells closest to the blood vessels. Heat sink effect is one of the factors we should consider during RFA procedure.

13.3.3 EUS-Guided RFA

Generally, the different size and shape of needle are not limited to the percutaneous RFA procedure. Various types of needle for percutaneous RFA can be modified into different probe design according to the size and the shape of tumors. However, EUS-guided RFA probe has some limitations of probe design. The length of needle should be more than 120 cm and requires flexibility in order to get through the working channel of an endoscope. The tip of the needle should be well visualized under EUS guidance.

EUSRA RF electrode (STARmed Co. Ltd.,) and Habib EUS-RFA catheters (EMcision Ltd.,) are now available for EUS-guided RFA of pancreatic tumors. These electrodes have different concepts of RFA technique. Habib probe uses a flexible 1-Fr electrode and should be inserted through EUS-FNA needle for RFA procedure. However, the volume size which can be ablated is limited due to high impedance. On the other hand, the distal end of EUSRA RF electrode is needle-shaped and echogenic on EUS. It is less flexible but has the ability to create large ablation zone due to the cooling system to decrease the impedance (Fig. 13.6).

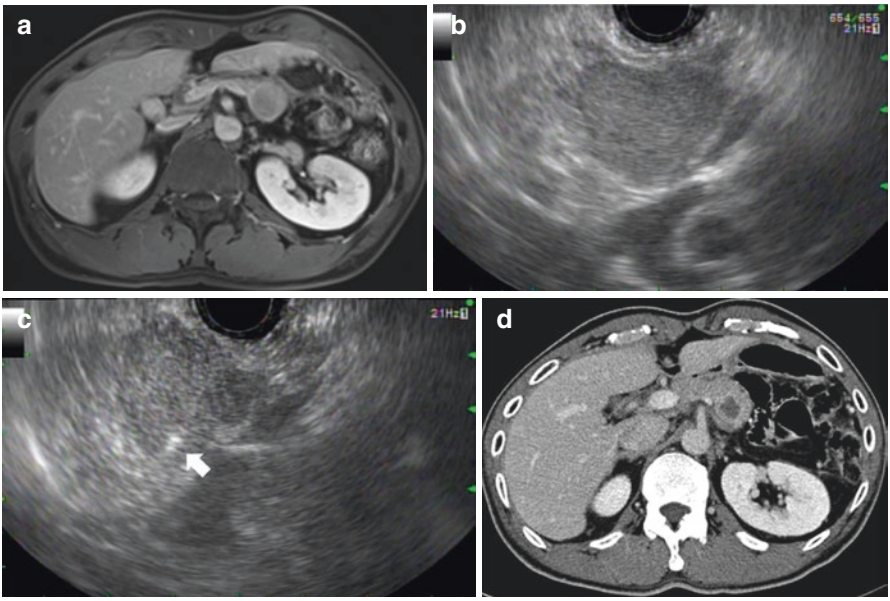

Fig. 13.6 (**a**) MRI shows neuroendocrine tumor at the pancreas body. (**b**) EUS shows well-demarcated hypoechoic mass at the pancreas. (**c**) EUS-guided RFA began at the right distal portion of the mass on EUS image (*arrow*). The ablation was repeated at different sites. (**d**) Follow-up CT on 1 month after RFA shows necrosis of the tumor

13.3.3.1 EUS-Guided RFA in Animal Studies

In 1999, the EUS-guided RFA in a porcine model was first studied by Goldberg and colleagues [35]. Under EUS guidance, a total of 13 pigs underwent RFA of the pancreatic tissue. During RF application, about 1–2-cm echogenic bubbles around ablation area were found. After RFA procedure, the pigs were sacrificed immediately for gross examination. The result showed acute coagulation necrosis of target lesion. Subsequently, modified RFA probes were tested in 2008 [36]. Carrara et al. reported their experiences with a hybrid cryotherm probe combining bipolar RFA with cryotechnology. They performed EUS-RFA for pancreas in 14 pigs and all animals well tolerated the procedure without mortality. However, there were several adverse events including necrotizing pancreatitis with peritonitis, pancreatitis without clinical symptoms, burn of the gastric wall, and adhesions between the pancreas and the gut. In 2009, Varadarajulu and colleagues used an umbrella-shaped retractable monopolar electrode array to ablate porcine livers [37]. The EUS-guided RFA of the porcine pancreas using Habib electrode was reported by Gaidhane et al. in 2012 [38]. Kim and colleagues also reported the feasibility, efficacy, and safety of EUS-RFA for porcine pancreatic body and tail in 2012. Moreover, Sethi et al. reported EUS-guided lymph node ablation with a RFA electrode in 2014 [39].

13.3.3.2 EUS-Guided RFA in Clinical Studies

Until recent years, there is a lack of clinical study on EUS-guided RFA (Table 13.4). In 2015, EUS-guided RFA for the cystic neoplasms and neuroendocrine tumors of pancreas was reported by Pai and colleagues [40]. A 1.2-mm Habib EUS-RFA was inserted through a 19- or 22-gauge FNA needle and treated the cystic neoplasms and neuroendocrine tumors of the pancreas using a 1-Fr wire Habib electrode. A total of eight patients were included. Among them, six patients had a pancreatic cystic neoplasm and the mean size of the cystic neoplasm was 36.5 mm. Two of them had neuroendocrine tumors with the mean size of 27.5 mm. It resulted in effective coagulation necrosis in the center of neuroendocrine tumor. As for the cystic neoplasm, 3–6-month follow-up showed completed resolution in two patients and 48% deduction in the volume size. The two patients had mild abdominal pain without major adverse events.

In recent human clinical study, Song et al. reported the technical feasibility and safety of EUS-guided RFA for advanced pancreatic cancer [34]. EUS-guided RFA was successfully performed in six patients. After the procedure, two patients experienced mild abdominal pain, but there was no serious adverse event. RFA for advanced pancreatic cancer is a type of cytoreductive therapy that does not aim to completely eradicate the tumor [41]. Combined multi-treatment followed by RFA is needed in addition to local control of the disease [42]. Several studies reported that thermal ablation therapy can stimulate and modulate the systemic immune response against the tumor [43, 44].

Table 13.4 The results of endoscopic ultrasound-guided radiofrequency ablation of the pancreas

	Pai et al. [40]	Song et al. [34]
Male: female	1:7	1:5
Median age (years, range)	65 (27–82)	62 (43–73)
Diagnosis	Pancreatic cyst ($n = 6$) Neuroendocrine tumor ($n = 2$)	Pancreatic cancer ($n = 6$)
RFA electrode	The Habib™ EUS-RFA probe	The EUSRA™ probe
Shape of electrode	1 Fr wire shape (inserted inside the hollow of the biopsy needle)	Needle shape (18-gauge integrated type)
Ablation power	5–25 W	20–50 W
Ablation time	90–120 s at one site and repeated as needed	10 s at one site and repeated as needed
Adverse events		
Major adverse events	0	0
Mild abdominal pain	3	1

13.3.4 Safety and Application of RFA

RFA demonstrated the ability to induce expectable and reproducible thermal injury on target tissue, unlike to the other previous anticancer therapy. Nevertheless, there is the potential risk of thermal damage to structures adjacent to a target lesion because of inaccurate targeting. The pancreas is a highly thermosensitive organ, and the thermal ablation of normal pancreatic tissue may lead to inflammation with edema and fibrotic and cystic transformation.

Intraoperative RFA was tried in patients with unresectable pancreatic cancer, and this procedure can be performed under clear view of the lesions with high energy. However, major adverse events including severe necrotizing pancreatitis and serious bleeding were reported following the procedure [45, 46]. Patients got injuries to a large artery or portal vein during the procedure. However, serious abdominal bleeding can occur several days after the procedure. Therefore, it is important to ablate lesions with sufficient safety margin. If adequate safety margin can be achieved, EUS-guided RFA can also be applied to other organs with difficult percutaneous access such as malignant lymph node metastases and malignant tumors of the liver, kidney, and adrenal glands.

In animal studies, adverse events including symptomatic pancreatitis, peritonitis, and gastric and intestinal wall injury were reported during/after EUS-guided RFA [47]. Up to now, no serious adverse events were observed after EUS-guided RFA in clinical studies.

13.3.5 Future Perspectives

The potential advantages of EUS-guided RFA approach are real-time imaging for target lesion. EUS-RFA may be a technically feasible and safe modality for the treatment of various pancreatic tumors. The effective tumor destruction can be achieved by combining tumor ablation with adjuvant therapy.

EUS-guided RFA of pancreatic tumor is still investigational in many areas such as variety types of electrodes and a method of RF delivery, and it needs more data and refinement of devices. EUS-guided RFA has great potential for future treatment of various pancreatic tumors and will be applied to other organs.

References

1. Brugge WR, Lauwers GY, Sahani D, Fernandez-del Castillo C, Warshaw AL. Cystic neoplasms of the pancreas. N Engl J Med. 2004;351(12):1218–26.
2. Oh HC, Kim MH, Hwang CY, Lee TY, Lee SS, Seo DW, et al. Cystic lesions of the pancreas: challenging issues in clinical practice. Am J Gastroenterol. 2008;103(1):229–39; quiz 8, 40. https://doi.org/10.1111/j.1572-0241.2007.01558.x. AJG1558 [pii].

3. Oh HC, Seo DW, Song TJ, Moon SH, Park DH, Soo Lee S, et al. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. Gastroenterology. 2011;140(1):172–9. https://doi.org/10.1053/j.gastro.2010.10.001. S0016-5085(10)01458-7 [pii].
4. Allen PJ, D'Angelica M, Gonen M, Jaques DP, Coit DG, Jarnagin WR, et al. A selective approach to the resection of cystic lesions of the pancreas: results from 539 consecutive patients. Ann Surg. 2006;244(4):572–82. https://doi.org/10.1097/01.sla.0000237652.84466.54. 00000658-200610000-00012 [pii].
5. Gaujoux S, Brennan MF, Gonen M, D'Angelica MI, DeMatteo R, Fong Y, et al. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. J Am Coll Surg. 2011;212(4):590–600.; discussion 600–3. https://doi.org/10.1016/j.jamcollsurg.2011.01.016.
6. Aslanian H, Salem RR, Marginean C, Robert M, Lee JH, Topazian M. EUS-guided ethanol injection of normal porcine pancreas: a pilot study. Gastrointest Endosc. 2005;62(5):723–7. https://doi.org/10.1016/j.gie.2005.06.048. S0016-5107(05)02537-X [pii].
7. Matthes K, Mino-Kenudson M, Sahani DV, Holalkere N, Brugge WR. Concentration-dependent ablation of pancreatic tissue by EUS-guided ethanol injection. Gastrointest Endosc. 2007;65(2):272–7. https://doi.org/10.1016/j.gie.2006.04.043. S0016-5107(06)01919-5 [pii].
8. Matthes K, Mino-Kenudson M, Sahani DV, Holalkere N, Fowers KD, Rathi R, et al. EUS-guided injection of paclitaxel (OncoGel) provides therapeutic drug concentrations in the porcine pancreas (with video). Gastrointest Endosc. 2007;65(3):448–53.
9. Gan SI, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc. 2005;61(6):746–52.
10. DeWitt J, DiMaio CJ, Brugge WR. Long-term follow-up of pancreatic cysts that resolve radiologically after EUS-guided ethanol ablation. Gastrointest Endosc. 2010;72(4):862–6. https://doi.org/10.1016/j.gie.2010.02.039. S0016-5107(10)00251-8 [pii].
11. Oh HC, Brugge WR. EUS-guided pancreatic cyst ablation: a critical review (with video). Gastrointest Endosc. 2013;77(4):526–33. https://doi.org/10.1016/j.gie.2012.10.033.
12. Gomez V, Takahashi N, Levy MJ, McGee KP, Jones A, Huang Y, et al. EUS-guided ethanol lavage does not reliably ablate pancreatic cystic neoplasms (with video). Gastrointest Endosc. 2016;83(5):914–20. https://doi.org/10.1016/j.gie.2015.08.069.
13. Bean WJ, Rodan BA. Hepatic cysts: treatment with alcohol. AJR Am J Roentgenol. 1985;144(2):237–41. https://doi.org/10.2214/ajr.144.2.237.
14. Gelczer RK, Charboneau JW, Hussain S, Brown DL. Complications of percutaneous ethanol ablation. J Ultrasound Med. 1998;17(8):531–3.
15. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med. 1995;332(15):1004–14. https://doi.org/10.1056/NEJM199504133321507.
16. DeWitt J, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. Gastrointest Endosc. 2009;70(4):710–23. https://doi.org/10.1016/j.gie.2009.03.1173. S0016-5107(09)01716-7 [pii].
17. Oh HC, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. Gastrointest Endosc. 2008;67(4):636–42. https://doi.org/10.1016/j.gie.2007.09.038. S0016-5107(07)02811-8 [pii].
18. Oh HC, Seo DW, Kim SC, Yu E, Kim K, Moon SH, et al. Septated cystic tumors of the pancreas: is it possible to treat them by endoscopic ultrasonography-guided intervention? Scand J Gastroenterol. 2009;44(2):242–7. https://doi.org/10.1080/00365520802495537. 904749592 [pii].
19. DiMaio CJ, DeWitt JM, Brugge WR. Ablation of pancreatic cystic lesions: the use of multiple endoscopic ultrasound-guided ethanol lavage sessions. Pancreas. 2011;40(5):664–8. https://doi.org/10.1097/MPA.0b013e3182128d06.
20. Oh HC, Seo DW, Song TJ. Resolution of a septated pancreatic cyst by booster endoscopic ultrasonography-guided ablation. J Dig Dis. 2011;12(6):497–9. https://doi.org/10.1111/j.1751-2980.2011.00538.x.

21. Oh HC, Seo DW, Kim SC. Portal vein thrombosis after EUS-guided pancreatic cyst ablation. Dig Dis Sci. 2012;57(7):1965–7. https://doi.org/10.1007/s10620-012-2103-x.
22. DeWitt JM, Al-Haddad M, Sherman S, LeBlanc J, Schmidt CM, Sandrasegaran K, et al. Alterations in cyst fluid genetics following endoscopic ultrasound-guided pancreatic cyst ablation with ethanol and paclitaxel. Endoscopy. 2014;46(6):457–64. https://doi.org/10.1055/s-0034-1365496.
23. Tseng JF, Warshaw AL, Sahani DV, Lauwers GY, Rattner DW, Fernandez-del CC. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. Ann Surg. 2005;242(3):413–9; discussion 9–21. 00000658-200509000-00012 [pii].
24. Khashab MA, Shin EJ, Amateau S, Canto MI, Hruban RH, Fishman EK, et al. Tumor size and location correlate with behavior of pancreatic serous cystic neoplasms. Am J Gastroenterol. 2011;106(8):1521–6. https://doi.org/10.1038/ajg.2011.117.
25. Xu XX, Du Y, Yang HF, Zhang Q, Li Y, Zee CS. CT-guided sclerotherapy with ethanol concentration monitoring for treatment of renal cysts. AJR Am J Roentgenol. 2011;196(1):W78–82. https://doi.org/10.2214/AJR.10.4671.
26. Puli SR, Kalva N, Bechtold ML, et al. Diagnostic accuracy of endoscopic ultrasound in pancreatic neuroendocrine tumors: a systematic review and meta analysis. World J Gastroenterol. 2013;19:3678–84.
27. Metz DC, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. Gastroenterology. 2008;135:1469–92.
28. Kitano M, Sakamoto H, Kudo M. Endoscopic ultrasound: contrast enhancement. Gastrointest Endosc Clin N Am. 2012;22:349–58, xi.
29. Levy MJ, Thompson GB, Topazian MD, et al. US-guided ethanol ablation of insulinomas: a new treatment option. Gastrointest Endosc. 2012;75:200–6.
30. Park do H, Choi JH, Oh D, et al. Endoscopic ultrasonography-guided ethanol ablation for small pancreatic neuroendocrine tumors: results of a pilot study. Clin Endosc. 2015;48:158–64.
31. Paik WH, Seo DW, Dhir V, Wang HP. Safety and efficacy of EUS-guided ethanol ablation for treating small solid pancreatic neoplasm. Medicine (Baltimore). 2016;95:e2538.
32. Deprez PH, Claessens A, Borbath I, et al. Successful endoscopic ultrasound-guided ethanol ablation of a sporadic insulinoma. Acta Gastroenterol Belg. 2008;71:333–7.
33. Kim MK. Endoscopic ultrasound in gastroenteropancreatic neuroendocrine tumors. Gut Liver. 2012;6:405–10.
34. Song TJ, Seo DW, Lakhtakia S, et al. Initial experience of EUS-guided radiofrequency ablation of unresectable pancreatic cancer. Gastrointest Endosc. 2016;83(2):440–3.
35. Goldberg SN, Mallery S, Gazelle GS, et al. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. Gastrointest Endosc. 1999;50:392–401.
36. Carrara S, Arcidiacono PG, Albarello L, et al. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. Endoscopy. 2008;40:321–6.
37. Varadarajulu S, Jhala NC, Drelichman ER. EUS-guided radiofrequency ablation with a prototype electrode array system in an animal model (with video). Gastrointest Endosc. 2009;70:372–6.
38. Gaidhane M, Smith I, Ellen K, et al. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of the pancreas in a porcine model. Gastroenterol Res Pract. 2012;2012:431451.
39. Sethi A, Ellrichmann M, Dhar S, et al. Endoscopic ultrasound-guided lymph node ablation with a novel radiofrequency ablation probe: feasibility study in an acute porcine model. Endoscopy. 2014;46:411–5.
40. Pai M, Habib N, Senturk H, et al. Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg. 2015;7:52–9.
41. Frigerio I, Girelli R, Giardino A, et al. Short term chemotherapy followed by radiofrequency ablation in stage III pancreatic cancer: results from a single center. J Hepatobiliary Pancreat Sci. 2013;20:574–7.

42. Cantore M, Girelli R, Mambrini A, et al. Combined modality treatment for patients with locally advanced pancreatic adenocarcinoma. Br J Surg. 2012;99(8):1083.
43. Haen SP, Pereira PL, Salih HR, et al. More than just tumor destruction: immunomodulation by thermal ablation of cancer. Clin Dev Immunol. 2011;2011:160250.
44. Waitz R, Solomon SB. Can local radiofrequency ablation of tumors generate systemic immunity against metastatic disease? Radiology. 2009;251:1–2.
45. Wu Y, Tang Z, Fang H, et al. High operative risk of cool-tip radiofrequency ablation for unresectable pancreatic head cancer. J Surg Oncol. 2006;94:392–5.
46. Elias D, Baton O, Sideris L, et al. Necrotizing pancreatitis after radiofrequency destruction of pancreatic tumours. Eur J Surg Oncol. 2004;30:85–7.
47. Yoon WJ, Brugge WR. Endoscopic ultrasonography-guided tumor ablation. Gastrointest Endosc Clin N Am. 2012;22:359–69, xi.

Chapter 14
EUS-Guided Celiac Plexus Neurolysis

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Abstract EUS-guided celiac plexus neurolysis (EUS–CPN) can be performed for alleviating pain originating from the upper abdominal organs and, particularly, when the primary indication for pain is pancreatic cancer pain. Two different techniques are currently used when applying EUS–CPN. The classic approach, known as the central technique, involves injection of a neurolytic agent at the base of the celiac axis, and the second approach, the bilateral technique, involves injection of the neurolytic agent on both sides of the celiac axis. Moreover, it was recently established that celiac ganglia can be examined and visualized by EUS. Therefore, EUS-guided direct celiac ganglia neurolysis (EUS–CGN) has been introduced as a new promising method. These techniques are performed with real-time imaging and with Doppler assessment of the interposing vessels. Therefore, they are more accurate, safe, and convenient than other classic approaches such as radiographic, fluoroscopic, or CT guidance. The effective rates reportedly vary from 50 to 90%. Common complications included transient diarrhea, transient pain exacerbation, transient hypotension, and inebriation, but they are not serious.

Keywords Celiac plexus neurolysis • EUS–CPN • EUS–CGN

14.1 Basic Theory of Celiac Plexus Neurolysis

The celiac plexus surrounds the celiac axis (CA) and the superior mesenteric artery (SMA) as it originates from the anterior of the abdominal aorta (Fig. 14.1). This plexus contains several ganglia and the interconnecting neural rami. It is responsible for transmitting pain sensations originating from the upper abdominal organs, including the pancreas, liver, gallbladder, stomach, and ascending and transverse colons.

Celiac plexus neurolysis (CPN) because of a neurolytic agent injected into the celiac plexus disrupts the transmission of pain signals from afferent nerves to the spinal cord.

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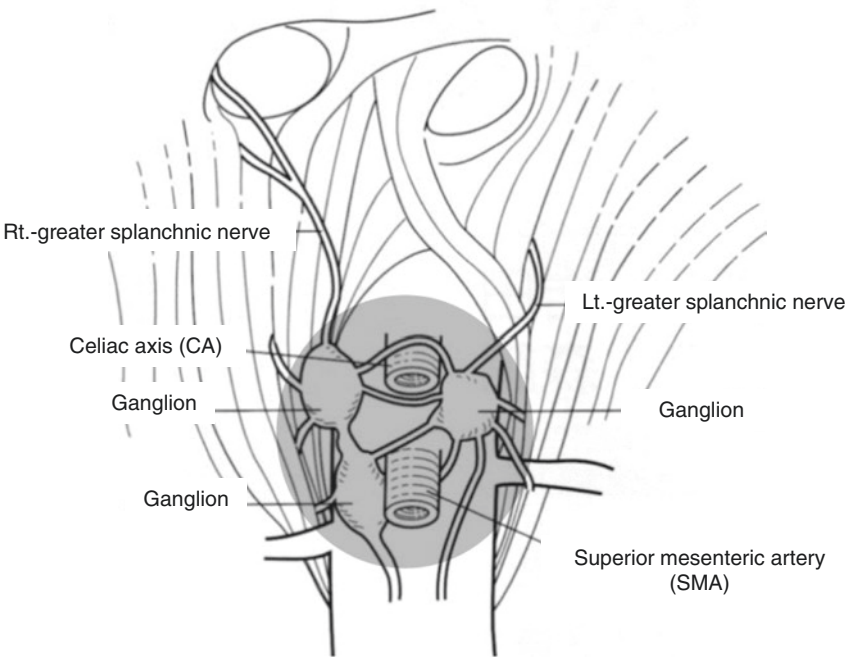

Fig. 14.1 Scheme showing the celiac plexus. The celiac plexus surrounds the celiac axis (CA) and the superior mesenteric artery (SMA) as it originates from the anterior of the abdominal aorta. It comprises several ganglia and connecting neural rami

14.2 History of CPN

The CPN was initially described as an intraoperative procedure by Kappis in 1914 [1]. Since then, it has been performed under the guidance of radiographic, fluoroscopic, computed tomographic (CT), or ultrasonographic imaging [2, 3]. Later, the endoscopic ultrasound-guided CPN (EUS–CPN) procedure was introduced by Faigel et al. [4] and Wiersema and Wiersema [5] in 1996. EUS–CPN can be performed under real-time imaging guidance and is thus considerably safer and more accurate than the traditional approaches. Indeed, a prospective randomized comparison of EUS-guided and CT-guided CPN showed that EUS–CPN provided more persistent pain relief than CT-guided CPN [6]. Thus EUS–CPN provided relatively a good pain relief, but it still sometimes failed to alleviate pain. The reason for this was that the neurolytic agents were injected at the probable vicinity of the celiac ganglia, which limited the efficacy of EUS–CPN in relieving pain effectively.

In 2006, Gerke et al. [7] and Levy et al. [8] reported that the celiac ganglia can be visualized precisely using EUS-guided procedures. After that, a new procedure involving the direct puncture and injection of a neurolytic agent or a steroid into an individual celiac ganglion was introduced by Levy et al. in 2008 [9]. This procedure was named EUS-guided celiac ganglia neurolysis (EUS–CGN). They may be safer

and more efficacious than EUS–CPN, because it allows for precise delivery of neurolytic agents into an individual celiac ganglion. Indeed, initial evaluations showed a high rate of success with this procedure [9].

14.3 Indications of EUS–CPN

The indications of EUS–CPN are pains originating from the upper abdominal organs, including the pancreas, liver, gallbladder, stomach, and ascending and transverse colons. Among them, the primary indication for EUS–CPN is pain associated with pancreatic cancer. Pain is experienced by 30–60% of pancreatic cancer patients in the early stages when the cancer is relatively limited. However, as the occurrence and severity of pain increase with cancer progression, more than 80% of patients in the advanced stages of pancreatic cancer experience pain [10]. Therefore, pain control is a major challenge in the management of pancreatic cancer patients. Second major indication of EUS–CPN is chronic pancreatitis.

14.4 Technique of EUS–CPN

EUS-guided procedures have several advantages over other approaches. They are highly accurate, safe, and convenient if performed with real-time-imaging and with Doppler assessment of the interposing vessels. Two approaches are currently used when performing EUS–CPN. The classic approach, known as the central technique, involves injection of a neurolytic agent at the base of the CA. In the second approach, the bilateral technique, the neurolytic agent is injected on both sides of the CA (Fig. 14.2).

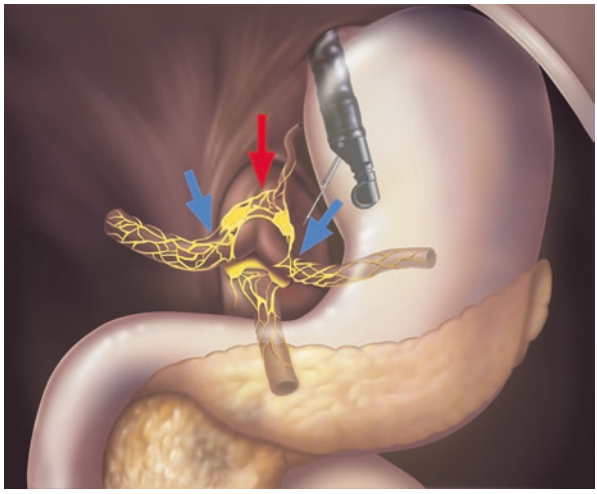

Fig. 14.2 Two approaches for EUS–CPN. In the central approach, a neurolytic agent is injected at the base of the celiac axis (*red arrow*). In the bilateral approach, the neurolytic agent is injected on both sides of the celiac axis (*blue arrows*)

In the EUS–CPN, absolute ethanol is usually used as a neurolytic agent [11], while phenol can be also used [12, 13]. In addition, 0.25–0.75% (mainly 0.25%) bupivacaine is usually used preceding the neurolytic agent. On the other hand, anesthetic agents such as bupivacaine with anti-inflammatory agents such as triamcinolone and Depo-Medrol are usually injected instead of a neurolytic agent for pain due to chronic pancreatitis [11]. This procedure is called EUS-guided celiac plexus block (EUS–CPB), and it is sometimes different from EUS–CPN.

14.4.1 Central Technique

In the central technique, the abdominal aorta is initially visualized in the longitudinal plane on the EUS image through the posterior wall of the upper gastric body. The aorta is then traced to identify the CA. Subsequently, a needle is pierced and advanced to a point just above the point where the CA originates from the aorta (Fig. 14.3). Absolute ethanol is injected into the region until the echogenic cloud widespread sufficiently. A total amount of ethanol is usually 10–20 mL.

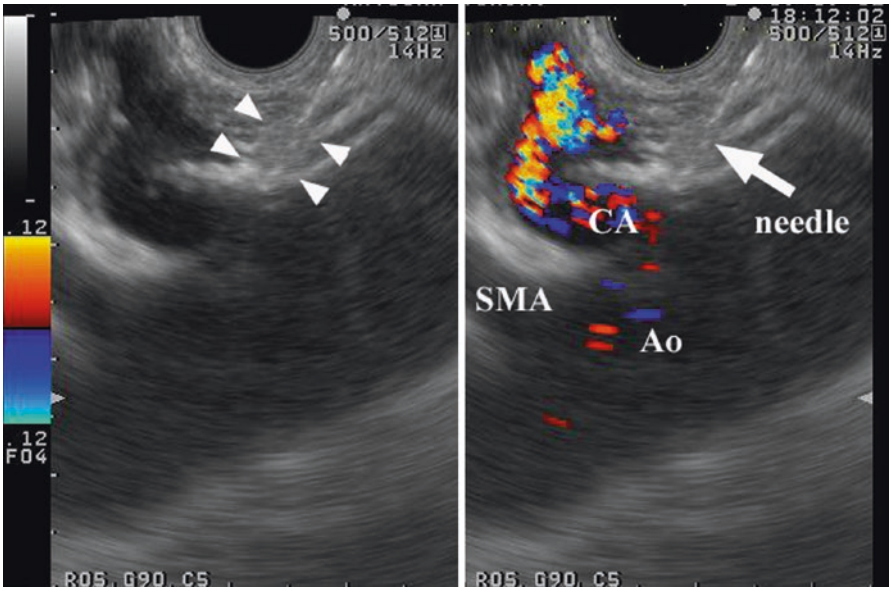

Fig. 14.3 EUS image during EUS–CPN (central approach). The needle was advanced to a point just above the aortal (Ao) origin of the CA. Following ethanol injection, a resultant echogenic cloud was observed spreading (*arrowheads*). *SMA* superior mesenteric artery

14.4.2 Bilateral Technique

After the origin of the CA is identified, the echoendoscope is rotated clockwise until the CA and SMA are no longer visible. The needle is then advanced toward the left, alongside the CA and SMA, up to a position lateral to the point where the SMA originates from the aorta. Absolute ethanol is injected into this region. Next, the needle is withdrawn, and the echoendoscope is rotated counterclockwise until the CA and SMA are no longer visible. The needle is advanced to the right lateral base of the SMA, and absolute ethanol is injected once again. The total amount of ethanol is the same as that in the central technique, 10–20 mL.

14.4.3 EUS–CGN

In this technique, the celiac ganglion (CG) must be identified first, and it may be a technical limitation of this technique. The visualization rate of CG has been reported between 63 and 88% in previous studies [7, 14–16]. However, our previous multicenter study showed that it varied between 67 and 100% depending on the institution, possibly reflecting inter-facility differences in experience [16]. From our experience, the CGs are identified between the aorta and the left adrenal gland in most cases and also cephalad to the origin of the CA in some cases. They are hypoechoic and often exhibit hypoechoic connections that probably represent the adjoining neural rami. They can be caterpillar-like (Fig. 14.4) or small and nodular.

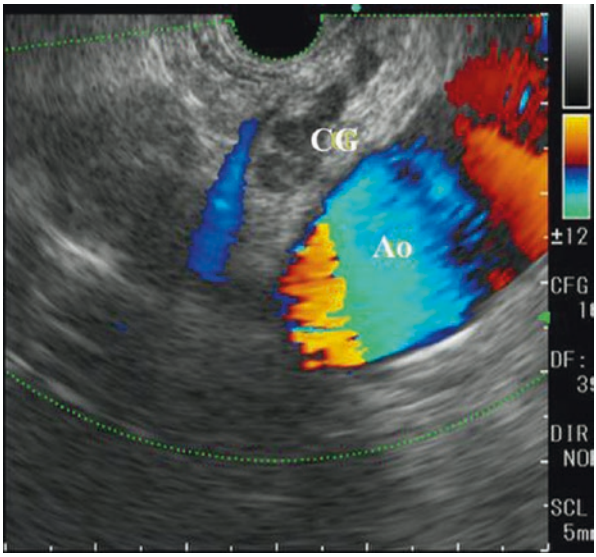

Fig. 14.4 EUS image showing a celiac ganglion (CG). *Ao* aorta

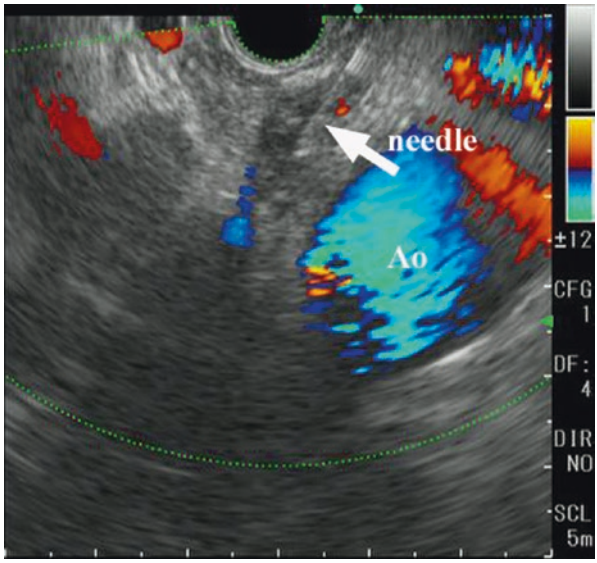

Fig. 14.5 EUS image during EUS–CGN. The tip of a needle is advanced deep within a ganglion. Thereafter, absolute ethanol is injected continuously as the needle is slowly withdrawn. After the injection, the ganglion becomes hyperechoic and difficult to visualize. *Ao* aorta

In our previous study, a mean of 2.9 CGs (range, 1–6) was visualized. The mean long dimension of the ganglia was 9.8 ± 5.9 mm (range, 3.0–35.0 mm), and mean short dimension of the ganglia was 4.6 ± 2.1 mm (range, 2.0–11.0 mm) [16].

After a CG has been identified, a needle is advanced to puncture the CG, and absolute ethanol is injected. The needle tip is advanced toward the center of the ganglion in case the observed ganglion is relatively small (approximately smaller than 8 mm within the axis of the needle plane). For any relatively large ganglion, the needle tip is advanced deeply within the ganglion. Thereafter, absolute ethanol is injected as the needle is slowly withdrawn. The injected ganglion becomes hyperechoic and difficult to visualize after the injection (Fig. 14.5). To ensure effective blockage, this procedure is repeated until identification of all ganglia becomes difficult. The volume of injected ethanol is usually 1–2 mL for small ganglia and 3–5 mL for relatively large ganglia.

14.5 Efficacy of EUS–CPN

Previous reports showed relatively good results in pain relief as shown in Table 14.1 [5, 6, 9, 11–13, 15–32]. In an initial evaluation by Wiersema [5], 79–88% of patients showed a long-lasting improvement in their pain scores, whereas 82–91% of patients required the same or less pain medication. Two meta-analysis have previous been published. Puli et al. [11] extracted the data from eight studies ($N = 283$) for EUS–CPN for pain due to pancreatic cancer and nine studies for chronic pancreatitis ($N = 376$). With EUS–CPN, the pooled proportion of patients with relief of pain due to pancreatic cancer was 80.12% (95% CI = 74.44–85.22) and that of patients with

Table 14.1 Previous reports and outcomes of EUS–CPN

	Author (year)	Indication	*N*	Study design	Technique	Pain relief	Complications
1	Wiersema (1996) [5]	PC (25), others(5)	30	Prospective?	CPN (bilateral)	Effective cases: 79–88% at 2–12 W	Diarrhea 13%, transient pain exacerbation 3.3%
2	Harada (1997) [17]	PC (33), others (12)	45	Prospective?	CPN (bilateral)	Effective cases: 82–89% at 2–16 W	Diarrhea 11%, transient pain exacerbation 2.2%
3	Gress (1999) [6]	CP	10	RCT: vs. CT-guided	CPB (bilateral)	Effective cases: 50%, persistent pain relief: 40% at 8 W, 30% at 24 W	Diarrhea 10%
4	Gress (2001) [19]	CP	90	Prospective	CPB (bilateral)	Effective cases: 55%, complete pain relief: 3%, persistent pain relief: 26% at 12 W, 10% at 24 W	Diarrhea 3%, peripancreatic abscess 1%
5	Gunaratnam (2001) [18]	PC	58	Prospective	CPN (bilateral)	Effective cases: 78%	Transient hypotension 20%, diarrhea 15.5%, transient pain exacerbation 8.6%
6	Sakamoto (2006) [20]	PC (12), others (1)	13	Prospective?	CPN (bilateral)	Effective cases: 61.5%	Transient hypotension 15.4%, inebriation 7.7%, transient pain exacerbation 7.7%
7	Tran (2006) [21]	PC	10	Retrospective	CPN (central)	Effective cases: 70%	Not described

(continued)

Table 14.1 (continued)

	Author (year)	Indication	*N*	Study design	Technique	Pain relief	Complications
8	Levy (2008) [9]	PC CP	18 18	Retrospective	CGN (17), CGB (1) CGN (5), CGB (13)	Effective cases: CGN 94%, CGB 0% Effective cases: CGN 80%, CGB 38%	Transient pain exacerbation 36%, transient hypotension 33%, diarrhea 22%
9	Sahai (2009) [22]	PC (30), CP (36), others (5)	71	Retrospective	Central: CPN (31)/CPB (40)	Effective cases: 50.7%, pain reduction rate (mean): 45.9%	None
		PC (42), CP (43), others (4)	89		Bilateral: CPN (41)/CPB (48)	Effective cases: 77.5%, pain reduction rate (mean): 70.4%	Retroperitoneal bleeding 1%
10	Puli (2009) [11]	PC CP	283 376	Meta-analysis	CPN (central 53/bilateral 226/unknown 17) CPN (bilateral 318/unknown (58)	Effective cases: 80.1% Effective cases: 59.5%	Diarrhea 0.7% Diarrhea 2.1%, transient pain exacerbation 0.3%, peripancreatic abscess 0.3%
11	O'Toole (2009) [23]	PC (2), CP (129) PC (21), CP (10)	189 31	Retrospective	CPB (central) CPN (central)	Not described	Hypotension 3.2%, pain 1.6%, retroperitoneal abscess 0.5%
12	Sakamoto (2010) [24]	PC (29), others (5) PC (31), others (2)	34 33	Retrospective	CPN (bilateral 34) BPN (33)	Mean VAS at 7 D, 30 D: CPN > BPN	None

13	Kaufman (2010) [25]	CP PC	221 119	Meta-analysis	CPB CPN	Effective cases: 51.46% Effective cases: 72.54%	Not available data
14	Iwata (2011) [26]	PC (40), others (7)	47	Retrospective	CPN (central)	Effective cases: 68.1%, complete pain relief 36.2%	Diarrhea 23.4%, transient hypotension 17.0%, inebriation 8.5%
15	LeBlanc (2011) [27]	PC	29 21	Prospective	CPN (central) CPN (bilateral)	Effective cases: 69%, median duration: 11 W Effective cases: 81%, median duration 14 W	Transient pain exacerbation 36%, transient hypotension 2%
16	Ascunce (2011) [15]	PC	64	Retrospective	CGN (40) CPN (bilateral 24)	Effective cases: 65.0% (83.3% at 1 M) Effective cases: 25.0% (50.0% at 1 M)	Diarrhea 23.4%, transient hypotension 1.6%, transient pain exacerbation 1.6%
17	Wyse (2011) [28]	PC	48	RCT: early CPN vs. conventional pain management	CPN (bilateral)	Mean reduction rate of Likert score: 18% at 1 M、49% at 3 M	Not described
18	Wiechowska-Kozlowska (2012) [29]	PC	29	Retrospective	CPN (central + bilateral)	Effective cases: 86% (76% at 2–3 M), complete pain relief 14%	Diarrhea 10.3%, transient pain exacerbation 6.9%, transient hypotension 3.4%

(continued)

Table 14.1 (continued)

	Author (year)	Indication	*N*	Study design	Technique	Pain relief	Complications
19	Seicean (2013) [30]	PC	32	Retrospective	CPN (central)	Effective cases: 75%	None
20	LeBlanc (2013) [31]	PC	10 10	Prospective	Alcohol 10 mL injection Alcohol 20 mL injection [CGN + central CPN (5), central CPN (5) in both groups]	Effective cases: 80%, mean duration 7.9 W Effective cases: 100%, mean duration 8.4 W (complete pain relief: 30% of cases in both groups)	Light-headedness 10%/0%, diarrhea 10%/50%, nausea and vomiting 0%/10%
21	Doi (2013) [16]	PC (30), others (4) PC (31), others (3)	34 34	RCT	CGN CPN (central)	Effective cases: 73.5%, complete pain relief 50.0% Effective cases: 45.5%, complete pain relief 18.2%	Transient hypotension 2.9%/6.0%, GI bleeding 2.9%/0%, inebriation 2.9%/3.0%, transient pain exacerbation 29.4%/21.2%, diarrhea 5.9%/9.1%
22	Tellez-Avila (2013) [32]	PC	21 32	Retrospective	CPN (central) CPN (bilateral)	Effective cases: 62.0% at 15 D, 47.6% at 30 D Effective cases: 59.4% at 15 D, 56.3% at 30 D	None Transient pain exacerbation 3%

23	Ishiwatari (2014) [12]	PC (5), others (1) PC (12), others (4)	6 16	Retrospective	Phenol (central CPN 3/ CGN 3) Ethanol (central CPN 4/ CGN 12)	Effective cases: 83% Effective cases: 69%	Diarrhea 17%/6.3%, transient pain exacerbation 0%/12.5%, inebriation 0%/12.5%, transient hypotension 0%/6.3%
24	Ishiwatari (2015) [13]	PC	9	Prospective case series	CPN (central; highly viscous phenol glycerol)	Effective cases: 89%, complete pain relief 44%, median duration 19.1 W	Transient hypotension 1.1%, transient pain exacerbation 1.1%, diarrhea 1.1%

PC pancreatic cancer, *CP* chronic pancreatitis, *RCT* randomized controlled trial, *CPN* celiac plexus neurolysis, *CPB* celiac plexus block, *CGN* celiac ganglia neurolysis, *CGB* celiac ganglia block, *BPN* broad plexus neurolysis, *VAS* visual analogue scale, *W* weeks, *M* months, *D* days

pain due to chronic pancreatitis was 59.45% (95% CI = 54.51–64.30). In the analysis by Kaufman et al. [25], six relevant studies comprising a total of 221 patients were identified for chronic pancreatitis and five relevant studies were identified with a total of 119 patients for pancreatic cancer. As a result, EUS–CPN was effective in alleviating pain in 72.54% of patients with pancreatic cancer and in 51.46% of patients with chronic pancreatitis.

14.5.1 Central vs. Bilateral

Puli et al. [11] compared the treatment efficacy between the two patient subgroups treated by the bilateral and unilateral procedures. The rate of pain relief was much higher in pancreatic cancer patients treated with the bilateral procedure (84.54%; 95% CI = 72.15–93.77) than in those treated by the central procedure (45.99%; 95% CI = 37.33–54.78). Sahai et al. [22] assessed the short-term safety and efficacy of central and bilateral EUS–CPN/EUS–CPB in 160 patients (71 treated centrally, 89 treated bilaterally). The mean pain reduction score was 70.4% in patients treated bilaterally compared to 45.9% in those treated centrally ($P = 0.0016$). A positive response (≥50% reduction in pain score) was also significantly more frequent in the bilaterally treated group (77.5%) than in the centrally treated group (50.7%) ($P = 0.0005$). The only predictor of a positive response was the use of the bilateral procedure (odds ratio = 3.55; 95% CI = 1.72–7.34). These results suggested that the bilateral procedure was more effective than the central procedure. However, later, an RCT showed no difference in pain relief between the central and bilateral technique (central 69% vs. bilateral 81%; $P = 0.340$) [27].

14.5.2 Broad Distribution of the Neurolytic Agent

Iwata et al. [26] examined predictive factors for pain relief after EUS–CPN. Their multivariate analysis revealed that direct invasion of the celiac plexus and distribution of ethanol only on the left side of the CA (to both side of the CA) were significant factors for a negative response to EUS–CPN (odds ratio = 4.82 and 8.67, $P = 0.0387$ and 0.0224). Sakamoto et al. [24] also reported the importance of broad distribution of the neurolytic agent. In their retrospective study, they compared the effectiveness of standard EUS–CPN and EUS-guided broad neurolysis (EUS–BPN) that extends over the SMA using a thin 25-gauge needle. As a result, ethanol was distributed more widely and better pain relief was obtained in EUS-BPN than in EUS–CPN. These study results suggested that broad distribution of the injected ethanol was an important factor to predict the good response to EUS–CPN. However, the volume of the injected ethanol does not appear to be associated with better results. LeBlanc et al. [31] compared the dose of alcohol used in

EUS–CPN, 20 mL vs. 10 mL. There were no major complications and pain relief was similar in both groups.

14.5.3 CPN vs. CGN

The EUS–CGN may be safer and more effective than EUS–CPN, because it allows for the precise delivery of neurolytic agents into an individual celiac ganglion. The initial report of EUS–CGN by Levy et al. [8] showed surprisingly high effective rate. The pain relief was achieved in 16 of 17 (94%) pancreatic cancer patients treated by EUS–CGN. In the case of chronic pancreatitis, 80% (4/5) of those who received alcohol injections reported pain relief versus 38% (5/13) of those who received steroid injections. However, the authors concluded that prospective trials are necessary to confirm the therapeutic efficacy of this method, because their study involved a small sample size [8]. In the retrospective study by Ascunce et al. [15], EUS–CGN was performed when the CGs were visible by EUS; otherwise bilateral EUS–CPN was performed. Multivariate analysis was performed to determine the predictive factors of response, and visualization of the CGs (EUS–CGN) was the best predictor of response; patients with visible CGs were 15 times more likely to respond (odds ratio 15.7; $P = 0.001$). After that, Doi et al. [16] conducted a multicenter, prospective randomized trial to compare the efficacies of EUS–CPN and EUS–CGN. As a result, the positive response rate was significantly higher in the EUS–CGN group (73.5%) than in the EUS–CPN group (45.5%; $P = 0.026$). The complete response rate was also significantly higher in the EUS–CGN group (50.0%) than in the EUS–CPN group (18.2%; $P = 0.010$).

14.5.4 Phenol Injection

Recently, Ishiwatari et al. [12] investigated the effectiveness of phenol instead of alcohol. They used phenol for 6 patients with alcohol intolerance and the effectiveness was compared with that of 16 patients used ethanol without alcohol intolerance. There was no significant difference in the positive response rate on day 7 (83% vs. 69%, $P = 0.6$). Moreover, no significant difference was found in the rate of complications between the two groups, but burning pain and inebriation occurred only in the ethanol group. Later, the same researchers investigated the feasibility of EUS–CPN by using highly viscous phenol glycerol [13]. The positive response was observed in 8 of 9 patients (89%), and the complete response rate was 44%. The median duration of pain relief was estimated to be 19.1 weeks. It provided adequate neurolytic agent distributions even by the central method. They suggested that the use of highly viscous phenol glycerol could provide excellent pain relief by enabling appropriate distribution of the neurolytic agent.

14.6 Complications of EUS–CPN

Common reported complications of EUS–CPN include transient diarrhea, transient pain exacerbation, transient hypotension, and inebriation as shown in Table 14.1. In most of cases, these complications are not serious. However, several major complications have been reported as shown in Table 14.2 [22, 23, 33–41]. Most of them, especially infectious complications, were reported in the setting of chronic pancreatitis. Retroperitoneal bleeding occurred in two cases that underwent the bilateral technique [22, 33]. Ischemic complications were lethal in three cases [38, 40, 41]. These vascular injuries and ischemic complications are probably due to injecting alcohol into an inappropriate site or excessive sessions of EUS–CPN.

Table 14.2 Major complications of EUS–CPN

Author (year)	Complication (*N*)	Indication	Technique	Substance
Gress (1997) [33]	Retroperitoneal bleeding (1) Retroperitoneal abscess (1)	CP	Bilateral	Alcohol + bupivacaine Triamcinolone + bupivacaine
Mahajan (2002) [34]	Empyema (3)	CP	Not described	Triamcinolone + bupivacaine
Muscatiello (2006) [35]	Retroperitoneal abscess (1)	PC	Not described	Alcohol + bupivacaine
Sahai (2009) [22]	Retroperitoneal bleeding (1)	CP	Bilateral	Triamcinolone + bupivacaine
O'Toole (2009) [23]	Retroperitoneal abscess (1)	CP	Not described	Triamcinolone + bupivacaine
Ahmed (2009) [36]	Ischemia (1)	CP	Not described	Alcohol + bupivacaine
Lalueza (2011) [37]	Brain abscess (1)	CP	Not described	Alcohol + bupivacaine
Gimeno-Garcia (2012) [38]	Celiac artery thrombosis + multiple organ infarction (1)[a]	CP	Bilateral	Alcohol 20 mL + bupivacaine 10 mL
Fujii (2012) [39]	Paraplegia (1)[a]	PC	CGN + CPN	Bupivacaine + alcohol 1 mL (CGN) + 23 mL (CPN)
Loeve (2013) [40]	Necrosis + perforation of stomach and aorta (1)[a]	CP	Multiple CPN (13 sessions for 4 years)	Bupivacaine 6–10 mL + alcohol 8–20 mL
Jang (2013) [41]	Infarction of the liver and spleen, and ischemia of the stomach and small intestine (1)[a]	Metastasis[b]	Central	Bupivacaine 5 mL + alcohol 10 mL + triamcinolone 1 mL + saline 3 mL

[a]Censored case
[b]Metastatic pancreatic cancer from lung cancer
CP chronic pancreatitis, *PC* pancreatic cancer

In the RCT of EUS–CPN and EUS–CGN [16], the overall complication rates were similar in the two groups, but the total volume of injected ethanol was significantly lower in the EUS–CGN group (12.1 ± 5.1 mL) than in the EUS–CPN group (18.4 ± 3.0 mL; $P < 0.001$). In addition, the puncture target is clearer in the EUS–CGN than in the EUS–CPN. This reduction in the injection volume and clearer target may help avoid serious ischemic complications.

14.7 Timing of EUS–CPN

Wyse et al. [28] compared the pain reduction and narcotic use after early EUS–CPN, at the time of EUS, with those of conventional pain management. They concluded that early EUS–CPN can reduce pain and might moderate morphine consumption in patients with painful, inoperable pancreatic cancers.

14.8 Conclusions

EUS–CPN is a safe and effective method for reducing pain originating from the upper abdominal organs, especially pancreatic cancer pain. Bilateral EUS–CPN and EUS–CGN may be more effective than central EUS–CPN.

References

1. Kappis M. Erfahrungen mit localanasthesie bie bauchoperationen. Verh Dtsch Gesellsch Chir. 1914;43:87–9.
2. Wong GY, Schroeder DR, Carns PE, et al. Effect of neurolytic celiac plexus block on pain relief, quality of life, and survival in patients with unresectable pancreatic cancer: a randomized controlled trial. JAMA. 2004;291:1092–9.
3. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007;102:430–8.
4. Faigel DO, Veloso KM, Long WB, et al. Endosonography-guided celiac plexus injection for abdominal pain due to chronic pancreatitis. Am J Gastroenterol. 1996;91:1675.
5. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc. 1996;44:656–62.
6. Gress F, Schmitt C, Sherman S, et al. A prospective randomized comparison of endoscopic ultrasound- and computed tomography-guided celiac plexus block for managing chronic pancreatitis pain. Am J Gastroenterol. 1999;94:900–5.
7. Gerke H, Silva RG Jr, Shamoun D, et al. EUS characteristics of celiac ganglia with cytologic and histologic confirmation. Gastrointest Endosc. 2006;64:35–9.
8. Levy M, Rajan E, Keeney G, et al. Neural ganglia visualized by endoscopic ultrasound. Am J Gastroenterol. 2006;101:1787–91.
9. Levy MJ, Topazian MD, Wiersema MJ, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct Ganglia neurolysis and block. Am J Gastroenterol. 2008;103:98–103.

10. Caraceni A, Portenoy RK. Pain management in patients with pancreatic carcinoma. Cancer. 1996;78:639–53.
11. Puli SR, Reddy JB, Bechtold ML, et al. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci. 2009;54:2330–7.
12. Ishiwatari H, Hayashi T, Yoshida M, et al. Phenol-based endoscopic ultrasound-guided celiac plexus neurolysis for East Asian alcohol-intolerant upper gastrointestinal cancer patients: a pilot study. World J Gastroenterol. 2014;20:10512–7.
13. Ishiwatari H, Hayashi T, Yoshida M, et al. EUS-guided celiac plexus neurolysis by using highly viscous phenol-glycerol as a neurolytic agent (with video). Gastrointest Endosc. 2015;81:479–83.
14. Gleeson FC, Levy MJ, Papachristou GI, et al. Frequency of visualization of presumed celiac ganglia by endoscopic ultrasound. Endoscopy. 2007;39:620–4.
15. Ascunce G, Ribeiro A, Reis I, et al. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). Gastrointest Endosc. 2011;73:267–74.
16. Doi S, Yasuda I, Kawakami H, et al. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. Endoscopy. 2013;45:362–9.
17. Harada N, Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc Clin N Am. 1997;7:237–45.
18. Gunaratnam NT, Sarma AV, Norton ID, et al. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. Gastrointest Endosc. 2001;54:316–24.
19. Gress F, Schmitt C, Sherman S, et al. Endoscopic ultrasound-guided celiac plexus block for managing abdominal pain associated with chronic pancreatitis: a prospective single center experience. Am J Gastroenterol. 2001;96:409–16.
20. Sakamoto H, Kitano M, Nishio T, et al. Value of computed tomography for evaluating the injection site in endosonography-guided celiac plexus neurolysis for pancreatic cancer pain. Dig Endosc. 2006;18:206–11.
21. Tran QN, Urayama S, Meyers FJ. Endoscopic ultrasound-guided celiac plexus neurolysis for pancreatic cancer pain: a single-institution experience and review of the literature. J Support Oncol. 2006;4:460–2, 464; discussion 463–4.
22. Sahai AV, Lemelin V, Lam E, et al. Central vs. bilateral endoscopic ultrasound-guided celiac plexus block or neurolysis: a comparative study of short-term effectiveness. Am J Gastroenterol. 2009;104:326–9.
23. O'Toole TM, Schmulewitz N. Complication rates of EUS-guided celiac plexus blockade and neurolysis: results of a large case series. Endoscopy. 2009;41:593–7.
24. Sakamoto H, Kitano M, Kamata K, et al. EUS-guided broad plexus neurolysis over the superior mesenteric artery using a 25-gauge needle. Am J Gastroenterol. 2010;105:2599–606.
25. Kaufman M, Singh G, Das S, 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. J Clin Gastroenterol. 2010;44:127–34.
26. Iwata K, Yasuda I, Enya M, et al. Predictive factors for pain relief after endoscopic ultrasound-guided celiac plexus neurolysis. Dig Endosc. 2011;23:140–5.
27. LeBlanc JK, Al-Haddad M, McHenry L, et al. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? Gastrointest Endosc. 2011;74:1300–7.
28. Wyse JM, Carone M, Paquin SC, et al. Randomized, double-blind, controlled trial of early endoscopic ultrasound-guided celiac plexus neurolysis to prevent pain progression in patients with newly diagnosed, painful, inoperable pancreatic cancer. J Clin Oncol. 2011;29:3541–6.
29. Wiechowska-Kozlowska A, Boer K, Wojcicki M, et al. The efficacy and safety of endoscopic ultrasound-guided celiac plexus neurolysis for treatment of pain in patients with pancreatic cancer. Gastroenterol Res Pract. 2012;2012:503098.

30. Seicean A, Cainap C, Gulei I, et al. Pain palliation by endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. J Gastrointestin Liver Dis. 2013;22:59–64.
31. LeBlanc JK, Rawl S, Juan M, et al. Endoscopic ultrasound-guided celiac plexus neurolysis in pancreatic cancer: a prospective pilot study of safety using 10 mL versus 20 mL alcohol. Diagn Ther Endosc. 2013;2013:327036.
32. Tellez-Avila FI, Romano-Munive AF, Herrera-Esquivel Jde J, et al. Central is as effective as bilateral endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. Endosc Ultrasound. 2013;2:153–6.
33. Gress F, Ciaccia D, Kiel S. Endoscopic ultrasound (EUS) guided celiac plexus block (CB) for management of pain due to chronic pancreatitis (CP): a large single center experience. Gastrointest Endosc. 1997;45:AB173.
34. Mahajan R, Nowell W, Theerathorn P. Empyema after endoscopic ultrasound guided celiac plexus pain block (EUS-CBP) in chronic pancreatitis: experience at an Academic Center. Gastrointest Endosc. 2002;55:AB101.
35. Muscatiello N, Panella C, Pietrini L, et al. Complication of endoscopic ultrasound-guided celiac plexus neurolysis. Endoscopy. 2006;38:858.
36. Ahmed HM, Friedman SE, Henriques HF, et al. End-organ ischemia as an unforeseen complication of endoscopic-ultrasound-guided celiac plexus neurolysis. Endoscopy. 2009;41(Suppl 2):E218–9.
37. Lalueza A, Lopez-Medrano F, del Palacio A, et al. Cladosporium macrocarpum brain abscess after endoscopic ultrasound-guided celiac plexus block. Endoscopy. 2011;43(Suppl 2 UCTN):E9–10.
38. Gimeno-Garcia AZ, Elwassief A, Paquin SC, et al. Fatal complication after endoscopic ultrasound-guided celiac plexus neurolysis. Endoscopy. 2012;44(Suppl 2 UCTN):E267.
39. Fujii L, Clain JE, Morris JM, et al. Anterior spinal cord infarction with permanent paralysis following endoscopic ultrasound celiac plexus neurolysis. Endoscopy. 2012;44(Suppl 2 UCTN):E265–6.
40. Loeve US, Mortensen MB. Lethal necrosis and perforation of the stomach and the aorta after multiple EUS-guided celiac plexus neurolysis procedures in a patient with chronic pancreatitis. Gastrointest Endosc. 2013;77:151–2.
41. Jang HY, Cha SW, Lee BH, et al. Hepatic and splenic infarction and bowel ischemia following endoscopic ultrasound-guided celiac plexus neurolysis. Clin Endosc. 2013;46:306–9.

Part III
IDUS

Chapter 15
IDUS: Introduction

Masatsugu Nagahama

Abstract Intraductal ultrasonography (IDUS) is a widely used imaging modality for evaluating gastrointestinal disorders. This modality provides ultrasound images from the inside of the bile or pancreatic duct with a high-frequency ultrasound probe with a thin diameter, particularly in the biliopancreatic region. The indications of IDUS for pancreatobiliary lesions include the diagnosis of small residual common bile duct stones after endoscopic extraction, differential diagnosis of biliary strictures, the diagnosis of pancreaticobiliary maljunction, the staging of biliary duct carcinomas, the diagnosis of invasion of intraductal papillary tumors, and the staging of periampullary carcinomas.

Keywords Intraductal ultrasonography • Biliopancreatic diseases • Biliopancreatic stricture

Intraductal ultrasonography (IDUS), which is superior in spatial resolution, is a widely used imaging modality for evaluating gastrointestinal disorders. This modality provides ultrasound images from the inside of the bile or pancreatic duct with a high-frequency (20–30 MHz) ultrasound probe with a thin diameter (2–3 mm), particularly in the biliopancreatic region. If endoscopic retrograde cholangiopancreatography (ERCP) can be performed, IDUS can be easily performed successively and does not require any special techniques. Furthermore, the advent of a thin guidewire-directed probe has allowed the probe to be advanced to a target site along the guidewire. This probe can be inserted into the bile and pancreatic ducts, pass through a stenotic area, and reach a target site, thereby allowing the consistent observation to be made (Figs. 15.1 and 15.2).

A useful feature of IDUS for biliopancreatic disorders is to depict proximal fine structures from the lumens of the bile and pancreatic ducts. IDUS is suitable for depiction of intramural structures, fine stones, and tumors in the bile and pancreatic ducts. IDUS at the time of ERCP may add useful information in the patient with suspected cholangiocarcinoma [1, 2]. Furthermore IDUS shows good results for

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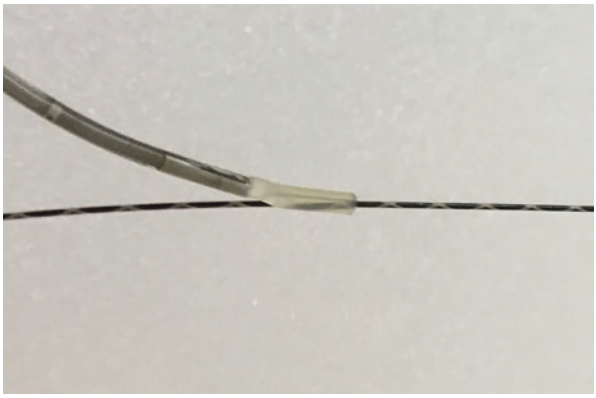

Fig. 15.1 The probe tip and guidewire

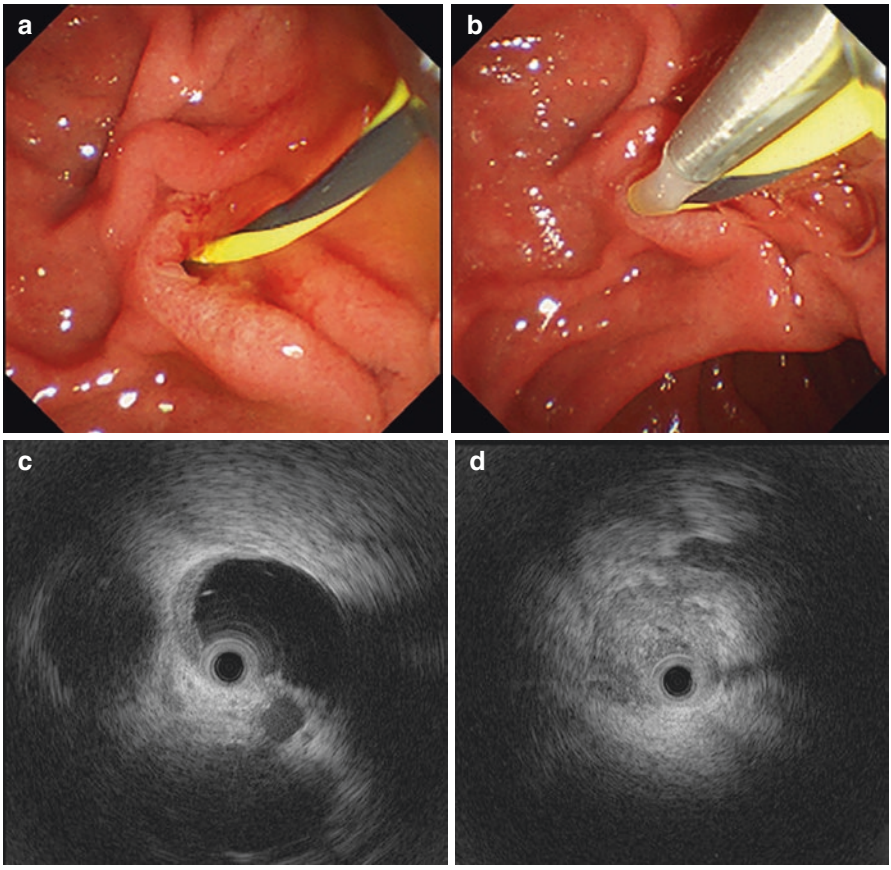

Fig. 15.2 A case of lower bile duct cancer. (**a**) Endoscopic view (1): A guidewire was inserted into the common bile duct through the papilla of Vater. (**b**) Endoscopic view (2): An intraductal ultrasonography probe was inserted into the common bile duct along the guidewire. (**c**) Intraductal ultrasonographic view (1): Dilated common hepatic duct was seen. (**d**) Intraductal ultrasonographic view (2): Intraductal ultrasonography of the lower bile duct revealed a tumorous lesion filling the lumen

accurate diagnostics of bile duct strictures of uncertain etiology [3–5]. IDUS are clinically useful in the diagnosis of microlithiasis [6, 7] at the time of recurrent idiopathic pancrestitis [8] and choledocholithiasis. Preoperative IDUS was useful in determining the type of surgery and the extent of resection [9]. It has also been reported to be useful for differentiating enlarged papilla from papillary diseases and diagnosing papillary carcinoma invasion [10]. In particular, IDUS is the only imaging modality that allows the sphincter of Oddi at the papilla to be directly visualized [11]; thus, it is considered to be an important modality for assessment before endoscopic papillectomy. With further advances in devices, IDUS has the potential to become a useful modality for assessing biliopancreatic diseases.

References

1. American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee, Anderson MA, Appalaneni V, et al. The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. Gastrointest Endosc. 2013;77(2):167–74.
2. Ito Y, Shibutani S, Egawa T, et al. Utility of intraductal ultrasonography as a diagnostic tool in patients with early distal cholangiocarcinoma. Hepato-Gastroenterology. 2015;62(140):782–6.
3. Tringali A, Lemmers A, Meves V, et al. Intraductal biliopancreatic imaging: European Society of Gastrointestinal Endoscopy (ESGE) technology review. Endoscopy. 2015;47(8):739–53.
4. Meister T, Heinzow HS, Woestmever C, et al. Intraductal ultrasound substantiates diagnostics of bile duct strictures of uncertain etiology. World J Gastroenterol. 2013;19(6):874–81.
5. Chen L, Lu Y, Wu JC, et al. Diagnostic utility of endoscopic retrograde cholangiography/intraductal ultrasound (ERC/IDUS) in distinguishing malignant from benign bile duct obstruction. Dig Dis Sci. 2016;61(2):610–7.
6. Kim DC, Moon JH, Choi HJ, et al. Usefulness of intraductal ultrasonography in icteric patients with highly suspected choledocholithiasis showing normal endoscopic retrograde cholangiopancreatography. Dig Dis Sci. 2014;59(8):1902–8.
7. Tsuchiya S, Tsuyuguchi T, Sakai Y, et al. Clinical utility of intraductal US to decrease early recurrence rate of common bile duct stones after endoscopic papillotomy. J Gastroenterol Hepatol. 2008;23(10):1590–5.
8. American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in benign pancreatic disease. Gastrointest Endosc. 2015;82(2):203–14.
9. Cheon YK, Cho YD, Jeon SR, et al. Pancreatic resection guided by preoperative intraductal ultrasonography for intraductal papillary mucinous neoplasm. Am J Gastroenterol. 2010;105(9):1963–9.
10. Okano N, Igarashi Y, Hara S, et al. Endosonographic preoperative evaluation for tumors of the ampulla of vater using endoscopic ultrasonography and intraductal ultrasonography. Clin Endosc. 2014;47(2):174–7.
11. Itoh A, Goto H, Naitoh Y, et al. Intraductal ultrasonography in diagnosing tumor extension of cancer of the papilla of Vater. Gastrointest Endosc. 1997;45(3):251–60.

Chapter 16
IDUS for Biliary Tract

Hironao Miyoshi and Kazuo Inui

Abstract Intraductal ultrasonography (IDUS) normally delineates 2–3 layers of the bile duct wall. On the other hand, IDUS can identify carcinoma as a hypoechoic area of irregular thickness. IDUS generally is reliable for diagnosis of extrahepatic bile duct cancer, but IgG4-related sclerosing cholangitis (IgG4-SC) can be difficult to distinguish from malignant strictures. Even so, in IgG4-SC, IDUS can depict circular, symmetric wall thickening with smooth outer and inner margins, associated with homogeneous internal echo in narrowed ducts. While endoscopic cholangiography is unreliable in detection of small gallstones after endoscopic lithotripsy, IDUS is more successful in detecting small gallstones in such cases. In conclusion, IDUS and 3D-IDUS are useful for differentiating between malignant biliary strictures and benign ones, including IgG4-SC, as well as for detection of small bile duct stones.

Keywords Biliary tract cancer • Bile duct stones • IgG4-related sclerosing cholangitis

16.1 Introduction

Intraductal ultrasonography (IDUS) first was reported by Silverstein et al. [1] in 1989 as experimental work in dogs. Many subsequent authors [2–7] found IDUS to be reliable clinically for diagnosis of extrahepatic cholangiocarcinoma and bile duct stones. Kallimanis et al. [8] introduced three-dimensional intraductal ultrasonography (3D-IDUS) in 1995. We subsequently reported the usefulness of 3D-IDUS for diagnosis of biliary tract cancer and common bile duct stones as a comprehensive image display, aided by ongoing developments involving both instruments and image-processing systems [9–11]. In this chapter we demonstrate the usefulness and clinical applicability of IDUS and 3D-IDUS for diagnosis of biliary tract diseases.

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16.2 Methods of IDUS and 3D-IDUS

We usually use a ropeway system probe, 2.5 mm in diameter, (UM-DG-35R, Olympus Medical Systems, Tokyo, Japan), incorporating a radial scanning system with a frequency of 20 MHz [12]. The probe is connected to an endoscopic ultrasonic observation unit (EU-M2000, Olympus Medical Systems) and controlled by a probe-driving unit (MAJ 2000, Olympus Medical Systems). For 3D-IDUS we use an ultrasound image-processing unit (EU-IP2, Olympus Medical Systems) to produce reconstruction images such as dual-plane reconstructions. The 3D ultrasonic probe consists of an external tube as an outer sheath and the probe itself with a diameter of 2.4 mm and a 20-MHz radial scan transducer at its tip. 3D ultrasonography is performed while the ultrasonic probe is withdrawn automatically in the outer sheath. The outer sheath remains withdrawn throughout scanning. Linear reconstruction images are produced by integrating 40 serial radial images. We can obtain 40–118 serial radial images. The length of the longitudinal images can be set at 10, 20, 30, or 40 mm, with pitches of 0.25, 0.5, 0.75, or 1.0 mm.

The probe passes easily through the 2.8-mm diameter biopsy channel of an electronic duodenoscope (JF 260V or TJF 200, Olympus Medical Systems). We perform IDUS by either a transpapillary or a percutaneous transhepatic approach: the area surveyed by the probe is confirmed by fluoroscopy.

16.3 IDUS for Diagnosis of Biliary Tract Cancer

The normal bile duct wall is delineated as having 2–3 layers. IDUS depicts a carcinoma as a hypoechoic image with irregular thickness (Figs. 16.1 and 16.2). When the tumor image extends to the highly echogenic layer of the bile duct, we can conclude that the tumor has invaded the subserosa. When the tumor reaches the parenchyma of the pancreas, the pancreas has been invaded. Important findings for diagnosis of tumor invasion of the pancreas include a hyperechoic layer between the bile duct and the pancreas. When the tumor image reaches the hyperechoic wall of the portal vein, the portal vein has been invaded.

We have correlated the results of IDUS and pathologic findings of tumor extension in 13 patients with bile duct carcinoma [13]. Overall accuracy for depth of tumor invasion was 84.6%, for tumor invasion of the pancreas 88.9%, and for invasion of the portal vein 92.3%.

IDUS can contribute importantly to differentiating benign from malignant biliary lesions. In a series of 93 patients suspected to have biliary tract cancer [14], we found that IDUS had a sensitivity and specificity of 89.7% and 84%, respectively, for diagnosing malignant biliary strictures.

In other reports, accuracy of IDUS in diagnosis of cancer invasion to the serosa was reported as 86–93% [15, 16]. Accuracy of invasion to the right hepatic artery

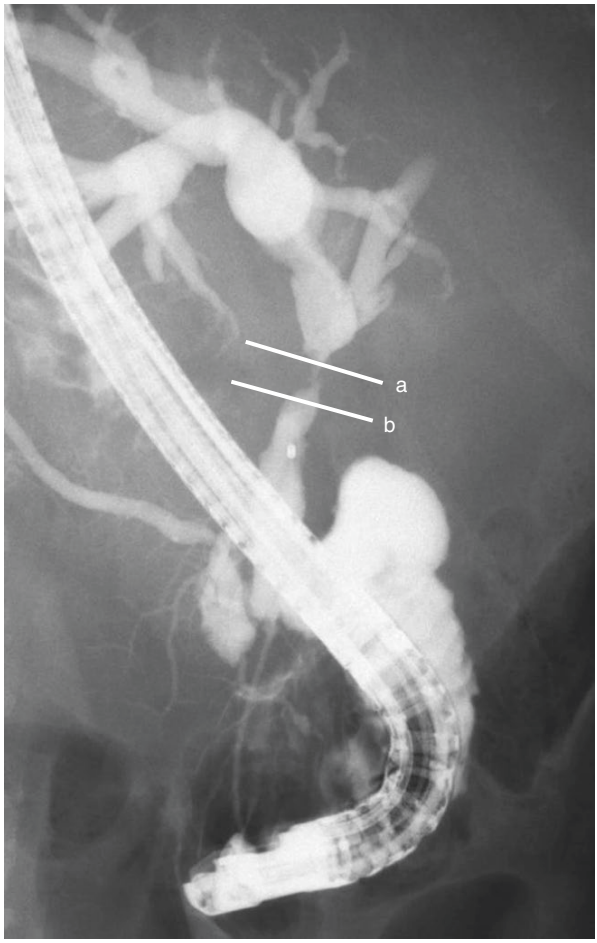

Fig. 16.1 Bile duct carcinoma. Endoscopic retrograde cholangiopancreatogram indicates a stricture of the upper part of the extrahepatic bile duct. IDUS scanning was performed at lines (*a*, *b*)

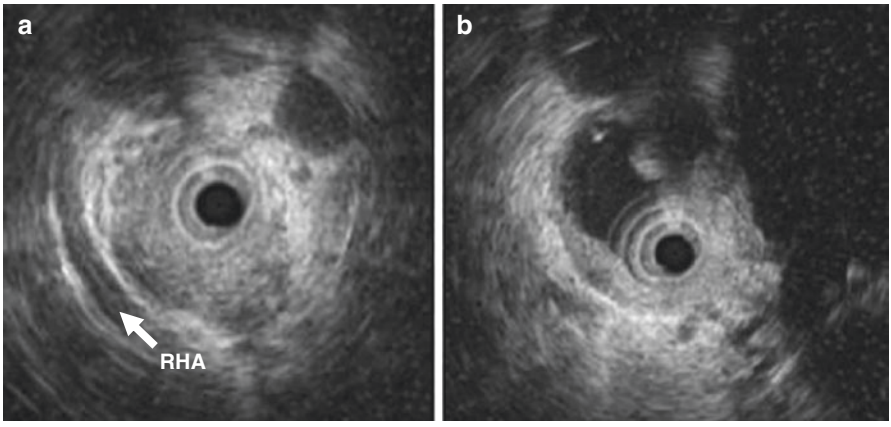

Fig. 16.2 (**a**) Intraductal ultrasonography (IDUS) depicts carcinoma as a hypoechoic image of irregular thickness. (**b**) IDUS indicates that the tumor echogram has reached the highly echoic layer of the bile duct, but not the right hepatic artery (RHA)

and portal vein was reported as 86–100% and 92–100%, respectively [3, 9, 15–19], while accuracy of diagnosis of pancreatic parenchymal invasion was reported as 93–100% [9, 10, 20]. While IDUS is useful for diagnosing depth of invasion as well as invasion of the portal vein, right hepatic artery, and pancreas, IDUS cannot reliably diagnose involvement of lymph nodes.

16.4 IDUS for Diagnosis of IgG4-Related Sclerosing Cholangitis

IgG4-related sclerosing cholangitis (IgG4-SC) is a distinct type of sclerosing cholangitis with an unknown pathogenetic mechanism. IgG4-SC patients have increased serum concentrations of IgG4, dense infiltration of IgG4-positive plasma cells with extensive fibrosis in the bile duct wall, and a good response to steroid therapy [21]. Autoimmune pancreatitis (AIP) frequently complicates IgG4-SC. Ultrasonography (US) detects thickening of the wall of the common bile duct about 60% of cases of AIP [22]. Thickening of the bile duct wall may show either a layered structure or parenchymal hypoechoic wall thickening [23]. Because thickening of duct walls can extend beyond extrahepatic bile ducts and also involve intrahepatic bile ducts in some cases, these sclerosing lesions may be difficult to distinguish from malignant strictures. In such instances, both endoscopic ultrasonography (EUS) and IDUS are useful. Although wall thickening in narrowed duct segments is not shown clearly by conventional US, EUS and IDUS depict circular, symmetric wall thickening with smooth outer and inner margins, associated with homogeneous internal echo in narrowed ducts (Figs. 16.3 and 16.4) [24, 25]. Sometimes, difficulty arises in correctly diagnosing IgG4-SC, when IDUS displays irregular wall thickening during the acute phase of disease. However, with steroid therapy, wall thickness decreases conspicuously [14].

16.5 IDUS for Diagnosis of Biliary Tract Stones

Endoscopic cholangiography is not a reliable method for detection of small gallstones after endoscopic lithotripsy (Fig. 16.5). On the other hand, EUS is better able to detect small gallstones after endoscopic treatment. IDUS is also reported to be useful for detecting small stones after endoscopic treatment for bile duct stones (Fig. 16.6) [7, 26]. A bile duct stone presents a strong echo with acoustic shadowing [13]. IDUS revealed air bubbles as comet-shaped echoes with acoustic shadowing when separated from the transducer or as fan-shaped high-echo signals when touching the transducer [27]. The detection rate of bile duct stones with IDUS is reported to be 96.8–100% [27, 28].

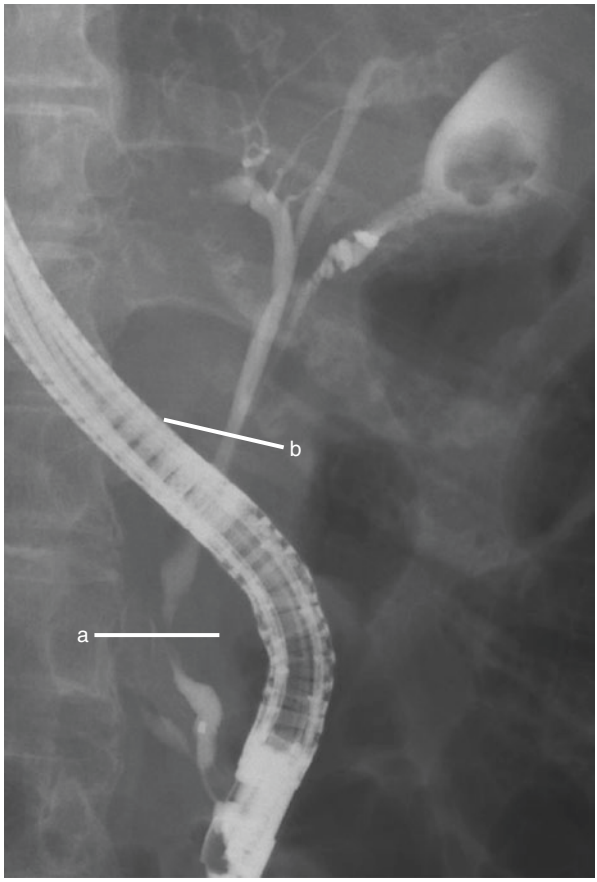

Fig. 16.3 IgG4-related sclerosing cholangitis. Endoscopic retrograde cholangiopancreatogram detects a stricture of the lower part of the extrahepatic bile duct. IDUS scanning was performed at lines (*a*, *b*)

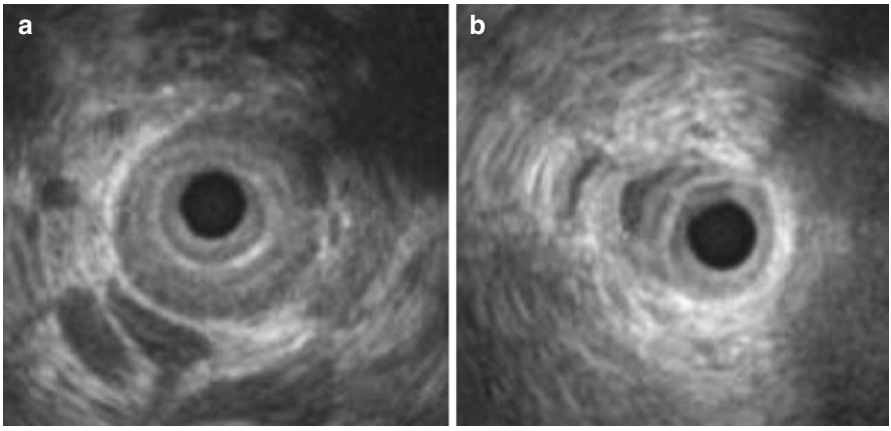

Fig. 16.4 (**a**) IDUS depict a circular, symmetric wall thickening with smooth outer and inner margins. (**b**) IDUS shows wall thickening in the region without strictures

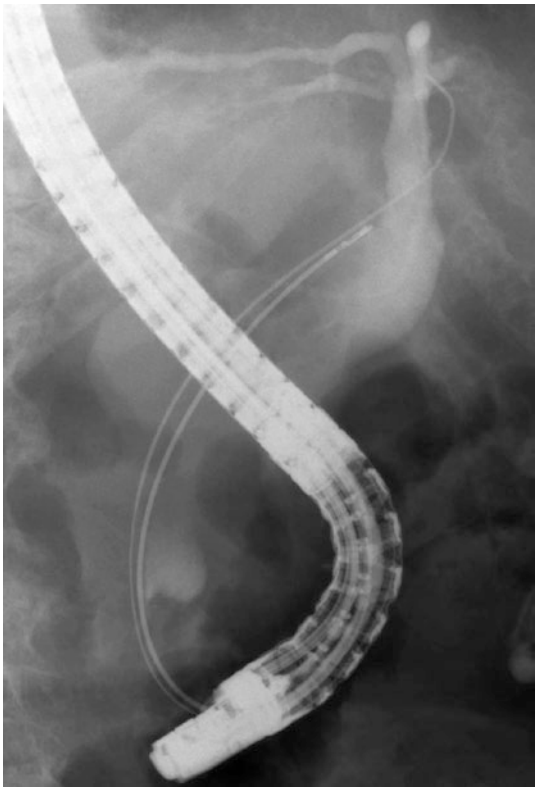

Fig. 16.5 After endoscopic removal of common bile duct stones, ultrasonic probe is inserted into the common bile duct along with a guidewire. ERCP detects no filling defects in the bile duct

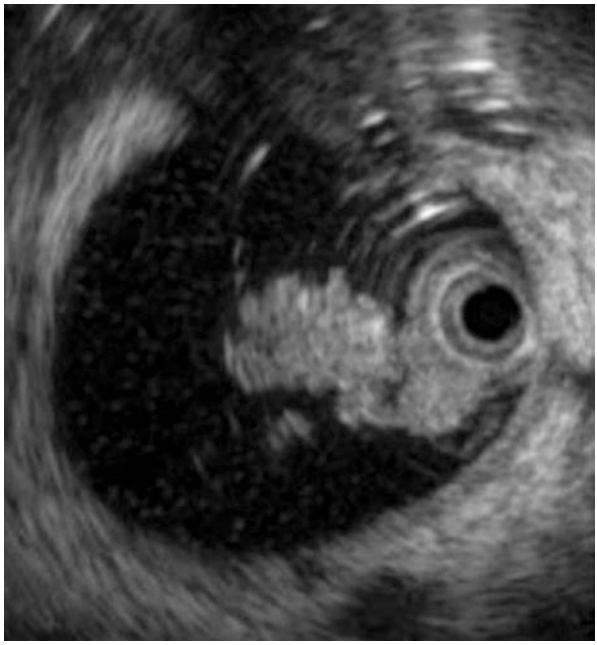

Fig. 16.6 IDUS detects a residual stone as a strong echo with no acoustic shadow

In one case series involving endoscopic papillary balloon dilation and balloon endoscopic retrograde cholangiography [27], IDUS was performed in 149 of the 182 patients (81.7%). No residual stones were confirmed in 107 of 149 patients (71.8%) at the final endoscopy session. When the 42 patients with residual stones underwent IDUS during the session, IDUS showed either stones or debris. Tsuchiya et al. [7] reported that additional IDUS to confirm complete stone clearance decreased the recurrence rate of common bile duct stones over a 3-year period after endoscopic sphincterotomy (EST).

16.6 Conclusions

IDUS is useful for differentiating between malignant and benign biliary strictures including IgG4-SC and for detecting small bile duct stones.

References

1. Silverstein FE, Martin RW, Kimmey MB, et al. Experimental evaluation of an endoscopic ultrasound probe: in vitro and in vivo canine studies. Gastroenterology. 1989;96:1058–62.
2. Kuroiwa M, Goto H, Hirooka Y, et al. Intraductal ultrasonography for the diagnosis of proximal invasion in extrahepatic bile duct cancer. J Gastroenterol Hepatol. 1998;13:715–9.
3. Fujita N, Noda Y, Kobayashi G, et al. Staging of bile duct carcinoma by EUS and IDUS. Endoscopy. 1998;30:A132–4.
4. Tamada K, Inui K, Menzel J. Intraductal ultrasonography of the bile duct system. Endoscopy. 2001;33:878–85.
5. Inui K, Miyoshi H. Cholangiocarcinoma and intraductal sonography. Gastrointest Endosc Clin N Am. 2005;15:143–55.
6. Palazzo L. Which test for common bile duct stones? Endoscopic and intraductal ultrasonography. Endoscopy. 1997;29:655–65.
7. Tsuchiya S, Tsuyuguchi T, Sakai Y, et al. Clinical utility of intraductal US to decrease early recurrence rate of common bile duct stones after endoscopic papillotomy. J Gastroenterol Hepatol. 2008;23:1590–5.
8. Kallimanis G, Garra BS, Tio TL, et al. The feasibility of three-dimensional endoscopic ultrasonography: a preliminary report. Gastrointest Endosc. 1995;41:235–9.
9. Kanemaki N, Nakazawa S, Inui K, et al. Three-dimensional intraductal ultrasonography: preliminary results of a new technique for the diagnosis of diseases of the pancreatobiliary system. Endoscopy. 1997;29:726–31.
10. Inui K, Nakazawa S, Yoshino J, et al. Ultrasound probes for biliary lesions. Endoscopy. 1998;30(Suppl 1):A120–3.
11. Inui K, Yoshino J, Miyoshi H. Development of three-dimensional intraductal ultrasonography in diagnosis for bile duct carcinoma. In: Niwa H, Tajiri H, Nakajima M, Yasuda K, editors. New challenges in gastrointestinal endoscopy. Tokyo: Springer; 2008. p. 526–31.
12. Fujita N, Noda Y, Yokohata K, et al. Newly developed ultrasonic probe with ropeway system for transpapillary intraductal ultrasonography of the bilio-pancreatic ductal system. Dig Endosc. 2000;12:250–4.
13. Inui K, Yoshino J, Okushima K, et al. Intraductal EUS. Gastrointest Endosc. 2002;4:S58–62.
14. Inui K, Yoshino J, Miyoshi H. Differential diagnosis and treatment of biliary strictures. Clin Gastroenterol Hepatol. 2009;7:S79–83. https://doi.org/10.1016/j.cgh.2009.08.027.

15. Kuroiwa M, Tsukamoto Y, Naitoh Y, et al. New technique using intraductal ultrasonography for the diagnosis of bile duct cancer. J Ultrasound Med. 1994;13:189–95.
16. Tamada K, Ido K, Ueno N, et al. Preoperative staging of extrahepatic bile duct cancer with intraductal ultrasonography. Am J Gastroenterol. 1995;90:239–46.
17. Tamada K, Tomiyama T, Ohashi A, et al. Preoperative assessment of extrahepatic bile duct carcinoma using three-dimensional intraductal US. Gastrointest Endosc. 1999;50:548–54.
18. Menzel J, Poremba C, Dietl KH, et al. Preoperative diagnosis of bile duct strictures—comparison of intraductal ultrasonography with conventional endosonography. Scand J Gastroenterol. 2000;35:77–82.
19. Stavropoulos S, Larghi A, Verna E, et al. Intraductal ultrasound for the evaluation of patients with biliary strictures and no abdominal mass on computed tomography. Endoscopy. 2005;37:715–21.
20. Tamada K, Ueno N, Ichiyama M, et al. Assessment of pancreatic parenchymal invasion by bile duct cancer using intraductal ultrasonography. Endoscopy. 1996;28:492–49.
21. Ohara H, Okazaki K, Tsubouchi H, et al. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012. J Hepatobiliary Pancreat Sci. 2012;19:536–42.
22. Kamisawa T, Egawa N, Nakajima H, et al. Comparison of radiological and histological findings in autoimmune pancreatitis. Hepatogastroenterology. 2006;53:953–6.
23. Hyodo N, Hyodo T. Ultrasonographic evaluation in patients with autoimmune-related pancreatitis. J Gastroenterol. 2003;38:1155–61.
24. Nakazawa T, Ando T, Hayashi K, et al. Diagnostic procedures for IgG4-related sclerosing cholangitis. J Hepatobiliary Pancreat Sci. 2011;18:127–36.
25. Kubota K, Kato S, Uchiyama T, et al. Discrimination between sclerosing cholangitis-associated autoimmune pancreatitis and primary sclerosing cholangitis, cancer using intraductal ultrasonography. Dig Endosc. 2011;23:10–6.
26. Tamada K, Ohashi A, Tomiyama T, et al. Comparison of intraductal ultrasonography with percutaneous transhepatic cholangioscopy for the identification of residual bile duct stones during lithotripsy. J Gastroenterol Hepatol. 2001;16:100–3.
27. Ueno N, Nishizono T, Tamada K, et al. Diagnosing extrahepatic bile duct stones using intraductal ultrasonography: a case series. Endoscopy. 1997;29:356–60.
28. Linghu EQ, Cheng LF, Wang XD, et al. Intraductal ultrasonography and endoscopic retrograde cholangiography in diagnosis of extrahepatic bile duct stones: a comparative study. Hepatobiliary Pancreat Dis Int. 2004;3:129–32.

Part IV
EST (Endoscopic Sphincterotomy)

Chapter 17
Endoscopic Papillary Large Balloon Dilation (EPLBD)

Shomei Ryozawa

Abstract Endoscopic papillary large balloon dilation (EPLBD) combined with endoscopic sphincterotomy (EST) was introduced to facilitate the removal of large or difficult bile duct stones. Several studies have reported that this technique is safe and effective in patients with large bile duct stones without an increased risk of severe pancreatitis or bile duct perforation. In addition, it appears to decrease procedure time and fluoroscopy time and reduce the need for mechanical lithotripsy. Further evaluation and standardization of the method are required.

Keywords Endoscopic papillary large balloon dilation • EPLBD • EST • Bile duct stone • Large balloon

17.1 Introduction

Endoscopic sphincterotomy (EST) is the most commonly used endoscopic technique for removal of bile duct stones. Although EST has become an established technique since it was described in 1974 [1, 2], bile duct stone removal using EST may be difficult in the setting of large size stones (>15 mm), multiple stones, barrel-shaped stones, and tapering or tortuosity of the distal common bile duct. Furthermore, difficult stone removal needs for mechanical lithotripsy (ML) or intraductal electrohydraulic or laser lithotripsy [3, 4]. Endoscopic papillary large balloon dilation (EPLBD) combined with EST was first reported by Ersoz et al. [5] in 2003 to facilitate the removal of large or difficult bile duct stones. Since then, EPLBD has become rapidly and widely adopted.

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17.2 Definition

EPLBD is used to create a larger biliary opening with a large diameter balloon ≥12 mm. The intended purpose of EPLBD is to simplify removing large or difficult bile duct stones without additional adverse events of EST alone. EST has been generally recommended before EPLBD because it was believed to be associated with a decreased risk of post procedure pancreatitis or perforation.

17.3 Indication

Bile duct stones may be difficult to remove endoscopically by using standard balloon and basket extraction techniques after mainly large EST in the setting of large size stones (>15 mm), multiple stones, barrel-shaped stones, and tapering or tortuosity of the distal common bile duct [6, 7]. In such situations, additional endoscopic procedures, mainly EML, are usually required. However, EML is a time-consuming procedure, raising problems such as impaction and fracture of the Dormia basket, and increases the risk of adverse events. EPLBD combined with EST can be used as the alternative to EML after EST for the removal of large or difficult bile duct stones, reducing the need for EML because it allows a larger biliary orifice to be achieved than full-incision EST.

In early trials of EPLBD, a supplementary EPLBD was performed when the standard balloon and basket extraction technique failed after large EST [5, 8]. However, preemptive EPLBD has recently been performed after limited EST or sometimes without EST in patients with large bile duct stones that are suspected to be difficult to remove by using standard extraction techniques even after large EST. Abdominal CT with coronal reconstruction and MRCP can be used to measure the number and size of bile duct stones and to determine the shape of the bile duct. Accordingly, this allows endoscopists to decide on the method to use for bile duct stone removal even before endoscopic retrograde cholangiopancreatography (ERCP) is performed.

EPLBD is not recommended in patients with obvious distal bile duct strictures or a nondilated bile duct because of the increased risk of perforation due to excessive dilation of the bile duct with a balloon [9].

17.4 Techniques

ERCP is performed using side-viewing video duodenoscope. After cholangiography (Fig. 17.1a), a guidewire is passed into the bile duct. Immediately after limited EST (Fig. 17.1b), a balloon catheter is passed over the guidewire and positioned across the main duodenal papilla. The size of balloon is matched to the diameters of the bile duct and the stones. The balloon is then gradually inflated with diluted

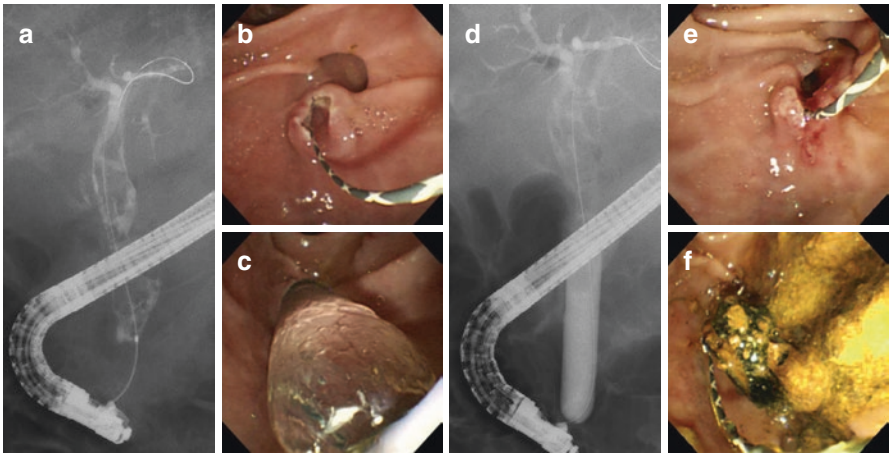

Fig. 17.1 Endoscopic papillary large balloon dilation (EPLBD) technique. (**a**) Cholangiogram showed large and multiple bile duct stones. (**b**) Endoscopic sphincterotomy (EST) was performed. (**c**) Papillary dilation with large balloon. (**d**) X-ray showed large balloon expanded. (**e**) Large biliary orifice can be seen after balloon deflation. (**f**) Large bile duct stone removal without crush

contrast medium under endoscopic and fluoroscopic guidance until adequate size to allow stone removal without lithotripsy regardless of disappearance of the balloon waist (Fig. 17.1c–e). The maximal inflated diameter of the balloon should not exceed the diameter of the distal bile duct to prevent the risk of perforation due to overinflation of the balloon. During EPLBD, the rapid and forcible inflation of the balloon across a tight distal bile duct stricture can lead to perforation and bleeding. The balloon should always be inflated slowly and gradually, starting from a smaller diameter than the intended maximal target, to recognize obscure bile duct strictures with attention paid to the balloon shape under fluoroscopy. If waist formation or longitudinally extensive narrowing of the balloon is recognized even using the maximum pressure for each balloon, additional inflation should not be performed. In contrast, once the waist disappeared, the balloon remained inflated for 30–60 s [10]. The stones are then removed from the bile duct with a basket or a retrieval balloon (Fig. 17.1f). When stone impaction is thought to occur, a mechanical lithotriptor should be used.

17.5 Outcomes

The initial success rate, which was defined as the rate of successful stone removal during the first ERCP session, of EPLBD with EST in the systematic review [10] was comparable to that of EST alone (84.0% vs. 80.8%, $p = 0.131$) in a meta-analysis by Weinberg et al. [11]. The overall success rates of EPLBD with EST in the systematic review [10] were comparable to that of EST alone (96.5% vs. 95.3%,

$p = 0.141$) in a meta-analysis [11]. There is speculation that EPLBD with EST can reduce the need for ML in patients with large bile duct stones ≥15 mm [12]. Itoi et al. [7] report that EPLBD with EST appears to decrease procedure time and fluoroscopy time compared to EST alone.

17.6 Special Cases

17.6.1 The Presence of a Periampullary Diverticulum

The prevalence of periampullary diverticula (PAD) increases with age. PAD tend to distort the anatomy of the duodenum and the sphincter, making a controlled EST more difficult and possibly increasing the risk of adverse events. Also, when EPLBD is performed in patients with PAD, the potential risk of perforation is of particular concern due to lack of sphincter muscle components around the ampulla. In retrospective comparison studies in patients with and without PAD, there were no significant differences in overall success rates of bile duct stone removal and rates of adverse events [13, 14].

17.6.2 In Patients with Surgically Altered Anatomy

It is well known that EST is usually difficult and may require special techniques or devices in patients with surgically altered anatomy. Despite the development of specific sphincterotomes, EST in patients with surgically altered anatomy is more difficult than in patients with unaltered anatomy because the papilla now has to be approached from an inverted anatomic structure. In such a situation, balloon dilation may be particularly suitable instead of EST (Fig. 17.2).

17.6.3 In Patients with Previous EST

In recurrent bile duct stones, extended incision of a previous EST site is sometimes required to remove large and difficult stones. However, it can increase the risk of adverse events such as bleeding and perforation. In such cases, EPLBD can be safely and effectively used to widen the ampullary orifice without performing a repeat EST.

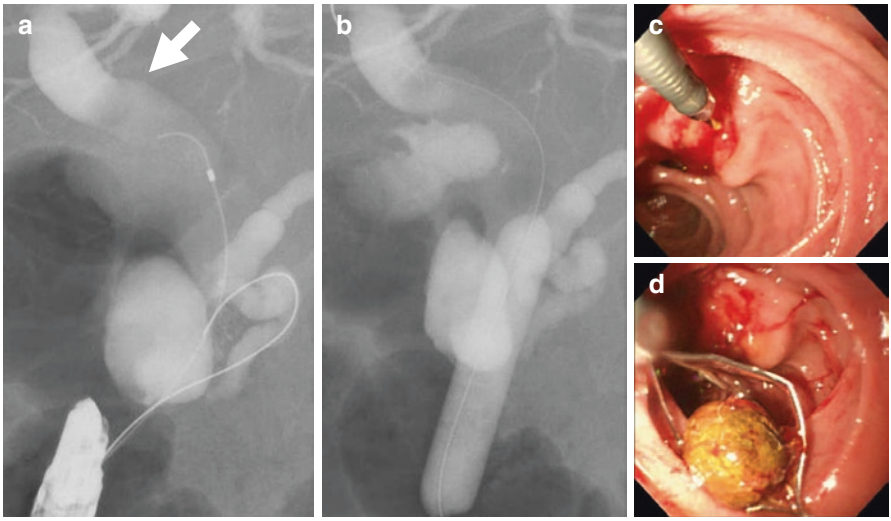

Fig. 17.2 EPLBD in patient with Billroth II gastrectomy. (**a**) Cholangiogram showed a bile duct stone (arrow). (**b**) X-ray showed large balloon expanded. (**c**) After EPLBD, a mechanical lithotriptor was used for stone extraction. (**d**) Large bile duct stone removed without crush

17.7 Adverse Events

Major adverse events typically related to both EST and EPLBD are pancreatitis, bleeding, and perforation. In the systematic review [10], the rate of overall adverse events was significantly lower for EPLBD with EST than that for EST alone in patients with large or difficult stones (8.3% vs. 12.7%, $p < 0.001$). The rate of pancreatitis in patients who underwent EPLBD with EST was significantly lower than that in patients who underwent EST alone (2.4% vs. 4.3%, $p < 0.006$). The rates of bleeding and perforation were not significantly different between the EPLBD with EST and EST alone (3.6% vs. 4.8%, 0.6% vs. 0.5%, respectively). The possible mechanism of the reduced pancreatitis rate for EPLBD with EST is that the radial force exerted by the dilating balloon shifts along the cutting direction made during EST toward the bile duct and away from the pancreatic orifice, resulting in less periampullary injury around the pancreatic duct. The other hypothesis about the mechanism of pancreatitis after EPLBD was suggested: the manipulation frequency of the Dormia basket and retrieval balloon catheter in EPLBD with EST can be reduced due to a sufficiently widened ampullary orifice, resulting in less periampullary trauma or edema and a lower risk of pancreatitis.

References

1. Kawai K, Akasaka Y, Murakami K, et al. Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc. 1974;20:148–51.
2. Classen M, Demling L. Endoskopische Sphinkterotomie der Papilla Vateri und Steinextraktion aus dem Ductus Choledochus. Dtsch Med Wschr. 1974;99:496–7.
3. Binmoeller KF, Brucke M, Trou F, et al. Treatment of difficult bile duct stones using mechanical, electrohydraulic and extra corporeal shock wave lithotripsy. Endoscopy. 1933;25:201–6.
4. Neuhaus H, Hoffman W, Zillinger C, et al. Laser lithotripsy of difficult stones under direct visual control. Gut. 1993;34:415–21.
5. Ersoz G, Tekesin O, Ozutemiz AO, et al. Biliary sphincterotomy plus dilation with a large balloon for bile duct stones that are difficult to extract. Gastrointest Endosc. 2003;57:156–9.
6. Kim HJ, Choi HS, Park JH, et al. Factors influencing the technical difficulty of endoscopic clearance of bile duct stones. Gastrointest Endosc. 2007;66:1154–60.
7. Itoi T, Itokawa F, Sofuni A, et al. Endoscopic sphincterotomy combined with large balloon dilation can reduce the procedure time and fluoroscopy time for removal of large bile duct stones. Am J Gastroenterol. 2009;104:560–5.
8. Maydeo A, Bhandari S. Balloon sphincteroplasty for removing difficult bile duct stones. Endoscopy. 2007;39:958–61.
9. Park SJ, Kim JH, Hwang JC, et al. Factors predictive of adverse events following endoscopic papillary large balloon dilation: results from a multicenter series. Dig Dis Sci. 2012;58:1100–9.
10. Kim JH, Yang MJ, Hwang JC, et al. Endoscopic papillary large balloon dilation for the removal of bile duct stones. World J Gastroenterol. 2013;19:8580–94.
11. Weinberg BM, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. Cochrane Database Syst Rev. 2006; CD004890.
12. Kim TH, Oh HJ, Lee JY, et al. Can a small endoscopic sphincterotomy plus a large-balloon dilation reduce the use of mechanical lithotripsy in patients with large bile duct stones? Surg Endosc. 2011;25:3330–7.
13. Kim KH, Kim TN. Endoscopic papillary large balloon dilation in patients with periampullary diverticula. World J Gastroenterol. 2013;19:7168–76.
14. Kim HW, Kang DH, Choi CW, et al. Limited endoscopic sphincterotomy plus large balloon dilation for choledocholithiasisi with periampullary diverticula. World J Gastroenterol. 2010;16:4335–40.

Part V
How to Treat Biliary Calculi

Chapter 18
Biliary Calculi

Masatsugu Nagahama

Abstract Cholelithiasis is one of the most common gastrointestinal disorders. Cholelithiasis is divided into gallbladder stone, common bile duct stone, and intrahepatic stone by site of development. Each type develops either secondarily to other conditions or independently. When asymptomatic common bile duct stones are detected, they are highly likely to become symptomatic. Thus, aggressive treatment is basically recommended regardless of the presence or absence of symptoms. Endoscopic treatment of common bile duct stones is established as the first treatment of choice for common bile duct stones at many facilities worldwide. Endoscopic sphincterotomy (EST) is usually performed in Western countries. However, in Japan, endoscopic papillary balloon dilation (EPBD) as well as EST is performed at many institutions. When the stone diameter exceeds the diameter of the EST- or EPBD-treated papilla, they need to be fragmented and removed through the papilla. Lithotripsy procedures include endoscopic mechanical lithotripsy (EML) and peroral cholangioscopy-guided electrohydraulic shockwave lithotripsy. In recent years, endoscopic papillary large balloon dilation (EPLBD) has come into clinical use.

Keywords Common bile duct stone • EST • EPBD

18.1 Biliary Calculi

Cholelithiasis is one of the most common gastrointestinal disorders. The prevalence of gallstones is high in Indian ethnic groups worldwide. In contrast, it is 5% or lower in sub-Saharan Africans and 14% in African Americans. Because the prevalence greatly varies among ethnic groups, lifestyles are speculated to contribute to the development of gallstones. The prevalence of gallstones in Asian countries is lower than that of 20% in Europe and the United States, whereas it is approximately 5% in Japan [1].

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18.2 Sites and Types of Gallstones

Cholelithiasis is divided into gallbladder stone, common bile duct stone, and intrahepatic stone by site of development. Each type develops either secondarily to other conditions or independently. According to stone compositions, gallstones are mainly categorized as cholesterol or pigmented type. Either type of gallstones can occur in the intrahepatic bile duct and gallbladder. When cholesterol gallstones are present in the common bile duct, they are considered to be stones developing secondarily to stones falling from the intrahepatic bile duct or gallbladder.

18.3 Endoscopic Treatment of Common Bile Duct Stones

When asymptomatic common bile duct stones are detected, they are highly likely to become symptomatic. Thus, aggressive treatment is basically recommended regardless of the presence or absence of symptoms [2, 3]. It has been reported that common bile duct stones concurrently developed in 5–10% of patients undergoing laparoscopic surgery for symptomatic gallbladder stones and were furthermore complicated by gallstone pancreatitis in 18–33% [1].

Endoscopic treatment of common bile duct stones can be relatively safely performed in a short time, is associated with a high success rate, and is established as the first treatment of choice for common bile duct stones at many facilities worldwide. In a meta-analysis comparing a combination of endoscopic treatment of common bile duct stones and cholecystectomy (two-staged operation) with surgical treatment (one-staged operation) (12 randomized controlled trials [RCTs] involving a total of 1357 patients with common bile duct stones complicated by gallbladder stones), there were no differences in stone extraction rate, mortality, or complication rate between the treatment methods. A subanalysis of laparoscopic surgery (5 RCTs) also revealed no differences in therapeutic outcomes [4].

When common bile duct stones are endoscopically treated through the papilla, it is necessary to dilate the bile duct orifice at the duodenal papilla, in order to extract the stones from the bile duct to the duodenum. Specifically, the papilla is incised or dilated with a duodenoscope (rear viewing scope), and stones are extracted with a basket or balloon catheter. In Europe and the United States, endoscopic sphincterotomy (EST) is the commonly performed procedure for the papilla. As more than 30 years have passed since EST was first reported by Sohma [5], Kawai [6], and Classen [7] in the early 1970s, this procedure has been established as the first-choice treatment of common bile duct stones (Fig. 18.1).

Meanwhile, endoscopic papillary balloon dilation (EPBD) is also performed at many facilities in Japan (Fig. 18.2). EPBD was first reported by Staritz et al. in 1982 [8], reappreciated by Mac Mathuna et al. in the mid-1990s [9], and recommended for its promotion mainly by Komatsu et al. in Japan [10].

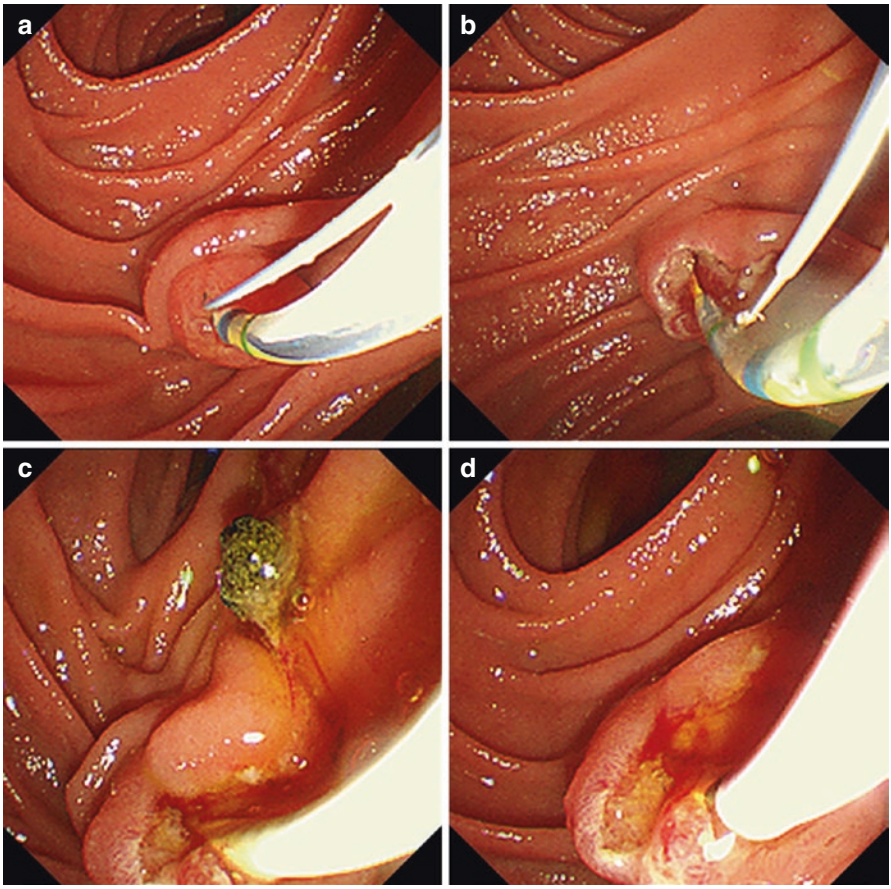

Fig. 18.1 <Endoscopic sphincterotomy: EST> Endoscopic view. (**a**) A EST knife was inserted to the papilla of Vater along the guidewire. (**b**) Sphincterotomy was performed to the papilla of Vater. (**c**) A stone was extracted with a retrieval balloon catheter. (**d**) An endoscopic nasobiliary drainage tube was inserted into the bile duct

According to several controlled trials on treatment outcomes and complications of EST and EPBD [11–13], the incidences of bleeding and pancreatitis are higher for EST and EPBD, respectively, although treatment outcomes are similar between the two methods. Since some patients died of pancreatitis after EPBD in a multicenter study conducted in the United States [14], EPBD has not been frequently performed particularly in Europe and the United States.

When the stone diameter exceeds the diameter of the EST- or EPBD-treated papilla, they need to be fragmented and removed through the papilla. Lithotripsy procedures include endoscopic mechanical lithotripsy (EML) and peroral cholangioscopy-guided electrohydraulic shockwave lithotripsy. In recent years, endoscopic papillary large balloon dilation (EPLBD) has come into clinical use. Because the diameter of the papilla treated by EPLBD is larger than that of the

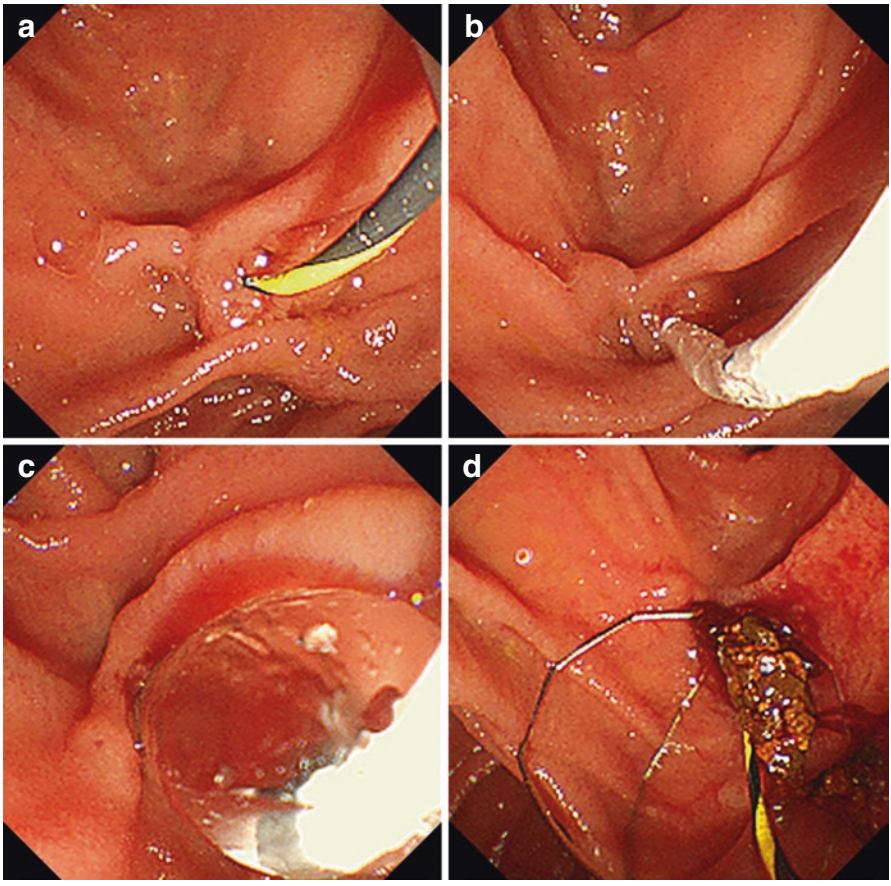

Fig. 18.2 <Endoscopic papillary balloon dilation: EPBD> Endoscopic view. (**a**) A guidewire was placed in the bile duct through the papilla of Vater. (**b**) A balloon catheter was inserted to the papilla of Vater. (**c**) The papilla of Vater was dilated with a balloon catheter. (**d**) A stone was extracted with a basket catheter

papilla treated by EST or EPBD, extraction of even large stones has become possible without lithotripsy. The details of these procedures are reported elsewhere.

References

1. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. Gut Liver. 2012;6(2):172–87.
2. ASGE Standards of Practice Committee, Maple JT, Ben-Menachem T, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. Gastrointest Endosc. 2010;71(1):1–9.

3. Williams EJ, Green J, Beckingham I, et al. Guidelines on the management of common bile duct stones (CBDS). Gut. 2008;57(7):1004–21.
4. Clayton ES, Connor S, Alexakis N, et al. Meta-analysis of endoscopy and surgery versus surgery alone for common bile duct stones with the gallbladder in situ. Br J Surg. 2006;93(10):1185–91.
5. Sohma S, Ichikawa T, Okamoto Y, et al. Endoscopic papillotomy: a new approach for extraction of residual stones. Mexico: The IIIrd International Congress of Gastrointestinal Endoscopy; 1974. p. 19–21.
6. Kawai K, Akasaka Y, Murakami K, et al. Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc. 1974;20(4):148–51.
7. Classen M, Demling L. Endoscopic sphincterotomy of the papilla of vater and extraction of stones from the choledochal duct (author's transl). Dtsch Med Wochenschr. 1974;99(11):496–7.
8. Staritz M, Ewe K, Meyer zum Büschenfelde KH. Endoscopic papillary dilatation, a possible alternative to endoscopic papillotomy. Lancet. 1982;1(8284):1306–7.
9. Mac Mathuna P, White P, Clarke E, et al. Endoscopic sphincteroplasty: a novel and safe alternative to papillotomy in the management of bile duct stones. Gut. 1994;35(1):127–9.
10. Komatsu Y, Kawabe T, Toda N, et al. Endoscopic papillary balloon dilation for the management of common bile duct stones: experience of 226 cases. Endoscopy. 1998;30(1):12–7.
11. Bergman JJ, Rauws EA, Fockens P, et al. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bile duct stones. Lancet. 1997;349(9059):1124–9.
12. Vlavianos P, Chopra K, Mandalia S, et al. Endoscopic balloon dilatation versus endoscopic sphincterotomy for the removal of bile duct stones: a prospective randomised trial. Gut. 2003;52(8):1165–9.
13. Fujita N, Maguchi H, Komatsu Y, et al. Endoscopic sphincterotomy and endoscopic papillary balloon dilatation for bile duct stones: a prospective randomized controlled multicenter trial. Gastrointest Endosc. 2003;57(2):151–5.
14. Disario JA, Freeman ML, Bjorkman DJ, et al. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. Gastroenterology. 2004;127(5):1291–9.

Chapter 19
Mechanical Lithotripsy for Common Bile Duct Stone

Keiji Hanada

Abstract Mechanical lithotripsy (ML) is one of the endoscopic techniques for large, buildup, or multiple common bile duct (CBD) stones. ML is successful in more than 80% of cases where conventional balloon or basket extraction cannot be performed. Stone impactions and large stones (more than 20 mm) are considered to be the most common reasons for failure of ML. Pancreatitis and bleeding have been reported as adverse events after ML. Difficult cases of CBD stones could be treated successfully with ML, and a plastic stent should be applied when CBD stones cannot be cleared completely. As for large stones with surgically altered anatomy, the short-type double-balloon endoscope could allow the use of conventional cannulas for wire-guided cannulation and conventional therapeutic devices of ML. Technical complications such as basket impaction and basket-wire fracture can be mostly managed using an emergency over the basket or an alternative modality. As for the need for ML, endoscopic sphincterotomy (EST) plus endoscopic papillary large balloon dilatation (EPLBD) was associated with a reduced need for ML compared to EST alone and was also associated with a reduction in the overall rate of adverse events.

Keywords Mechanical lithotripsy • Bile duct stone • EST • EPLBD

19.1 Management of Common Bile Duct Stones

19.1.1 Indications of Mechanical Lithotripsy

The endoscopic methods for the removal of common bile duct (CBD) stones have been well established. They involve extraction using various devices after endoscopic papillary balloon dilatation (EPBD) [1] or endoscopic sphincterotomy (EST) [2, 3]. Recently, the success rate for the removal of CBD stones has reached at least 90% after conventional EST [4, 5].

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However, in cases of giant or incarcerated stones, a normal extraction is not always successful. It should be necessary to perform a stone fragmentation to remove the stone. Stone fragmentation can be performed mechanically using a fragmentation basket, extracorporeal shock wave lithotripsy (ESWL), electrohydraulic lithotripsy (EHL), or laser lithotripsy. Among these methods, a mechanical lithotripsy (ML) has been widely accepted, and it is easy to perform [6]. The strategy of management for CBD stones is shown in Fig. 19.1. ML is the most common technique and should be performed in cases with a risk of impaction due to large or buildup stones. The extent of biliary orifice dilatation with EST or EPBD was less than 15 mm, and it is difficult to remove stones with more than 15 mm. Lauri et al. reported that the success rate of removing such large stones using a conventional EST method was only 12% [7]. In such cases, additional fragmentation of large stones using ML or dilatation of the biliary orifice using endoscopic papillary large balloon dilatation (EPLBD) should be performed via conventional EST or EPBD.

19.1.2 Clinical Guidelines for Common Bile Duct Stones

The standards of practice committee of the American Society for Gastrointestinal Endoscopy (ASGE) published a guideline (GL) for management of CBD stones. This GL defined clinical situations associated with difficult bile duct stone extraction

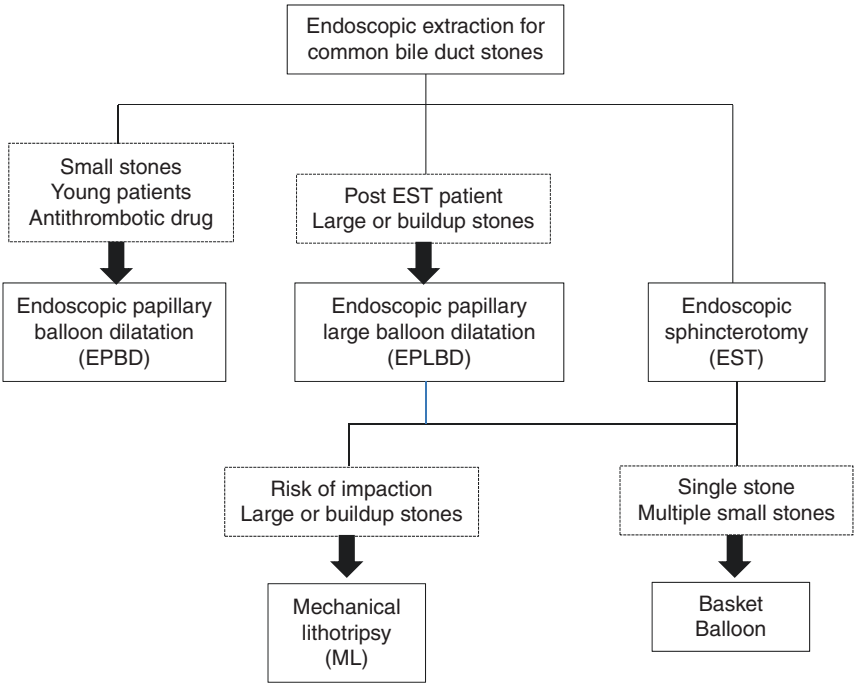

Fig. 19.1 Strategies for treating common bile duct stones

Table 19.1 Clinical situations associated with difficult bile duct stone extraction [9]

• Stones >15 mm
• Stones that cannot be captured in a basket for extraction or mechanical lithotripsy
• Stones associated with complex biliary strictures (e.g., primary sclerosing cholangitis, recurrent pyogenic cholangitis), including hepatolithiasis
• Stones in patients with surgically altered upper gut anatomy (e.g., Roux-en-Y gastric bypass, Billroth II gastrojejunostomy) and Mirizzi syndrome

(Table 19.1) [8]. In this GL, there were 15 recommendations for role of endoscopy in the management of CBD stones. Two out of these 15 recommendations referred to ML. For large, nonimpacted CBD stones refractory to initial extraction efforts, GL suggests that ML and EPBD after EST be considered as next steps, given their effectiveness, ease of use, and acceptable safety profiles. This GL also suggests that in patients with large and/or impacted CBD stones refractory to ML, intraductal lithotripsy (EHL or laser lithotripsy) is preferred over ESWL, given the superior rates of ductal clearance [8].

19.1.3 Clinical Impacts of Mechanical Lithotripsy

The success rate of ML for bile duct stones depends on the character of each stone. Schneider et al. reported that the success rate (SR) of ML was 87.6% in 209 cases with a median stone diameter of 18 mm and that SR of ML decreased to 67.6% in cases with very large stones more than 25 mm in diameter [9]. Hintze et al. evaluated the effectiveness of ML. In unselected series of 704 cases, complete stone clearance by EST and basket extraction was possible in 87.6%, and additional ML led to a success rate of 98.4%. Fragmentation was successful in 77 out of 84 (91.7%) cases treated by ML [10]. Other studies have reported that the success rate of stone fragmentation using ML ranged from 68 to 92% when applied to CBD stones more than 20 mm in diameter [4, 11–14]. Additionally, predictors of unsuccessful ML and endoscopic clearance of large bile duct stones have been reported. Garg et al. reported that the success rate of lithotripsy in 87 cases with large stones that required ML was 79%. They concluded that the impaction, size, shape, and composition of the stone could represent some valuable predictive factors for unsuccessful ML [14]. Due to low rates of stone removal in cases with very large stones, surgery or other alternative nonsurgical procedures such as ESWL or long-term biliary stenting could be a better option [4].

19.2 Techniques of Mechanical Lithotripsy

19.2.1 Devices

Firstly, ML requires capturing bile duct stones with the basket. Then, the basket is pulled back to crush the stones mechanically. Recently, there are many types of basket for ML commercially available. Lithotripsy baskets differ in the method used

Table 19.2 Comparisons of main mechanical lithotripters

Company	Product number	Guidewire guidance	Diameter of basket opening (mm)	Application channel (mm)	Number of wires
Zeon Medical	LBGS-7420S	Absent	30	2.8	4
	LBGS-7320S	Absent	30	2.8	3
	LBGS-8420S	Absent	30	3.2	4
	LBGT-7620S	Absent	30	2.8	6
	LBMT320	Present	30	3.7	3
	LBMT420	Present	30	3.7	4
	LBMT620	Present	30	3.7	6
Olympus	BML-V437QR-30	Present	30	3.7	4
	BML-V232QR-26	Absent	26	3.2	4
	BML-V232QR-30	Absent	30	3.2	4
	BML-V237QR-30	Absent	30	3.7	4
Boston Scientific	1088	Present	25	3.2	4
	1089	Present	30	3.2	4
Medi-Globe	GML-11-26-430	Absent	30	2.8	4
	GML-11-26-630	Absent	30	2.8	6
Cook Medical	G48277	Present	20	4.2	4
	G48278	Present	30	4.2	4

to deliver the guidewire, the full-opened diameter of the basket, and the application channel of the endoscope (Table 19.2). Recently, two main types of mechanical lithotripters are commercially available. One is the through-the-scope lithotripsy baskets with a reusable cranking handle (integrated type). Another type is used after removal of the scope over the basket wires (salvage type).

19.2.2 Standard Procedure of Extraction for Large Stones

The procedure requires capturing the stone within the lithotripter basket into the strong metallic wire mesh. After advancement of the sheath onto the basket with the trapped stone, the handle of the cranking device should be turned slowly to reduce the risk of basket breakdown to crush the stone in smaller fragments [15].

After the procedure of EST, a 0.025″ or 0.035″ guidewire (GW) is introduced into the CBD or intrahepatic bile duct. The lithotripsy basket is introduced into the CBD through the GW in close proximity to the stone, because the stone could be pushed toward the intrahepatic bile duct if the basket is deployed closer to the lower end of the CBD. The metal coil sheath of the lithotripter is identified on the fluoroscope monitor, and the basket is expanded from the distal tip of the coil spring catheter along the stone. With the arms of the basket fully opened, the basket is manipulated forward and backward against the stone until the arms of the basket catch the stone. Moving the basket forward and backward and observing the simul-

taneous movement of the stone contained within the basket can confirm the entrapment of the stone. Targeted stones should be moved as close as possible to the middle of the CBD before being crushed. After the stones are captured, the operator should not close the basket wires too tightly to protect incarceration of the basket. Then stones are captured and mechanically crashed by twisting the handle. It is essential to close the lithotripter basket gently and smoothly to prevent a break of the basket. The stone was fragmented into multiple small pieces, which could be removed subsequently by the basket. The small residual stones can then be retrieved in the traditional way by a basket or balloon (Fig. 19.2).

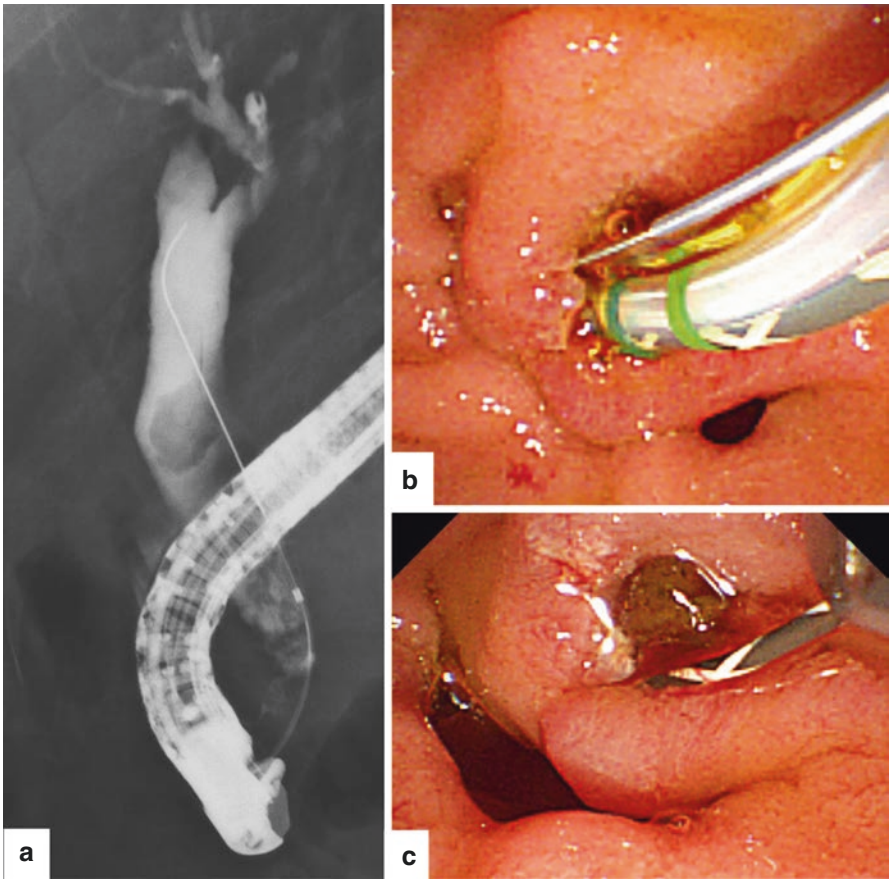

Fig. 19.2 Mechanical lithotripsy and extraction of large common bile duct stones. (**a**) The fluoroscopic view demonstrates multiple stones in the lower common bile duct. (**b**) Endoscopic sphincterotomy is performed through a 0.025″ guidewire. (**c**) A 0.025″ guidewire is introduced into the common bile duct. (**d**, **e**) A lithotripter basket is guided to a location beyond the stones and deployed under the fluoroscopic view. (**f**) Large stone fragments are extracted under the endoscopic view. (**g**) A balloon catheter is introduced into the common bile duct. (**h**, **i**) Small stone fragments are extracted under the endoscopic view

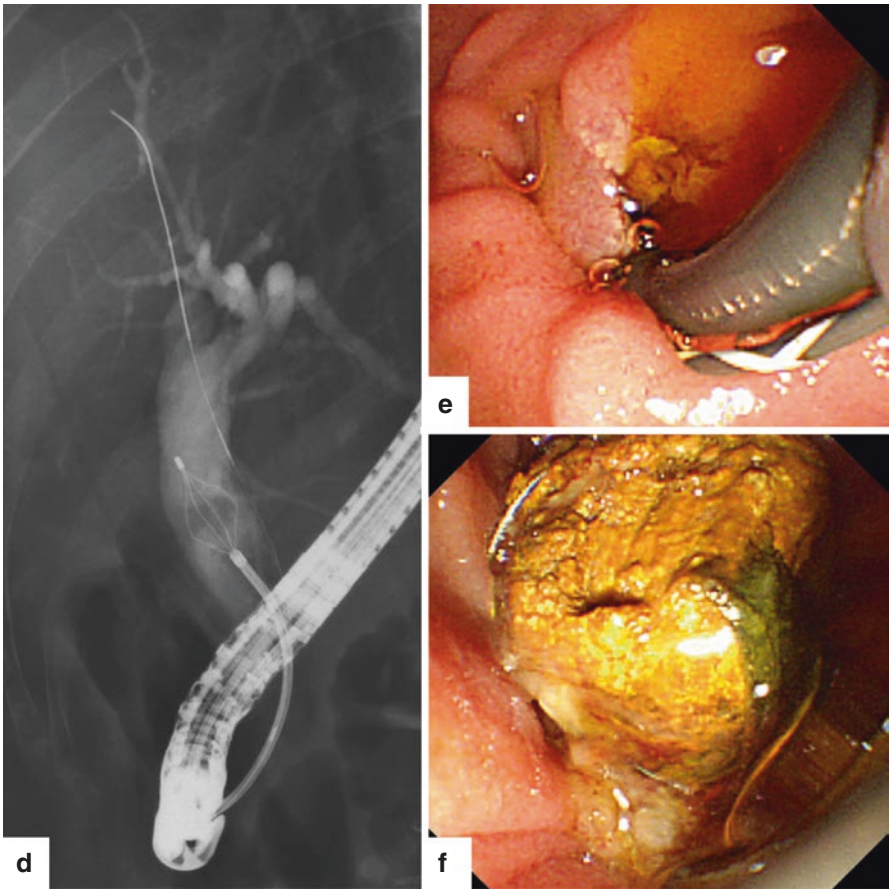

Fig. 19.2 (continued)

ML should be used from the beginning if stone extraction is considered to be difficult because of large stones larger than the diameter of the duodenal scope, hard stones, the presence of multiple buildup stones, or the narrow diameter of the lower end of the CBD [3]. If the stones on the portal side are accidentally captured, the stones closer to the lower end could get in the way to prevent the risk of basket incarceration.

19.2.3 Large Stones with Surgically Altered Anatomy

The endoscopic treatment of CBD stones is challenging in cases with previous reconstructive surgery of Billroth II gastrostomy (Bill-II) and Roux-en-Y reconstruction (R-Y). The GL issued by ASGE suggests that patients who have

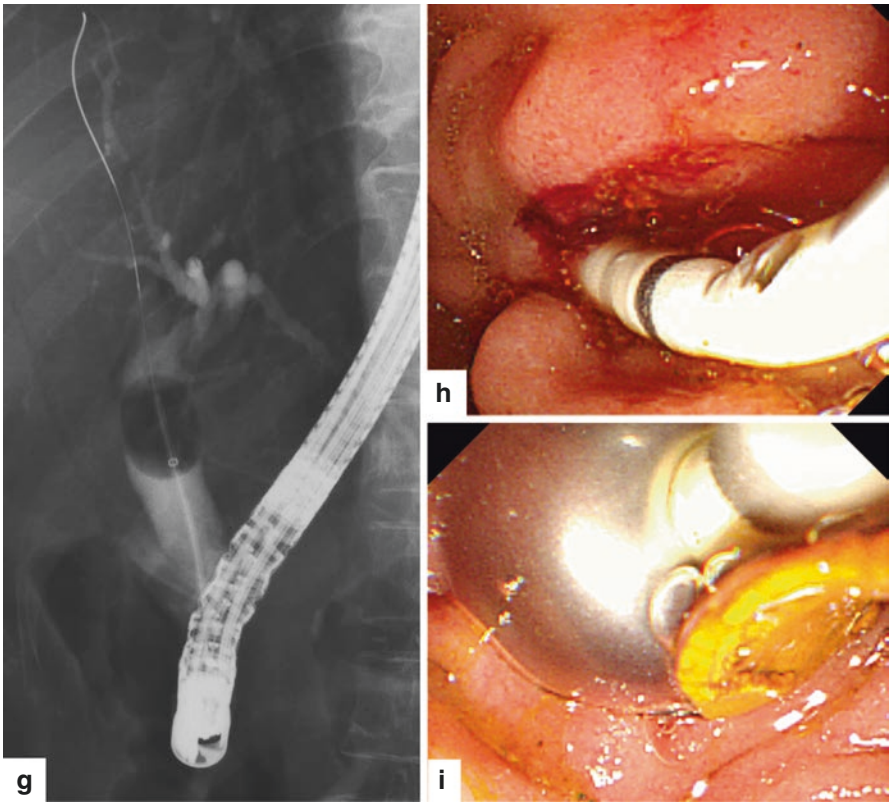

Fig. 19.2 (continued)

undergone these reconstructions should be referred to biliary centers of excellence because of increased complications and lower success rate of endoscopic management of CBD stones [8]. Before removal of CBD stones, it is very important to evaluate the previous surgical record, and required endoscopes and devices should be also considered. The maximum size of working channel in a standard forward-viewing endoscope (FVE), double-balloon endoscope (DBE), and single-balloon endoscope (SBE) is only 2.8 mm; therefore, the ability of ML is so limited [16].

In cases with Bill-II or R-Y, when the endoscope reached the papilla through the afferent loop, the view of the papilla is rotated 180°. It is difficult to cannulate into the papilla with a FVE or DBE because of lack of an elevator for control of cannulation into the CBD. Shimatani et al. reported that the position of the working channel of DBE is located at 6:30, an attempt to bring the papilla in a 6 o'clock direction in the monitor will allow a down-angled maneuver that helps to fix the papilla by a direct power pressure, which facilitates a stable cannulation [17] (Fig. 19.3). It could be recommended that short-type DBE with working length of 1520 mm may be the appropriate endoscope for cannulation in cases with papilla. It has been reported that the overall ERCP success rate using the short-type DBE is 90%. The

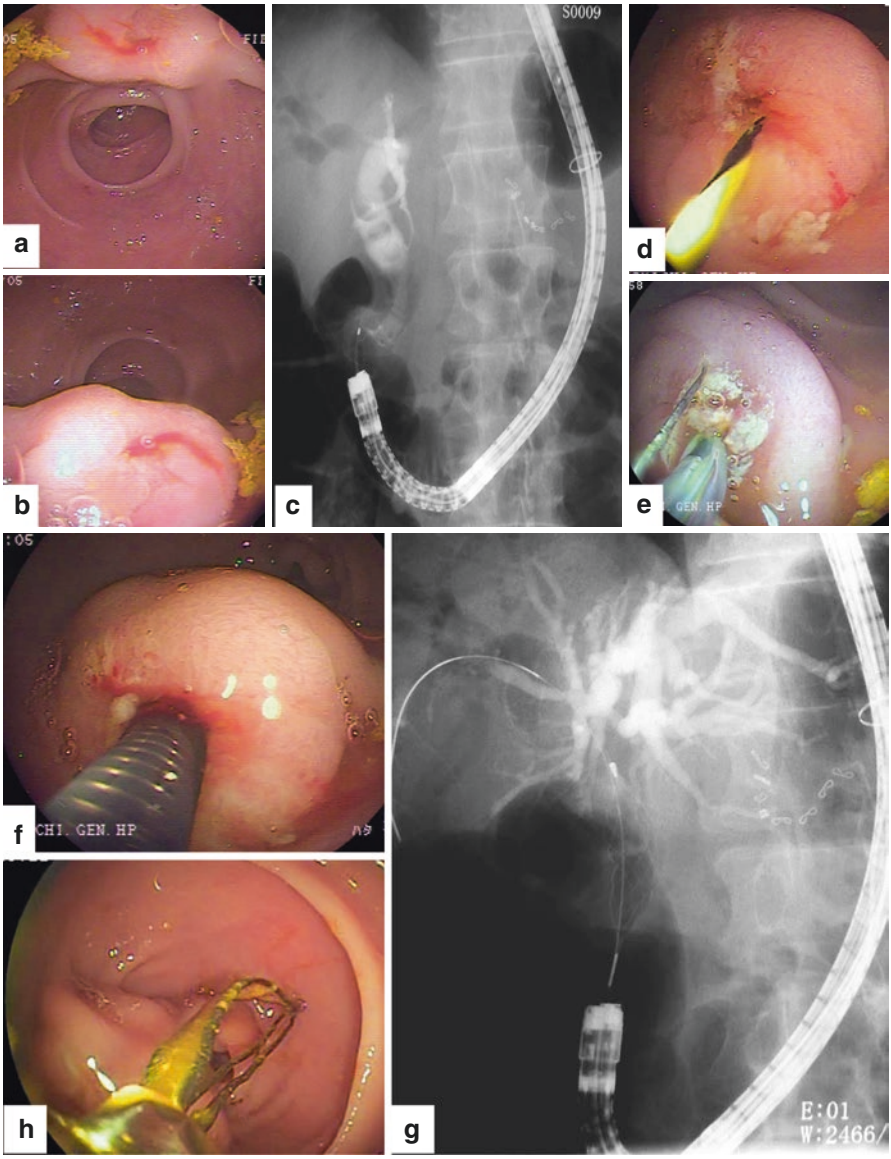

Fig. 19.3 Mechanical lithotripsy in a case with Billroth II gastrostomy treated by a short-type DBE (EI-530B, FUJIFILM, Osaka, Japan). (**a**) Papilla when the blind end was accessed. (**b**, **c**) Locating papilla in 6 o'clock direction in the monitor and performing cannulation and cholangiography. (**d**) Introducing a 0.025″ guidewire into the CBD. (**e**) EST was performed into 12 o'clock direction along the biliary duct. (**f**) A basket catheter for ML was introduced into the CBD. (**h**) Stone fragments were extracted under the endoscope. (**g**) The stones were fragmented into multiple small pieces, which can be removed subsequently by the basket

short-type DBE could allow the use of conventional cannulas for wire-guided cannulation and conventional therapeutic devices [18].

19.2.4 Complications and Trouble Shootings of Mechanical Lithotripsy

The reported incidence of complication with ML ranged from 6 to 13% in large retrospective studies [12, 14]. Pancreatitis, hemobilia, perforation, and sepsis have been reported as common adverse events [19]. Additionally, technical complications, such as basket impaction and traction wire fracture, rarely occur and may pose special management problems. Impaction of a biliary basket due to a hard stone is not an uncommon complication, reported in 0.8–5.9% of cases [20]. Recently, most technical complications can be managed using an external salvage lithotripter or an alternative modality (Fig. 19.4) [8]. It is essential that endoscopy units should have the equipment available to perform a salvage lithotripsy.

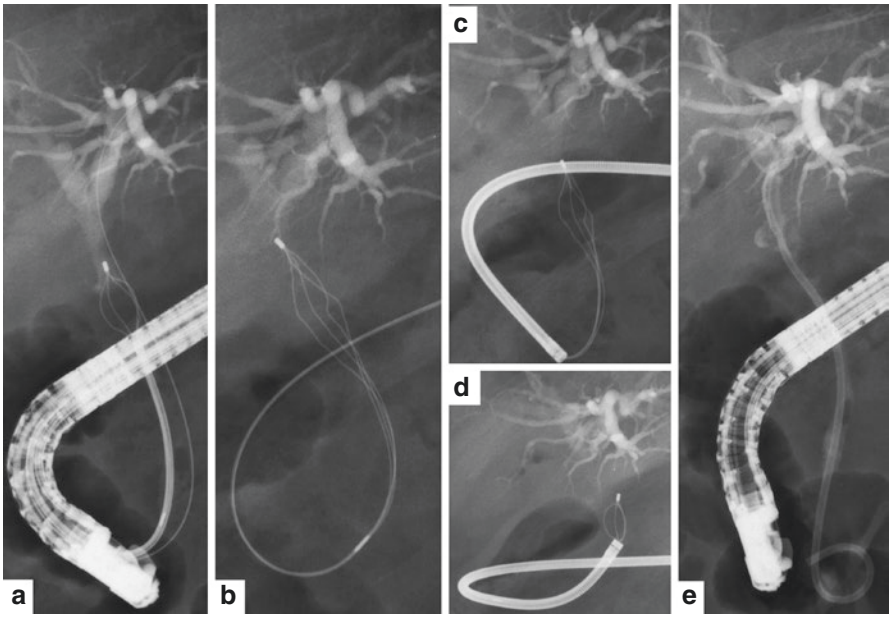

Fig. 19.4 The external salvage lithotripsy for basket or an alternative modality. (**a**) After a large stone was captured by a mechanical lithotripter, basket impaction and traction wire fracture occurred. (**b**) A metal sheath of the mechanical lithotripter and an endoscope was removed. (**c**, **d**) The external salvage lithotripter was introduced through the basket wire and then advanced alongside the basket to crash the impacted stone. (**e**) After the salvage lithotripsy, a double pigtail-type plastic stent was introduced into the common bile duct

19.3 Mechanical Lithotripsy and Biliary Stenting

If ML fails to extract CBD stones, stent insertion may be considered to prevent impaction of stone fragments and reduce the risk of cholangitis.

It has been reported that some resistant stones could be removed easily after stent insertion, and some stones may be expelled [4, 21, 22].

Akcakaya et al. reported 744 ERCP procedures in 592 cases with CBD stones. Stone extraction was performed by basket and/or balloon catheter in 610 ERCP procedures, and ML was performed in 70 ERCP procedures. Stent insertion was performed in 44 cases, and stent replacement was performed in 20 cases. These results suggested that difficult cases of CBD stones could be treated successfully with ML and a plastic stent should be applied when the CBD cannot be cleared completely [23].

19.4 Mechanical Lithotripsy and Large Balloon Dilatation

Recently, EPLBD following EST is a technique that appeared to be safe and effective [24, 25]. Stefanidis et al. designed a prospective randomized controlled trial to compare the therapeutic benefits and complications between EST followed by EPLBD and EST followed by ML for the management of large bile duct stones (>12 mm). They reported that EST followed by EPLBD is equally effective as EST followed by ML for the removal of large bile duct stones, although it is associated with fewer complications [26]. Recently, Madhoun et al. reported a systematic review and meta-analysis by searching nine medical databases for reports published between 1994 and 2013. The aims of this report were to compare EST plus EPLBD versus EST alone for overall clearance of stone, clearance of stones at first session, need for ML, and rate of adverse events. As for the need for ML, EST plus EPLBD was associated with a reduced need for ML compared to EST alone and was also associated with a reduction in the overall rate of adverse events.

19.5 Conclusions

This article documents basic clinical information, techniques, and tips of ML for large CBD stones. For successful lithotripsy for large CBD stones by ML, proper treatment strategies, appropriate devices, and basic techniques should be needed.

References

1. Staritz M, Ewr K, Meyer zum Buschenfelde KH. Endoscopic papillary dilatation, a possible alternative to endoscopic papillotomy. Lancet. 1982;1:1306–7.

2. Kawai K, Akasaka Y, Murakami K, et al. Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc. 1974;20:148–51.
3. Classen M, Demling L. Endoskopishe shinkterotomie der papilla Vateri und Stein extraction aus dem Duktus Choledochus. Dtsch Med Wochenschr. 1974;99:496–7 (In German).
4. Cipolletta L, Costamagna G, Bianco M, et al. Endoscopic mechanical lithotripsy of difficult common bile duct stones. Br J Surg. 1997;84:1407–9.
5. Hochberger J, Tex S, Miass J, et al. Management of common bile duct stones. Gastrointest Endosc Clin Am. 2003;13:623–34.
6. Shim CS. Should biliary stones be managed? Gut Liver. 2010;4:161–72.
7. Lauri A, Horton RC, Davidson BR, et al. Endoscopic extraction of bile duct stones: management related to stone size. Gut. 1993;34:1718–21.
8. The standards of practice committee of American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of choledocholithiasis. Gastorintest Endosc. 2011;74:731–44.
9. Schneider MU, Matek W, Bauer R, et al. Mechanical lithotripsy of bile duct stones in 209 patients–effect of technical advances. Endoscopy. 1988;20:248–53.
10. Hintze RE, Adler A, Veltzke W, et al. Outcome of mechanical lithotripsy of bile duct stones in an unselected series of 704 patients. Hepato-Gastroenterology. 1996;43:473–6.
11. Shaw MJ, Mackie RD, Moore JP, et al. Results of a multicenter trial using a mechanical lithotripter for the treatment of large bile duct stones. Am J Gastroenterol. 1993;88:730–3.
12. Chang WH, Chu CH, Wang TE, et al. Outcome of simple use of mechanical lithotripsy of difficult common bile duct stones. World J Gastroenterol. 2005;11:593–6.
13. Van Dam J, Sivak MV Jr. Mechanical lithotripsy of large common bile duct stones. Cleve Clin J Med. 1993;60:38–42.
14. Garg PK, Tandon RK, Ahuja V, et al. Predictors of unsuccessful mechanical lithotripsy and endoscopic clearance of large bile duct stones. Gastrointest Endosc. 2004;59:601–5.
15. Neuhaus H. Endoscopic and percutaneous treatment of difficult bile duct stones. Endoscopy. 2003;35:S31–4.
16. Katanuma A, Maguchi H, Osanai M, et al. Endoscopic treatment of difficult common bile duct stones. Dig Endosc. 2010;22(Suppl 1):S90–7.
17. Shimatani M, Takaoka M, Tokuhara M, et al. Review of diagnostic and therapeutic endoscopic retrograde cholangiopancreatography using several endoscopic methods in patients with surgically altered gastrointestinal anatomy. World J Gastrointest Endosc. 2015;7:617–27.
18. Siddiqui AA, Chaaya A, Shelton C, et al. Utility of the short double-balloon enteroscope to perform pancreatobiliary interventions in patients with surgically altered in a US multicenter study. Dig Dis Sci. 2013;58:858–64.
19. Sim CS. How should biliary stones be managed? Gut Liver. 2010;4:161–72.
20. Siegel JH. Stone extraction. In: Siegel JH, editor. Endoscopic retrograde cholangiopancreatography: technique, diagnosis, and therapy. New York: Raven Press; 1992. p. 243.
21. Binmoller KF, Brückner M, Thonke F, et al. Treatment of difficult bile stones using mechanical, electrohydraulic and extracorporeal shock wave lithotripsy. Endoscopy. 1993;25:201–6.
22. Chan AC, Ng EK, Chung SC, et al. Common bile duct stones become smaller after endoscopic biliary stenting. Endoscopy. 1998;30:256–359.
23. Akcakaya A, Ozkan OV, Bas G, et al. Mechanical lithotripsy and/or stenting in management of difficult common bile duct stones. Hepatobiliary Pancreat Dis Int. 2009;5:524–8.
24. Itoi T, Itokawa A, Sofuni A, et al. Endoscopic sphincterotomy combined with large-balloon dilatation can reduce the procedure time and fluoroscopy time for removal large bile duct stones. Am J Gastroenterol. 2009;104:560–5.
25. Draganov PV, Evans W, Fazel A, et al. Large size balloon dilatation of the ampulla after biliary sphincterotomy can facilitate endoscopic extraction of difficult bile duct stones. J Clin Gastroenterol. 2009;43:782–6.
26. Madhoun MF, Wani S, Hong S, et al. Endoscopic papillary balloon dilatation reduces the need for mechanical lithotripsy in patients with large bile duct stones: a systematic review and meta-analysis. Diagn Ther Endosc. 2014;2014:309618. https://doi.org/10.1155/2014/309618. Epub 2014 Mar 6.

Chapter 20
Electrohydraulic Lithotripsy and Laser Lithotripsy

Koji Uno and Kenjiro Yasuda

Abstract Mechanical lithotripsy is usually employed for the fragmentation of large common bile duct (CBD) stones. However, refractory CBD stones, stones larger than 2 cm in size, those firmly impacted, those located above a bile duct stricture, and those located in the intrahepatic bile duct, or cases of Mirizzi syndrome are difficult to treat. Recently, electrohydraulic lithotripsy (EHL) or laser lithotripsy has been indicated for the foregoing cases. EHL and laser lithotripsy are usually performed under cholangioscopic guidance with irrigation inside the CBD in order to clearly visualize the lumen and remove debris. The stone clearance rates of EHL and laser lithotripsy range from 74% to 95% and from 88% to 97%, respectively. Most complications related to EHL or laser therapy are associated with endoscopic retrograde cholangiopancreatography or percutaneous transhepatic biliary drainage, such as pancreatitis, hemorrhage, perforation, and sepsis. The overall complication rate of EHL or laser lithotripsy was reported to be 7–9%, including hemobilia and cholangitis. Perforation of the bile duct due to EHL or laser lithotripsy is rare. Further refinements of the EHL instruments, laser lithotripsy instruments, and cholangioscope are required for improving the ease of use of EHL and laser lithotripsy.

Keywords Electrohydraulic lithotripsy • Laser lithotripsy • Bile duct stone

20.1 Introduction

Since endoscopic sphincterotomy (EST) was developed in 1974 [1], endoscopic treatment of common bile duct (CBD) stones has been refined gradually. Nowadays, although most CBD stones can be extracted via a basket or balloon catheter after EST, large stones require lithotripsy. Mechanical lithotripsy is usually employed for

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the fragmentation of CBD stones [2]. However, refractory CBD stones that are larger than 2 cm in size are difficult to treat. Recently, the use of shock waves, which are generated by electrohydraulic or laser technology, within the bile duct has been indicated for the foregoing cases (Figs. 20.1 and 20.2) [3, 4]. We have reported the usefulness of electrohydraulic lithotripsy (EHL) for CBD stones using peroral cholangioscopy (mother and baby system, TJF-M20 and CHF-B20; Olympus Medical Systems) [5]. In this chapter, the present status of EHL and laser lithotripsy is described on their techniques, indications, and results.

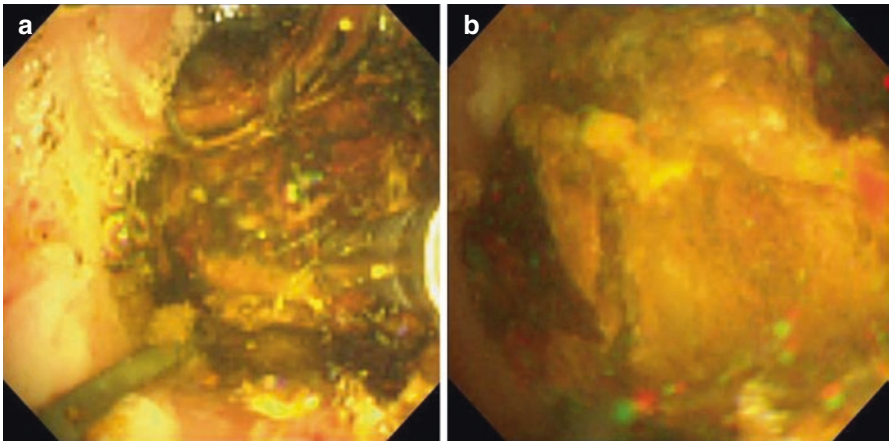

Fig. 20.1 Cholangioscopy showing a common bile duct stone treated with electrohydraulic lithotripsy (EHL). (**a**) Before EHL. (**b**) After EHL

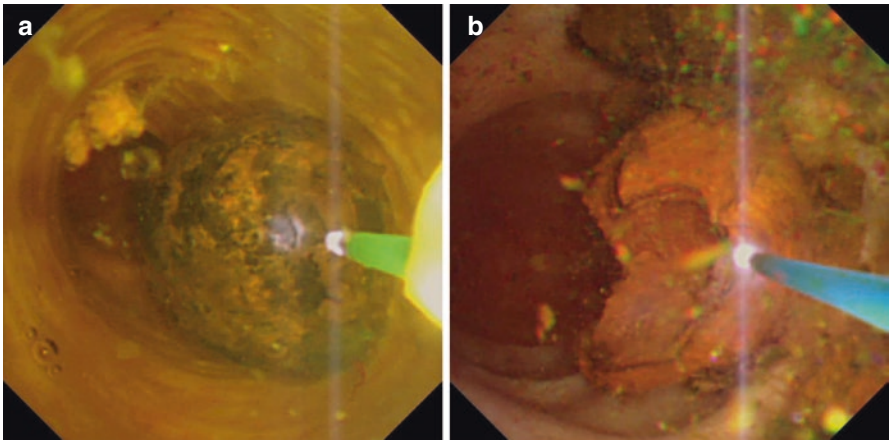

Fig. 20.2 Cholangioscopy showing a common bile duct stone treated with holmium:yttrium-aluminum-garnet laser lithotripsy. (**a**) Before laser lithotripsy. (**b**) After laser lithotripsy. Images provided by Prof. Chan Sup Shim (Konkuk University Medical Center)

20.2 Electrohydraulic Lithotripsy

20.2.1 Instruments and the Examination Technique

The electric sparks discharged from the tip of the EHL probe generate shock waves, which crush the bile duct stones. Although EHL for CBD stones was previously applied using balloon catheters under fluoroscopic guidance, this procedure could injure the CBD wall. Nowadays EHL is usually performed under peroral or percutaneous cholangioscopic guidance to adequately advance the EHL probe close to the CBD stone (Figs. 20.3 and 20.4) [3].

The tip of the EHL probe, which is available in Japan (AUTOLITH®, Northgate Technologies, Inc., Elgin, IL, USA), is 1.9 Fr (0.66 mm) in diameter, and this probe can be inserted through the 1.2-mm working channel of the cholangioscope (CHF-B260; Olympus Medical Systems, Tokyo, Japan) (Tables 20.1 and 20.2). The cholangioscope is usually inserted through the working channel of the therapeutic duodenoscope (TJF-260V; Olympus Medical Systems) in peroral cholangioscopy (mother and baby scope system), which is usually preferred to percutaneous transhepatic cholangioscopy. While inserting the EHL probe into the working channel of the cholangioscope, the operator should be careful not to injure the inner surface of the working channel, because the tip of the EHL probe is rigid. In order to avoid

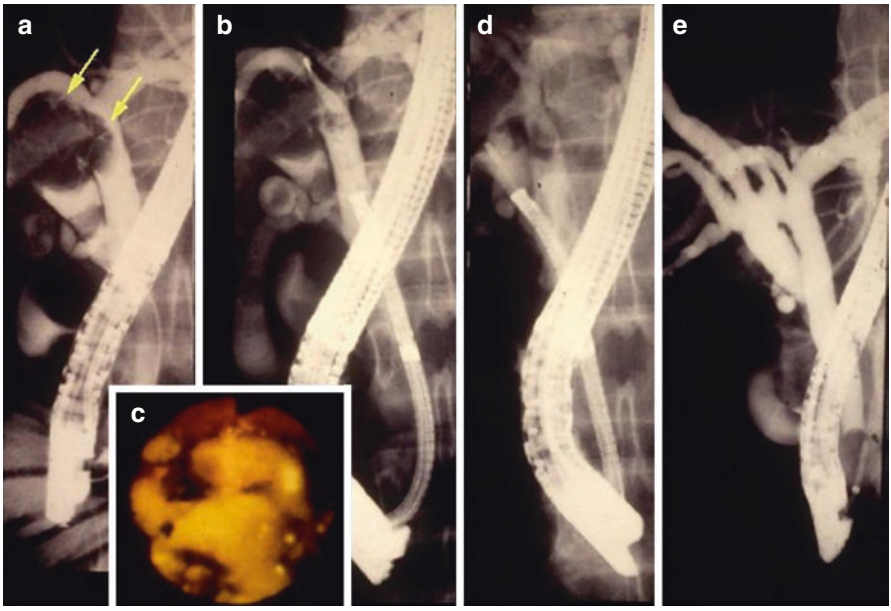

Fig. 20.3 (**a**) Cholangiography showing an intrahepatic stone (arrow). (**b**) Cholangiography showing extraction of stones by the basket catheter. (**c**, **d**) Cholangioscopy and cholangiography showing electrohydraulic lithotripsy (EHL) under cholangioscopic guidance. (**e**) After stone removal

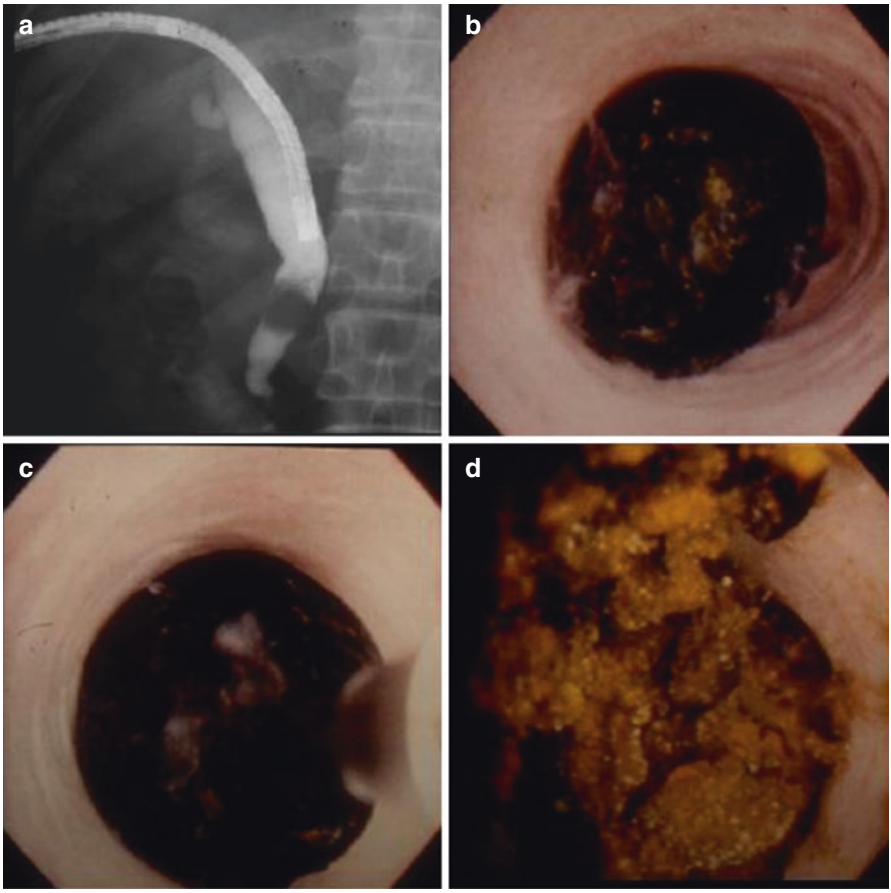

Fig. 20.4 (**a**, **b**) Cholangiography and cholangioscopy showing a CBD stone. (**c**) Cholangioscopy showing electrohydraulic lithotripsy (EHL) for the CBD stone. (**d**) After EHL

Table 20.1 Characteristics of electrohydraulic lithotripsy and laser lithotripsy

	Electrohydraulic	Laser lithotripsy
Visualization device	Cholangioscope	Cholangioscope
Tip diameter of the probe (mm)	0.66	≤1
Cost of the system	Relatively low	High
Stone clearance rate	74–95%	88–97%
Complication rate	7–9%	7–9%

damage to the working channel, a lubricating liquid such as olive oil or liquid silicone is injected into the working channel before inserting the EHL probe. While advancing the EHL probe through the working channel, the bending parts of the duodenoscope and cholangioscope have to be straightened. During EHL, irrigation inside the CBD is necessary to transmit shock wave energy for clearly visualizing

Table 20.2 Specifications of the cholangioscopes

	CHF-B260	SpyGlass
Type of image	Videoscope	Fiberscope[a]
Tip diameter (mm)	3.4	3.3 (delivery catheter)
Internal diameter of the working channel (mm)	1.2	1.2 (0.6: irrigation channel)
Bending section	Two-way deflection	Four-way deflection

[a]Recently, a videoscope has been developed

the lumen and removing debris. After EHL, the crushed stones are removed via ordinary methods such as basket or balloon catheterization.

Recently, a single-operator peroral cholangioscope (SpyGlass, Boston Scientific Corporation, Natick, MA, USA), which consists of a delivery catheter and a fiber optic probe, was developed (Table 20.2) [6]. This cholangioscope system is relatively durable, and this system is used for EHL. Currently, new digital single-operator peroral cholangioscope instruments are being developed.

A direct peroral cholangioscopy using ultraslim endoscope for diagnosis and treatment of biliary disorders is currently under development. This technique can be applied for EHL.

20.2.2 Indications and Clinical Outcomes

Most large CBD stones can be treated with mechanical lithotripsy (success rate 79–92%) [4]. Recently, some cases of large CBD stones in the dilated CBD were treated via endoscopic papillary balloon dilation using a large-sized balloon after EST. However, the remaining refractory cases such as larger than 2-cm stones, firmly impacted stones, stones located above a bile duct stricture, or intrahepatic bile duct stones are indications for EHL. EHL is also used for stone removal in some cases of Mirizzi syndrome.

The cost of the EHL system is relatively low compared to other shock wave lithotripsies such as laser lithotripsy or extracorporeal shock wave lithotripsy (ESWL). In case of lithotripsy with ESWL, several sessions and targeting via cholangiography using nasobiliary drainage are usually required. Furthermore, in most CBD stones treated with ESWL, fragments must be removed via ordinary endoscopic extraction.

For bile duct stones, the fragmentation rate of EHL ranges from 82% to 98%, and the clearance rate of EHL ranges from 74% to 95% (Table 20.1) [4]. Binmoeller et al. reported that the clearance rate of EHL via peroral cholangioscopy for refractory CBD stones was 98% (64/65), and a cholangioscope could not be passed through a CBD stricture in one case of treatment failure [7]. Adamek et al. reported the treatment results for patients with CBD stones that could not be treated via conventional endoscopic procedures. According to their report, the clearance rate was 78.5% in 79 patients treated with ESWL and 74% in 46 patients treated with

EHL. The overall success rate of combined treatment including ESWL, EHL, and laser lithotripsy was 94% [8]. Adamek et al. also reported the treatment results for patients with intrahepatic stones that could not be treated via conventional endoscopic procedures. According to their report, the stone fragmentation rate was 33% in 27 patients treated with ESWL, 41.6% in 12 patients treated with EHL, and 75% in 16 patients treated with laser lithotripsy. The overall success rate of combined treatment including ESWL, EHL, and laser lithotripsy was more than 90% [9].

Most complications related to EHL or laser therapy are associated with endoscopic retrograde cholangiopancreatography or percutaneous transhepatic biliary drainage, such as pancreatitis, hemorrhage, perforation, and sepsis. The overall complication rate of EHL or laser lithotripsy was reported to be 7–9%, including hemobilia and cholangitis (Table 20.1) [3]. Although perforation of the bile duct due to EHL or laser lithotripsy can occur, its frequency is rare.

20.3 Laser Lithotripsy

20.3.1 Instruments and the Examination Technique

Pulsed laser discharged from the tip of the laser probe produces shock waves, which fragment bile duct stones. Previously, several laser lithotripsy systems have been developed. Recently, the holmium:yttrium-aluminum-garnet (YAG) laser is the preferred alternative endoscopic procedure for refractory bile duct stones (Fig. 20.2). Previously, laser lithotripsy for bile duct stones was applied under fluoroscopic guidance; however, the laser could damage the bile duct wall. Nowadays laser lithotripsy is usually performed under peroral or percutaneous cholangioscopic guidance, because it is necessary to advance the tip of the laser probe to the bile duct stone in order to achieve effective fragmentation and avoid injury to the bile duct wall (Table 20.1). The tip of the laser probe is 1000 μm or below in diameter, and this probe can be inserted through the working channel of the cholangioscope. As with EHL, irrigation inside the CBD is necessary in order to clearly visualize the lumen and remove debris during laser lithotripsy. After laser lithotripsy, fragmented stones are removed via ordinary endoscopic extraction [3].

20.3.2 Indications and Clinical Outcomes

For bile duct stones, the indications for laser lithotripsy are the same as these for EHL. Because the cost of the laser system is high compared to the EHL system, their routine use is limited to specialized centers.

The clinical effectiveness of laser lithotripsy is similar to that of EHL in patients with bile duct stones. The clearance rate of laser lithotripsy for bile duct stones is

reported to range from 88% to 97% (Table 20.1) [4]. Jakobs et al. reported the results of lithotripsy in patients with refractory extrahepatic bile duct stones. According to their study, the complete stone fragmentation rate of laser lithotripsy (82.4%) was higher than that of ESWL (52.4%), and that of the combined method was 91.2%. Furthermore, the number of fragmentation sessions and additional endoscopic sessions was less in patients treated with laser lithotripsy [10]. Patel et al. reported the results of laser lithotripsy using the holmium:YAG laser under cholangioscopic guidance for intrahepatic or extrahepatic bile duct stones in their multicenter study. According to their study, the complete clearance rate was 97%, and one session was required for stone clearance in most patients [11]. Jiang et al. reported the results of laser lithotripsy under cholangioscopic guidance with or without hepatectomy compared to the traditional surgical technique. According to their study, the final stone clearance rate was 93.3% in patients treated with laser lithotripsy and 85.4% in patients treated with the traditional surgical technique. The complication rate of patients in the laser lithotripsy group was relatively lower than that of the patients in the traditional operation group (11.1% vs. 22.9%, $p = 0.13$) [12].

The complications related to laser lithotripsy are as previously described (see Sect. 20.2.2).

20.4 Conclusion

EHL and laser lithotripsy are effective and relatively safe for patients with refractory bile duct stones, which are difficult to remove via mechanical lithotripsy. However, the applications of EHL and laser lithotripsy are limited because the instruments for these procedures are quite expensive, especially that used for laser lithotripsy, and the ability of a cholangioscope, which is applied for direct visualization while using EHL or laser lithotripsy, is insufficient. Further refinements of not only the EHL or laser lithotripsy instruments but also the cholangioscope are required in order to improve the ease of use of EHL and laser lithotripsy.

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References

1. Kawai K, Akasaka Y, Murakami K, et al. Endoscopic sphincterotomy of the ampulla of Vater. Gastrointest Endosc. 1974;20:148–51.
2. Nakajima M, Yasuda K, Cho E, et al. Endoscopic sphincterotomy and mechanical basket lithotripsy for management of difficult common bile duct stones. J Hepato-Biliary-Pancreat Surg. 1997;4:5–10.
3. DiSario J, Chuttani R, Croffie J, et al. Biliary and pancreatic lithotripsy devices. Gastrointest Endosc. 2007;65:750–6.

4. ASGE Standards of Practice Committee. The role of endoscopy in the management of choledocholithiasis. Gastrointest Endosc. 2011;74:731–44.
5. Yasuda K, Nakajima M, Cho E, et al. Comparison of peroral and percutaneous cholangioscopy. Endoscopy. 1989;21:347–50.
6. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc. 2007;65:832–41.
7. Binmoeller KF, Brückner M, Thonke F, et al. Treatment of difficult bile duct stones using mechanical, electrohydraulic and extracorporeal shock wave lithotripsy. Endoscopy. 1993;25:201–6.
8. Adamek HE, Maier M, Jakobs R, et al. Management of retained bile duct stones: a prospective open trial comparing extracorporeal and intracorporeal lithotripsy. Gastrointest Endosc. 1996;44:40–7.
9. Adamek HE, Schneider AR, Adamek MU, et al. Treatment of difficult intrahepatic stones by using extracorporeal and intracorporeal lithotripsy techniques: 10 years' experience in 55 patients. Scand J Gastroenterol. 1999;34:1157.
10. Jakobs R, Adamek HE, Maier M, et al. Fluoroscopically guided laser lithotripsy versus extracorporeal shock wave lithotripsy for retained bile duct stones: a prospective randomised study. Gut. 1997;40:678–82.
11. Patel SN, Rosenkranz L, Hooks B, et al. Holmium-yttrium aluminum garnet laser lithotripsy in the treatment of biliary calculi using single-operator cholangioscopy: a multicenter experience (with video). Gastrointest Endosc. 2013;79:344–8.
12. Jiang ZJ, Chen Y, Wang WL, et al. Management hepatolithiasis with operative choledochoscopic FREDDY laser lithotripsy combined with or without hepatectomy. Hepatobiliary Pancreat Dis Int. 2013;12:160–4.

Chapter 21
Intrahepatic Stone

Ichiro Yasuda, Shinpei Doi, and Masatoshi Mabuchi

Abstract Surgical resection of the affected liver segment has been considered to play a primary role in treating intrahepatic stones, because of their strong association with intrahepatic cholangiocarcinoma and the high incidence of recurrent stones after nonoperative treatments. Percutaneous transhepatic cholangioscopy-guided lithotripsy (PTCS-L) is safe and effective for removing intrahepatic stones when surgical resection is not suitable or is refused by patients. However, if the patient had biliary stricture, the stricture should be carefully evaluated in order not to overlook accompanying biliary cancer. In addition, stones should be removed as completely as possible, and the stricture should be treated to reduce later complications such as recurrent stones and cholangiocarcinoma. The endoscopic transpapillary approach is also available in cases without biliary stricture. However, its indication for intrahepatic stones remains controversial because of its low success rate and high recurrence rate. In postoperative cases (after hepaticojejunostomy), PTCS-L has also been attempted. However, more recently, balloon-assisted enteroscopes have also been used for stone extraction in postoperative cases.

Keywords Intrahepatic stone • PTCS • POCS • Enteroscope

21.1 Epidemiology, Pathogenesis, and Symptoms

Intrahepatic stones are extremely rare in Western countries but are more frequent in Eastern Asia. The relative proportion of intrahepatic stones among all gallstone diseases is 0.6–1.3% in Western countries, 47.3% in Taiwan, 38.0% in China, 17.0% in Korea, 11.7% in Malaysia, and 2.1% in Japan [1]. They were common in Japan as in other East Asian countries until the 1950s. However, the number of affected patients decreased consistently after that and significantly decreased after the 1990s [2].

The pathogenesis of intrahepatic stones is complicated and probably involves a combination of bile stasis, biliary infection, malnutrition, and parasitic infesta-

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tion. Bile stasis associated with biliary stenosis primarily leads to bacterial colonization and stone formation. Biliary stricture is present in most patients with intrahepatic stones (~80%) [1]. It can be caused by biliary injury, sclerosing cholangitis, biliary cancer, and anatomical anomalies such as choledochal cysts and Caroli's disease. However, the cause of the stricture is often unclear. In addition, postoperative biliary strictures, such as after biliary surgeries, partial hepatectomy, and liver transplantation, have recently become popular causes of intrahepatic stones.

Primary intrahepatic stones occur more frequently in the left hepatic lobe than in the right hepatic lobe. The left hepatic duct forms an acute angle at the junction with the common bile duct and tends to induce cholestasis when associated with biliary strictures [1].

Intrahepatic stones lead to recurrent cholangitis, which presents as abdominal pain, fever, and jaundice. Chronic cholangitis causes cholestasis with symptoms of jaundice and pruritus, leading to liver abscess and/or secondary liver cirrhosis. However, a more important complication associated with intrahepatic stones is cholangiocarcinoma, which has an incidence of 2–10% in patients with intrahepatic stones [3–5]. From a nationwide Japanese survey, cholangiocarcinoma was identified in 1.3–5.9% of patients with hepatolithiasis [2]. In addition, it appears to develop in 10% of patients with intrahepatic stones, even after complete removal of intrahepatic stones [1]. Thus, careful follow-up is important, regardless of whether the stones are removed.

21.2 Treatment Strategy for Intrahepatic Stones

Surgical resection of the affected liver segment has been considered to play a primary role in treating patients with intrahepatic stones because long-standing intrahepatic stones are known to lead to intrahepatic cholangiocarcinoma, and stone recurrence is often observed after nonoperative treatments [6, 7]. A history of choledochoenterostomy and liver atrophy is a significant predictive factor for cholangiocarcinoma associated with hepatolithiasis [8]. Therefore, in cases of liver atrophy suspected of being associated with malignancy, surgical resection is strongly recommended. Percutaneous transhepatic cholangioscopy-guided lithotripsy (PTCS-L) is an alternative therapeutic technique when surgical resection is refused by patients or when it is not suitable as a result of the patient's condition or the presence of stones in multiple segments. In addition, endoscopic transpapillary removal of intrahepatic stones can be also attempted. However, such removal is often difficult, because most patients with intrahepatic stones have biliary strictures in the downstream bile duct, with stone impaction and ductal angulation of the hilar and intrahepatic bile ducts. Therefore, the indication of endoscopic transpapillary therapy is generally limited to cases without biliary stricture.

If any symptoms are not present and malignant features are not suspected based on imaging and blood tests, patients can be observed carefully. However, if a patient

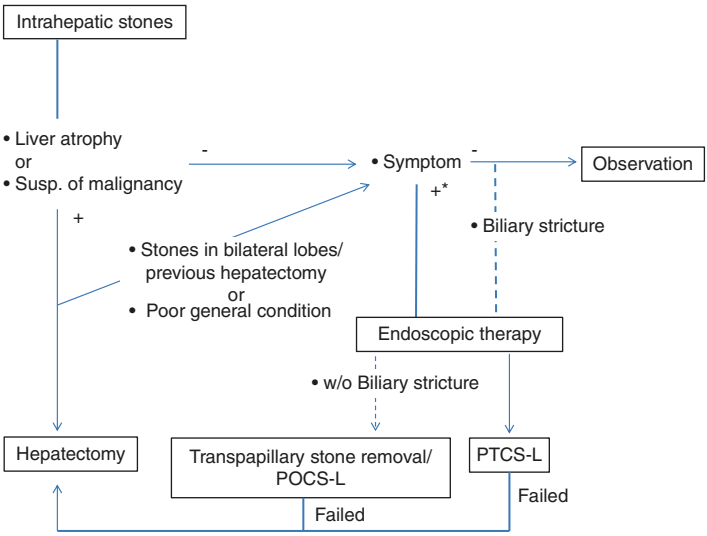

Fig. 21.1 Treatment strategy for intrahepatic stones. *POCS-L* peroral cholangioscopy-guided lithotripsy, *PTCS-L* percutaneous transhepatic cholangioscopy-guided lithotripsy

has had a biliary stricture, careful evaluation, including endoscopic pathological sampling (such as brush cytology and/or biopsy), should be considered to rule out biliary cancer before choosing observation (Fig. 21.1).

Based on nationwide Japanese survey data collected over a period of 40 years [2], surgery was the primary treatment for intrahepatic stones until 1998, but nonsurgical procedures have since became increasingly more popular. PTCS-L has been the most frequently performed nonsurgical technique. However, more recently, endoscopic transpapillary stone extraction has also been frequently attempted [2]. The reasons have not been clearly indicated. However, intrahepatic stones sometimes cause severe cholangitis, and they are often refractory to treatment with antibiotics. In such situations, percutaneous transhepatic or endoscopic transpapillary biliary drainage is first considered as a method of resolution. Afterward, subsequent stone removal may be attempted via the same routes. However, endoscopic transpapillary drainage is usually technically difficult and has not been established for intrahepatic stones, as previously noted. Therefore, percutaneous transhepatic biliary drainage (PTBD) appears to be preferentially recommended (Fig. 21.1).

21.3 Endoscopic Therapies

Endoscopic therapies are divided into two approaches, namely, the percutaneous transhepatic approach and the transpapillary approach. The transpapillary approach is further divided by whether or not peroral cholangioscopy (POCS) is used.

21.3.1 PTCS

In 1976, Yamakawa et al. [9] reported the usefulness of stone removal using PTCS for retained biliary stones after the surgical exploration of bile duct stones. In that report, the cholangioscope was inserted into the bile duct through the T-tube. Later, Nimura [10] introduced PTCS-L for intrahepatic stones through the PTBD route in 1981.

Currently, PTCS-L is an alternative therapeutic technique when surgical resection is not suitable as a result of the patient's condition or the presence of stones in multiple segments.

In this technique, the PTBD was initially placed in the affected intrahepatic bile duct. The placed catheter was then stepped up to a diameter of 16–18Fr in a single or repeated sessions, and the tract was dilated in order to pass the cholangioscope.

The PTBD fistula is usually established in 2 weeks. After that, the cholangioscope can be inserted into the bile duct through the fistula. A basket catheter is inserted via the working channel of the scope, and the stones are captured using the basket catheter under the guidance of direct vision with cholangioscopy or fluoroscopy. Then, the stones are extracted from the body by pulling out the scope. However, the fistula usually has too small a diameter to extract the stones as they are. Therefore, electrohydraulic lithotripsy (EHL) or laser lithotripsy is used to disintegrate the stones [11]. After the disintegration, the stone fragments are removed through the tract. During the procedure, normal saline is infused via the working channel of the scope so that a clear endoscopic view is maintained (Fig. 21.2).

Biliary stricture is primarily found in patients with intrahepatic stones, and it affects the short- and long-term outcomes, as described below. Therefore, the stricture should be treated during or after the stone removal session. After insertion of a guidewire through the stricture, a balloon dilation catheter and/or a drainage catheter itself is inserted to dilate the stricture (Fig. 21.2).

Previous reports have demonstrated a complete clearance rate of 80–89.4% with a complication rate of 15–23%. Complications are usually not serious and are primarily caused by temporary cholangitis. Serious complications have been reported to occur in 0–2.1% of cases, including liver lacerations, disruption of the PTBD fistula, intra-abdominal abscesses, hemobilia, and septic shock [4, 12–16].

During long-term follow-up after PTCS-L, the overall recurrence rate of the stones and/or cholangitis was reported to be 35–63.2%. In these cases, intrahepatic duct strictures are considered to be the main factors contributing to incomplete clearance and stone recurrence [4, 13–16].

Thus, PTCS-L is an effective and safe alternative to surgery for removing intrahepatic stones. However, more than 2 weeks are usually required for creation and dilation of the percutaneous transhepatic tract [17]. In addition, a PTBD tube must be kept in place throughout the treatment period. Therefore, this technique is somewhat invasive, time-consuming, and painful.

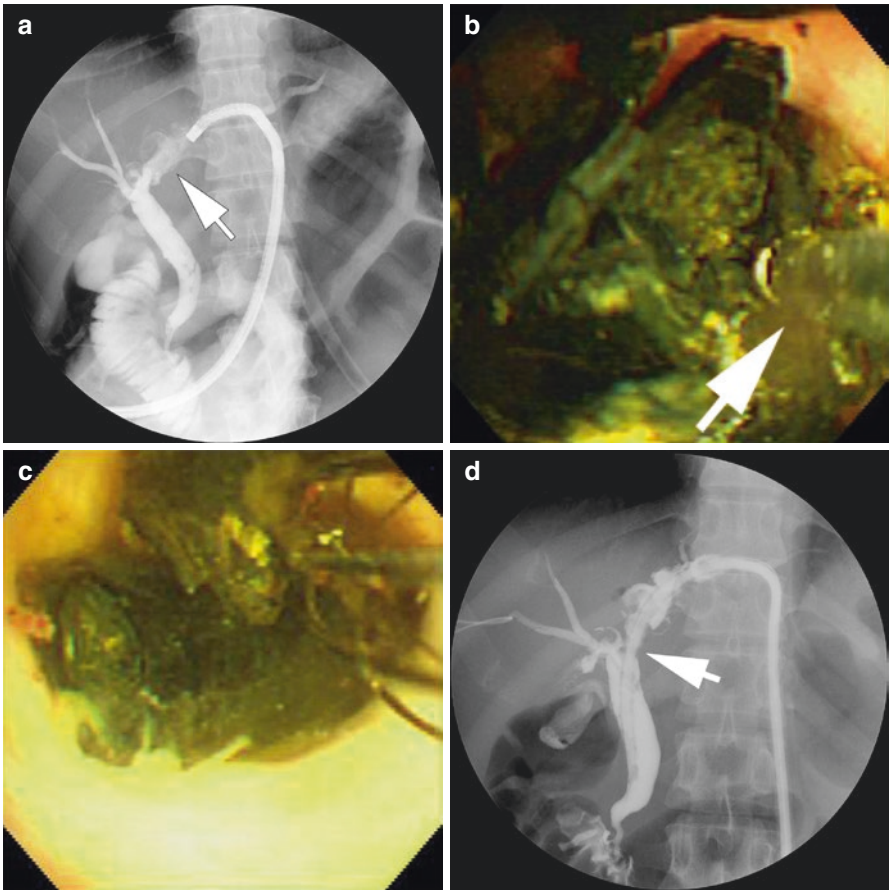

Fig. 21.2 PTCS-guided lithotripsy (PTCS-L). (**a**) The white arrow indicates the stone in the left hepatic duct. (**b**) PTCS-guided electrohydraulic lithotripsy (EHL) was performed. The white arrow indicates an EHL probe. (**c**) Stone fragments were extracted using a basket catheter. (**d**) After the initial session of PTCS-L, a PTBD catheter was placed through the biliary stricture to dilate it. The white arrow indicates the stricture site

21.3.2 Endoscopic Transpapillary Stone Extraction

In contrast to PTCS-L, endoscopic transpapillary stone extraction may be less invasive and more convenient. Endoscopic transpapillary stone extraction following endoscopic sphincterotomy (ES) is a well-established standard technique for treating bile duct stones. However, as mentioned above, most patients with intrahepatic stones have biliary strictures in the downstream bile duct. Therefore, dilation of the stricture is required before stone extraction can be attempted. A balloon catheter for biliary dilation might be helpful for dilating the stricture. However, sufficient

dilation is often difficult to achieve due to severe and hard strictures, stone impaction, and the angulation of the hilar and intrahepatic bile ducts.

Tanaka et al. [18] retrospectively reviewed 57 patients with intrahepatic stones who previously had ES to remove their common bile duct stones. Intrahepatic stones were removed completely in only 21 patients (37%), while the stones partly remained in 36 patients (63%) despite the combined use of surgery and/or PTCS-L. During a mean follow-up period of 114 months after treatment, late complications occurred in ten patients (28%) with the remaining stones, including 7 cases of cholangitis (fatal in two patients) and 3 of liver abscess (fatal in one patient). In contrast, those with complete clearance developed no complications. Thus, the authors concluded that every effort should be made to remove the intrahepatic stones as completely as possible shortly after sphincterotomy if the patient is to be managed endoscopically and adverse effects are to be avoided.

21.3.3 POCS

POCS was recently developed to evaluate indeterminate biliary strictures and to treat large bile duct stones [7]. Direct visualization of the stricture is useful for diagnosis and adequate pathological sampling. It also enables EHL/laser lithotripsy under direct vision. However, the large diameter and limited maneuverability of the POCS make it difficult to access the intrahepatic bile duct above the stricture.

Cheon et al. [19] compared treatment outcomes following endoscopic treatment with those of hepatectomy in their retrospective cohort study of 311 patients with hepatolithiasis. Complete stone clearance rates were 83.3% in hepatectomy, 63.9% in PTCS-L, and 57.1% in POCS-L. After a median follow-up period of 8.0 years, stone recurrence and late development of cholangiocarcinoma were observed in 30.9% and 4.8% of all patients, respectively. Recurrent stones and cholangitis were associated with nonoperative therapy, biliary cirrhosis, residual stones, and biliary stricture.

Thus, the indication for endoscopic transpapillary therapy is very limited in cases without biliary strictures. In addition, before treatment, the stricture should be evaluated to determine whether it is malignant. Transpapillary brush cytology and biopsy can be attempted to evaluate the stricture, but sampling at the adequate site is often difficult in the transpapillary approach, and results are not reliable.

The recent nationwide Japanese surveys reported that nonsurgical treatments, especially endoscopic transpapillary stone extraction, have been performed more frequently than has surgery in recent years. However, the incidences of residual stones and recurrent stones after endoscopic transpapillary treatment were higher than those after percutaneous transhepatic cholangioscopy-guided lithotomy (PTCS-L) and surgery. The short-term outcomes after endoscopic transpapillary stone extraction are not sufficient, and long-term outcomes are unclear. In addition, stone removal only as the initial treatment was a significant risk factor for the later development of cholangiocarcinoma [2].

21.3.4 Endoscopic Therapy in Postoperative Conditions

Bilioenteric strictures occur in 8–40% of patients after bilioenterostomy for benign pancreatobiliary diseases, and associated intrahepatic stones were found in 5–41% [20–22]. Peroral endoscopic treatment is the best technique for treating it because it is less invasive and more convenient than is a surgical or percutaneous transhepatic procedure. Access to the intrahepatic ducts is easy in patients who had previously undergone choledochoduodenostomy, which is usually located in the first part of the duodenum. A forward-viewing endoscope may provide a better view of the opening than a side-viewing duodenoscope in such patients. Dilation of the anastomotic site can be easily achieved with a balloon catheter, and intrahepatic stones can be removed as for ERCP. On the other hand, the anastomotic site had been considered inaccessible after Roux-en-Y bilioenterostomy. Therefore, PTCS-L has been preferentially performed in such patients (Fig. 21.3). Bonnel et al. [20] treated a total of 110 consecutive patients with bilioenteric strictures by percutaneous transhepatic balloon dilation and catheter stenting. The immediate technical success rate was 99% with a complication rate of 10%, including hemobilia, bile pleural effusion, and intraperitoneal biloma. Associated stones were found in 45 patients (41%), and all patients with intrahepatic stones were treated successfully by PTCS-L.

Recently, the effectiveness of a balloon-assisted enteroscope for diagnostic and therapeutic endoscopic retrograde cholangiography (ERC) in patients with altered surgical anatomy of the gastrointestinal tract has been reported. Several studies included some patients with intrahepatic stones who had undergone bilioenteric anastomosis [23–27]. In addition, Ono et al. [28] reported the successful management of intrahepatic stones by double-balloon enteroscopy after Roux-en-Y hepaticojejunostomy for choledochal cyst.

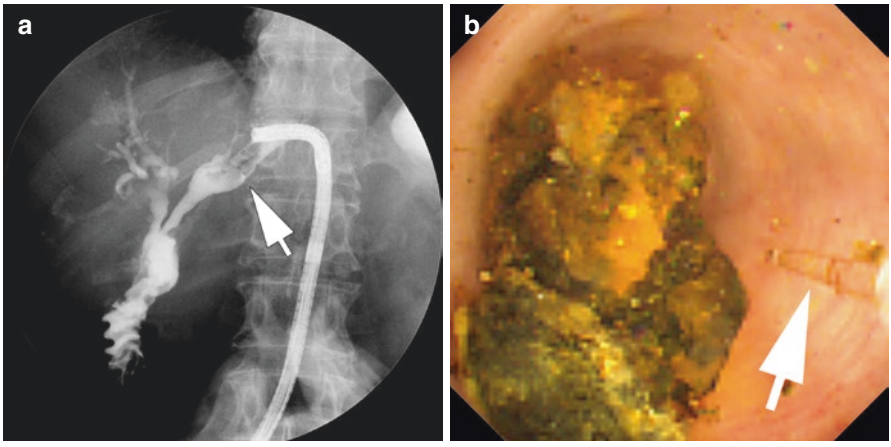

Fig. 21.3 Intrahepatic stones after bilioenteric anastomosis. (**a**) The white arrow indicates the stones in the left intrahepatic duct. (**b**) PTCS-guided laser lithotripsy was performed. The white arrow indicates a laser probe

Moreover, the combination therapy of a balloon-assisted enteroscope and peroral direct cholangioscopy (PDCS) using an ultraslim endoscope for the treatment of postoperative intrahepatic stones has most recently been demonstrated. In the treatment of intrahepatic stones, a residual stone is a risk factor for recurrent stones [19]. The concept of this technique was that evaluation and removal of residual stones by PDCS might reduce recurrent stones after endoscopic treatment. Itoi et al. [29] and Matsumoto et al. [30] evaluated the effectiveness of this technique in 7 and 14 patients with intrahepatic stones after hepaticojejunostomy. In these studies, following stone removal by a double-balloon enteroscope (DBE), the scope was exchanged for an ultraslim endoscope through the balloon overtube for PDCS. The PDCS procedure was successful in 100% and 85.7% of the patients. The residual stones were detected in 42.8% and 41.7% of the patients, and they were removed completely in all patients without any complications. The recurrence rates of bilioenteric strictures or hepatolithiasis after percutaneous treatment were reported to be 14–30% at a median follow-up period of 28–65 months, but their recurrence rate was 8.3% during a 21-month follow-up period [30]. Therefore, the authors concluded that PDCS can effectively detect and remove stones completely and may decrease the stone recurrence rate.

21.4 Conclusions

PTCS-L is safe and effective for removing intrahepatic stones when surgical resection is not suitable or is refused by patients. In cases in which a PTBD is placed for cholangitis, PTCS-L may be a treatment option. However, in the case of biliary stricture, the stricture site should be evaluated very carefully in order not to overlook the accompanying biliary cancer. In addition, stones should be removed as completely as possible, and the stricture should be treated to reduce later complications, such as recurrent stones and cholangiocarcinoma. The endoscopic transpapillary approach is also available for use in cases without biliary stricture. However, its indication for intrahepatic stones remains controversial because of its low success rate and high recurrence rate. With respect to postoperative cases (after hepaticojejunostomy), PTCS-L has been attempted as a first-line treatment. However, balloon-assisted enteroscopes are currently used at several institutions. In addition, a novel technique of PDCS after stone removal by balloon-assisted enteroscopes was most recently introduced, and it might be useful to evaluate and remove residual stones.

References

1. Tazuma S. Gallstone disease: epidemiology, pathogenesis, and classification of biliary stones (common bile duct and intrahepatic). Best Pract Res Clin Gastroenterol. 2006;20:1075–83.
2. Suzuki Y, Mori T, Yokoyama M, et al. Hepatolithiasis: analysis of Japanese nationwide surveys over a period of 40 years. J Hepatobiliary Pancreat Sci. 2014;21:617–22.

3. Pitt HA, Venbrux AC, Coleman J, et al. Intrahepatic stones. The transhepatic team approach. Ann Surg. 1994;219:527–35; discussion 535–7.
4. Jan YY, Chen MF. Percutaneous trans-hepatic cholangioscopic lithotomy for hepatolithiasis: long-term results. Gastrointest Endosc. 1995;42:1–5.
5. Sheen-Chen SM, Chou FF, Eng HL. Intrahepatic cholangiocarcinoma in hepatolithiasis: a frequently overlooked disease. J Surg Oncol. 1991;47:131–5.
6. Mori T, Sugiyama M, Atomi Y. Gallstone disease: management of intrahepatic stones. Best Pract Res Clin Gastroenterol. 2006;20:1117–37.
7. Yasuda I, Itoi T. Recent advances in endoscopic management of difficult bile duct stones. Dig Endosc. 2013;25:376–85.
8. Suzuki Y, Mori T, Abe N, et al. Predictive factors for cholangiocarcinoma associated with hepatolithiasis determined on the basis of Japanese Multicenter study. Hepatol Res. 2012;42:166–70.
9. Yamakawa T, Mieno K, Noguchi T, et al. An improved choledochofiberscope and non-surgical removal of retained biliary calculi under direct visual control. Gastrointest Endosc. 1976;22:160–4.
10. Nimura Y. Percutaneous transhepatic cholangioscopy (PTCS). Stomach Intest. 1981;16:681–9 (Japanese).
11. Chen MF, Jan YY. Percutaneous transhepatic cholangioscopic lithotripsy. Br J Surg. 1990;77:530–2.
12. Yamakawa T. Percutaneous cholangioscopy for management of retained biliary tract stones and intrahepatic stones. Endoscopy. 1989;21(Suppl 1):333–7.
13. Lee SK, Seo DW, Myung SJ, et al. Percutaneous transhepatic cholangioscopic treatment for hepatolithiasis: an evaluation of long-term results and risk factors for recurrence. Gastrointest Endosc. 2001;53:318–23.
14. Huang MH, Chen CH, Yang JC, et al. Long-term outcome of percutaneous transhepatic cholangioscopic lithotomy for hepatolithiasis. Am J Gastroenterol. 2003;98:2655–62.
15. Chen C, Huang M, Yang J, et al. Reappraisal of percutaneous transhepatic cholangioscopic lithotomy for primary hepatolithiasis. Surg Endosc. 2005;19:505–9.
16. Yeh YH, Huang MH, Yang JC, et al. Percutaneous trans-hepatic cholangioscopy and lithotripsy in the treatment of intrahepatic stones: a study with 5 year follow-up. Gastrointest Endosc. 1995;42:13–8.
17. Neuhaus H. Endoscopic and percutaneous treatment of difficult bile duct stones. Endoscopy. 2003;35:S31–4.
18. Tanaka M, Ikeda S, Ogawa Y, et al. Divergent effects of endoscopic sphincterotomy on the long-term outcome of hepatolithiasis. Gastrointest Endosc. 1996;43:33–7.
19. Cheon YK, Cho YD, Moon JH, et al. Evaluation of long-term results and recurrent factors after operative and nonoperative treatment for hepatolithiasis. Surgery. 2009;146:843–53.
20. Bonnel DH, Fingerhut AL. Percutaneous transhepatic balloon dilatation of benign bilioenteric strictures: long-term results in 110 patients. Am J Surg. 2012;203:675–83.
21. Glas L, Courbiere M, Ficarelli S, et al. Long-term outcome of percutaneous transhepatic therapy for benign bilioenteric anastomotic strictures. J Vasc Interv Radiol. 2008;19:1336–43.
22. Cantwell CP, Pena CS, Gervais DA, et al. Thirty years' experience with balloon dilation of benign postoperative biliary strictures: long-term outcomes. Radiology. 2008;249:1050–7.
23. Aabakken L, Bretthauer M, Line PD. Double-balloon enteroscopy for endoscopic retrograde cholangiography in patients with a Roux-en-Y anastomosis. Endoscopy. 2007;39:1068–71.
24. Shimatani M, Matsushita M, Takaoka M, et al. Effective "short" double-balloon enteroscope for diagnostic and therapeutic ERCP in patients with altered gastrointestinal anatomy: a large case series. Endoscopy. 2009;41:849–54.
25. Itoi T, Ishii K, Sofuni A, et al. Single-balloon enteroscopy-assisted ERCP in patients with Billroth II gastrectomy or Roux-en-Y anastomosis (with video). Am J Gastroenterol. 2010;105:93–9.

26. Osoegawa T, Motomura Y, Akahoshi K, et al. Improved techniques for double-balloon-enteroscopy-assisted endoscopic retrograde cholangiopancreatography. World J Gastroenterol. 2012;18:6843–9.
27. Tsutsumi K, Kato H, Muro S, et al. ERCP using a short double-balloon enteroscope in patients with prior pancreatoduodenectomy: higher maneuverability supplied by the efferent-limb route. Surg Endosc. 2015;29:1944–51.
28. Ono S, Maeda K, Baba K, et al. The efficacy of double-balloon enteroscopy for intrahepatic bile duct stones after Roux-en-Y hepaticojejunostomy for choledochal cysts. Pediatr Surg Int. 2013;29:1103–7.
29. Itoi T, Sofuni A, Itokawa F, et al. Diagnostic and therapeutic peroral direct cholangioscopy in patients with altered GI anatomy (with videos). Gastrointest Endosc. 2012;75:441–9.
30. Matsumoto K, Tsutsumi K, Kato H, et al. Effectiveness of peroral direct cholangioscopy using an ultraslim endoscope for the treatment of hepatolithiasis in patients with hepaticojejunostomy (with video). Surg Endosc. 2016;30(3):1249–54.

Part VI
How to Treat Chronic Pancreatitis

Chapter 22
Tips for Using SpyGlass Peroral Pancreatoscopy and X-Ray-Guided Electrohydraulic Lithotripsy for Refractory Pancreatic Stones

Ken Ito, Yoshinori Igrashi, Naoki Okano, Kensuke Yoshimoto, Susumu Iwasaki, Seiichi Hara, Kensuke Takuma, and Yui Kishimoto

Abstract Objective: Extracorporeal shock wave lithotripsy (ESWL) and endoscopic stone lithotomy (EL) are minimally invasive procedures that are useful for treating pancreatic stones. However, large-diameter and impacted stones can be refractory to these treatments. We retrospectively evaluated the efficacy of peroral pancreatoscopy (POPS) and X-ray-guided electrohydraulic lithotripsy (EHL) in treating refractory pancreatic stones. **Methods:** From May 2005 to April 2014, 159 chronic pancreatitis and pancreatic lithiasis patients were treated with ESWL and EL. EHL was performed as a second attempt for unsuccessful ESWL and EL cases. For refractory cases, we used the 10 Fr SpyGlass Direct Visualization System for POPS-guided EHL. X-ray-guided EHL (using a 7 Fr biliary dilator as an outer sheath) was performed when a 10 Fr SpyGlass system was difficult to insert into the main pancreatic duct. **Results:** A total of 18 patients were included in this study. The mean stone diameter was 12.3 ± 4.5 mm, with 7 patients having a single stone and 11 patients having multiple stones. POPS-guided EHL was performed in nine cases and X-ray-guided EHL was performed in nine cases. Fragmentation was successful in nine (50%) patients: four treated with POPS-guided EHL and five treated with X-ray-guided EHL. Two patients developed mild post-ERCP pancreatitis following X-ray-guided EHL. **Conclusions:** POPS-guided and X-ray-guided EHL may be an alternative treatment for refractory stones. Because EHL can cause severe complications, adequate precautions are necessary for these treatments.

Keywords Electrohydraulic lithotripsy • Pancreatic stones • Peroral pancreatoscopy

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22.1 Introduction

Chronic pancreatitis stones in the main pancreatic duct (PD) can result in pain due to increased MPD pressure. Pancreatic stone extraction is a suitable treatment for pain reduction and prevents acute exacerbation of pancreatitis. Extracorporeal shock wave lithotripsy (ESWL) is typically the first treatment option because it is minimally invasive and produces fewer early complications than do other treatments [1]. A complication of ESWL is acute obstructive pancreatitis due to stone lithotripsy, and patients should therefore be admitted for postsurgical monitoring for prevention of complications requiring endoscopic pancreatic sphincterotomy (EPST) [2]. However, large-diameter stones and impacted stones are sometimes refractory to these treatments [3]. Management in cases of large-diameter stones requires lithotripsy, for which combined endoscopic treatment (ET) and ESWL therapy (ET/ESWL) are more effective than ESWL therapy alone [4]. However, in cases where such combination therapy is unsuccessful, surgical or substitute intervention is typically required for symptomatic patients [5]. Electrohydraulic lithotripsy (EHL) is one such intervention that has been shown to be effective, with few reports demonstrating the efficacy of EHL for cases refractory to endoscopic stone extraction methods or ESWL treatments [3, 6]. Accordingly, we previously reported the efficacy of using EHL as an alternative secondary treatment option for refractory pancreatic stones [7]. Here, we report additional cases so as to evaluate the efficacy of SpyGlass pancreatoscopy and X-ray-guided EHL treatments for refractory pancreatic stones treated at our institution.

22.2 Materials and Methods

The management of chronic pancreatic stones and indication of EHL performed at our center are shown in Fig. 22.1. Chronic pancreatitis patients with pancreatic stones were treated with combined ESWL and endoscopic treatments. Endoscopic retrograde cholangiopancreatography (ERCP) was performed with a TJF240 or TJF260V duodenoscope (Olympus Medical Systems, Tokyo, Japan). Endoscopic pancreatic duct sphincterotomy (EPST) was always performed as the first step. When main PD stricture was shown on pancreatography, dilation was performed using either a Soehendra biliary dilatation catheter (Wilson Cook Medical, Winston-Salem, NC; SBDC) or a Soehendra stent retriever catheter (Wilson Cook Medical), with a 7–10 Fr endoscopic pancreatic stent (EPS) being placed as far as possible. Finally, an ESWL session was initiated. To improve the efficacy of lithotripsy, a slow shock wave (45 pulses/min) was applied using an electromagnetic Siemens Lithoskop (Siemens AG, Munich, Germany). Contraindication to ESWL included coagulation disorders, pregnancy, implanted cardiac pacemakers or defibrillators, and the presence of bone, calcified aneurysms, or lung tissue in the shock wave path [8, 9]. If the endoscopic lithotomy/ESWL combination was unsuccessful, EHL was

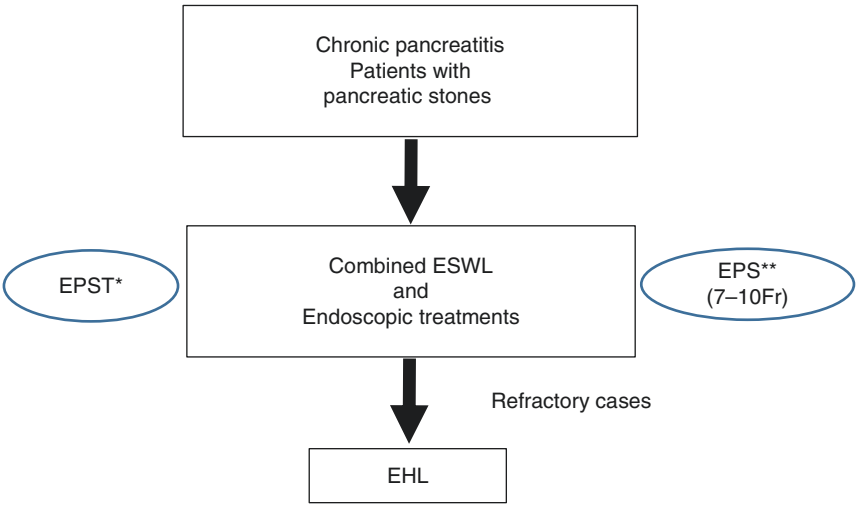


Fig. 22.1 Indications for EHL

performed as a second attempt. Figure 22.2 shows the algorithm and devices for EHL. For all EHL procedures, a 4.2 mm channel duodenoscope (TJF240/TJF260; Olympus Medical Systems, Tokyo, Japan) was used as a mother scope. We have used a 10 Fr SpyGlass Direct Visualization System (Boston Scientific, Natick, MA) for babyscope as EHL at our hospital since 2010 and have termed this procedure, "SpyGlass-guided EHL" method. For cases in which we could not insert a 10 Fr SpyGlass system through the main PD, EHL was performed using a pancreatoscope, and we termed this the "X-ray-guided EHL" method. For X-ray-guided EHL, we used a 7 or 9 Fr SBDC (in which the tip was a handmade cutoff) as a sheath for alternative equipment, which allowed to pass several main PD strictures (Fig. 22.3). Both devices were inserted into the main PD without guidewires, and EHL was performed by only one highly skilled endoscopist. For the EHL probe, a NORTECH® MICRO II 1.9 Fr 250 cm EHL Probe (Northgate Technologies Inc. Elgin, IL) was used. Accordingly, the NORTECH® AUTOLITH® EHL Generator (Northgate Technologies Inc.) was optimized for use with the EHL. While performing the "X-ray-guided EHL" procedures, the probe was placed into the improved SBDC first before inserting the SBDC into the biopsy valve to prevent the kinking of the thin fragile EHL probe.

Clinical outcomes were evaluated according to the following parameters: technical success of stone fragmentation, adverse events, such as post-ERCP pancreatitis (PEP), bleeding, perforation, technical reasons for failure cases, and final outcomes of failure cases. Stone location in the main PD was defined as the head or body. Stone number was defined as single or multiple (>1) stones in the main PD. In

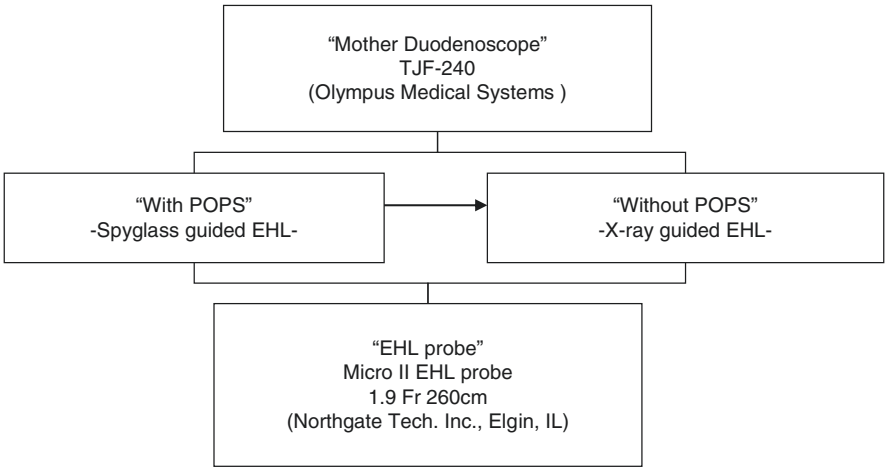
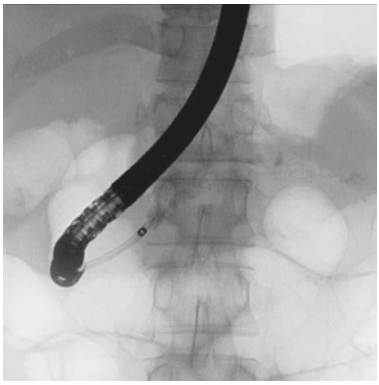


Fig. 22.2 Algorithm and devices for EHL

EHL without POPS
"X-ray guided EHL"
-Using Soehendra Biliary Dilator-
(Wilson Cook Medical, Winston-Salem, NC)



- ✓ Small caliber (7 or 9 Fr)
- ✓ Allows to pass severe MPD strictures
- ✓ 2-dimensional fluoroscopic targeting
- ✓ Visualized under fluoroscopy during EHL session

Fig. 22.3 X-ray-guided EHL

addition, using logistic regression analysis, risk factors of stone clearance were assumed using the following four factors: stone size, stone CT Hounsfield units (HU) value, total ESWL shots before EHL, and PD stenting before EHL. Written informed consent was obtained from each patient prior to performing treatment. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review committee of Toho University Omori Medical Center.

22.2.1 Statistical Analysis

Statistical analysis was performed using SPSS for Windows, version 11.0 J (SPSS Inc., Chicago, IL). All continuous variables are presented as mean ± standard error. A p value <0.05 was considered significant. Comparisons of the outcome variable (stone fragmentation) were analyzed using the Chi-squared test or Fisher's exact test.

22.3 Results

A total of 159 patients with symptomatic chronic pancreatitis and patients with pancreatic stones were treated with combined ESWL and/or endoscopic lithotripsy (EL) treatments at our center between May 2005 and April 2014 (Table 22.1). Of these, 141 successful stone lithotripsy cases were completed, of which we retrospectively studied 18 patients who had undergone EHL procedures as the second treatment modality. Patient backgrounds and stone characteristics are shown in Table 22.2. The etiology of chronic pancreatitis was alcohol consumption in 15 cases and idiopathic in 3. The median stone size was 12.3 ± 4.5 mm (range 7–27 mm). There was a single stone in 7 cases and multiple stones in 11 cases, which were located in the head in 14 cases and the body in 4 cases, with the main PD stricture being observed in 16 cases.

Table 22.1 Objectives

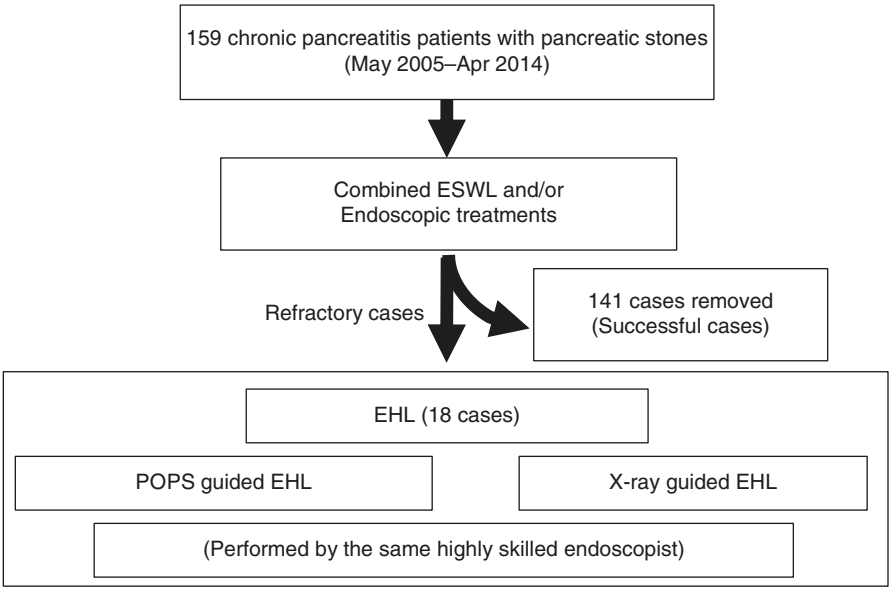


Table 22.2 Patients backgrounds and stone characteristics ($n = 18$)

Factor	*n*
Age (median, range)	47.9 ± 11.2(25–76)
Sex male/female	15/3
Etiology alcoholic/idiopathic (%)	15/3 (80/20)
Smoke, yes/no (%)	16/2 (88.9/11.1)
Max stone diameter; mm (median, range)	12.3 ± 4.5 (7–27)
Stone location	
Single/multiple	7/11
Head/body	14/4
Existence of MPD stricture[a] yes/no	16/2

[a]Requiring PD dilatation and MPD stenting

Table 22.3 shows the 18 cases where "SpyGlass-guided EHL" and "X-ray-guided EHL" were performed. There was no statistical difference between stone location and maximum stone diameter. Stone fragmentation by "SpyGlass-guided EHL" succeeded in four of nine patients (44.4%), whereas "X-ray-guided EHL" succeeded in five of nine patients (55.5%), thereby showing no difference between the two methods. Complications occurred in three cases of "SpyGlass-guided EHL" and "X-ray-guided EHL," respectively, thereby showing no statistical difference between the two groups. The following complications were observed: two cases of moderate PEP in the failed "X-ray-guided EHL" cases, one case of severe PEP with submucosal bleeding by "X-ray-guided EHL," one case of moderate PEP with micro guidewire perforation in a successful "SpyGlass-guided EHL" case, and two cases of moderate PEP and micro guidewire perforation in failed "SpyGlass-guided EHL" cases. All cases were treated using conservative management.

Table 22.4 shows the stone fragmentation factor between the outcomes, which is limited to the pancreatic head stones. The maximum stone diameter, as indicated by stone CT Hounsfield units (HU), was measured on CT and indicated no difference between the two groups. Moreover, total ESWL shots before EHL and PD stenting before EHL was analyzed, which also indicated no difference between the two groups.

Data relating to the nine cases that ended in failure are shown in Table 22.5. The common cause of failure fragmentation was direct vision failure given the acute angulation of the main PD. Two cases resulted in failure because the impacted stones in these cases were too near the papilla of Vater and SpyGlass pancreatoscope, thereby making it difficult to perform EHL in the correct position. For the "X-ray-guided EHL," we had anticipated success in cases that had severe stricture; however, in two cases there was difficulty in insertion of the 7 Fr outer sheath because of the severe main PD stricture at the head.

Table 22.6 shows the final outcomes of the nine failed cases. Five cases were successfully treated with long-term ESWL. Three cases only underwent observa-

Table 22.3 Treatment outcomes ($n = 18$)

	Spyglass-guided EHL	X-ray-guided EHL	*p* value
n	9	9	
Stone location, head/body	8/1	6/3	*n.s*
Max stone diameter; mm average (range)	12.3 ± 2.3 (10–17)	12.1 ± 5.6 (7–12.2)	*n.s*
Fragmentation success (%) Head/body	4 (44.4) 2/2	5 (55.5) 4/1	*n.s*
Complications (%) PEP[a] (suc/fail[b]) +Bleeding (suc/fail[b]) +Perforation[c] (suc/fail[b])	3 (33.3) 0/0 0/0 1/2	3 (33.3) 0/2 0/1 0/0	*n.s*

[a]Post-ERCP pancreatitis (using cotton classification)
[b]Success group/failure group
[c]Treatment outcomes of "SpyGlass-guided EHL" and "X-ray-guided EHL"

Table 22.4 Stone factor across outcomes (pancreatic head stones)

	Success group	Failure group	*p*
n (Spyscope/X-ray guided)	6 (2/4)	8 (5/3)	
Max stone diameter[a] (mm)	11.7 ± 3.0 (8–16)	13.8 ± 5.9 (10–27)	*n.s*
Hounsfield units (HU)[a]	1560 ± 517 (1186–2528)	1394 ± 316 (917–1764)	*n.s*
Total ESWL shots before EHL	33,311 ± 6277 (34,500–52,500)	53,875 ± 19,998 (8500–182,000)	*n.s*
PD stenting before EHL (%)	4 (66.6)	3 (37.5)	*n.s*

[a]Valued using computed tomography

Table 22.5 Technical reasons for the failure cases ($n = 9$)

	Spyglass guided EHL	X-ray guided EHL
n (%)	5 (62.5)	4 (40)
Reasons for failure		
Direct vision failure	1	2
Close range[a]	2	0
Severe stricture	0	2
Equipment failure	1	0
Other technical failure	1	0

[a]Impaction stones near the Papilla Vater

Table 22.6 Final outcomes of failure cases ($n = 9$)

	Spyglass-guided EHL, ($n = 8$)	X-ray-guided EHL ($n = 10$)
n (%)	5 (62.5)	4 (40)
Final outcomes		
Long-term outpatient ESWL	3	2
Observation	2	1
Surgery	0	1

tion with no treatment because no abdominal pain occurred after the EHL session. However, because there was no improvement in abdominal pain in one "X-ray-guided EHL" failure case, surgical treatment was performed.

22.4 Discussion

The enhanced safety and efficacy of ESWL makes it the preferred treatment for patients with painful calcified chronic pancreatitis, and it has been the treatment of choice for fragmenting radiopaque pancreatic stones [1, 2, 10, 11]. Combined systematic endoscopy with ESWL has been reported to increase the cost of patient care without improving the outcomes of pancreatic pain [12]. Cholangioscopy using the mother–baby system has been used to evaluate indeterminate pancreatobiliary diseases [3]. Intraductal laser or EHL has provided discordant success rates for stone fragmentation in small case series, after the reported failure of ESWL to fragment stones [3, 13]. Advantages of pancreatoscopes are that it makes it possible to visualize the process of stone fragmentation.

Rios et al. mentioned that EHL may represent an alternative to resection of the head of the pancreas in the management of chronic fibrocalcific pancreatitis [14]. Attwell et al. reported the efficacy of EHL performed by an endoscope-based peroral pancreatoscopy (POPS) and catheter-based POPS, with no statistical difference between the two [15]. Howell reported that successful endoscopic extraction is related to the size (<10 mm), number (<3), and PD location (head/body) of the stones and that it may not be possible if strictures are present or when the stones are impacted in the main PDl [16, 17]. However, conventional endoscope-based POPS includes fragile instruments, requiring frequent repairs [18, 19]. Indeed, the SpyGlass optical probe, which is 0.9 mm in diameter and can be inserted through an endoscopic retrograde cholangiopancreatography (ERCP) catheter [20]. SpyScope is a disposable catheter, which makes it cost-effective; it is considered that it might be the first choice for pancreatic lithiasis EHL cases [21].

For the "POPS-guided EHL" failure cases, there are case reports that do not use POPS for pancreatic stones and biliary stones but instead use a balloon catheter as an outer sheath for EHL [22, 23]. Although an EHL probe is a fragile instrument, clinicians must carefully insert the thin 1.9 Fr probe into the device without kinking. To prevent kinking of the thin probe at the tip of the outer sheath, we tried the biliary

dilator, with which the tapered tip was cut off while pursuing an alternative idea. Importantly, the EHL probe was inserted first before inserting the biopsy valve. This may allow the smooth advancement of the cannula and EHL probe to the target pancreatic stone. Because of this, we report no failures in EHL in our nine cases of "X-ray-guided EHL."

When considering the stone characteristics, we are limited by pancreatic head stones. The characteristics of pancreatic stones are appropriate and require many ESWL cases to have sufficient cases for the study. We found no difference between the two groups, which revealed the refractory period of the ESWL treatment and the absence of technical success between the two groups.

Next, we considered treatment complications, including PEP, hemorrhage, and perforation. PEP was seen in two cases, both of which showed no atrophic parenchyma on CT/US. Perhaps this was because the invasive procedure stimulated PEP. Bleeding with PEP occurred in one case, while a hemorrhage occurred when the patient was undergoing the "X-ray-guided" EHL. In this blind technique, it is likely that the tip of the probe was contacting the main PD wall, which was a technical failure that should have been reflected. Furthermore, perforation was observed in three cases of "SpyGlass-guided EHL." As shown, perforation was common to all cases, which may be the result of an absence of a suitable position for placement due to the main PD characteristic. Additionally, leakage of the main PD was observed upon pancreatography after the EHL procedure. The final problem was the failure to place ENPD because of the presence of the remaining stones. During the procedures, the main PD underwent extensive invasive damage at the pinpoint, which suggests that preventing these events requires attentiveness and use of flexible guidewires tips. Indeed, clinicians should seek to create a gentle curve tip at the tip of the guidewire.

Third, we focused on the major technical causes of failure. The common causes of failure for "SpyGlass-guided EHL" were the absence of direct vision and lack of control of the pancreatic stone location near the papilla of Vater. In the cases of acute angulation of the main PD, even the four-way angled system of the SpyGlass Direct Visualization System is difficult to maintain in the stable direct position. Furthermore, for the stones located near the papilla of Vater cases, the range between the POPS and impacted stone is too close to be maintained in a stable position during the procedures. The most common reason for failure of "X-ray-guided EHL" is the severity of the main PD stricture. Because of the limited operation of the SBDC outer sheath, it is difficult to keep it in the correct position. Furthermore, it is also difficult to encounter the 7 Fr SBDC in the main PD without using GW.

There are several limitations to this study. First, it is a retrospective study. Second, the use of "SpyGlass-guided EHL" or "X-ray-guided EHL" was determined based on the response to the combined endoscopic and ESWL treatment survey and the selection was not randomized. Third, both cases of EHL were performed by the same highly skilled endoscopist, which may be one of the factors contributing to the successful outcomes.

22.5 Conclusions

POPS-guided and X-ray-guided EHL may be an alternative treatment for refractory stones. However, EHL can sometimes cause severe complications. Therefore, it is necessary to carefully perform these treatments.

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Conflict of Interests: The authors declare no conflict of interests relevant to this article.

References

1. Ohara H, Hoshino M, Hayakawa T, et al. Single application extracorporeal shock wave lithotripsy is the first choice for patients with pancreatic duct stones. Am J Gastroenterol. 1996;91:1388–94.
2. Sauerbruch T, Holl J, Sackmann M, et al. Disintegration of a pancreatic duct stone with extracorporeal shock waves in a patient with chronic pancreatitis. Endoscopy. 1987;19:207–8.
3. Howell DA, Dy RM, Hanson BL, et al. Endoscopic treatment of pancreatic duct stones using a 10F pancreatoscope and electrohydraulic lithotripsy. Gastrointest Endosc. 1999;50:829–33.
4. Inui K, Tazuma S, Yamaguchi T, et al. Treatment of pancreatic stones with extracorporeal shock wave lithotripsy: results of a multicenter survey. Pancreas. 2005;30:26–30.
5. Dumonceau JM, Costamagna G, Tringali A, et al. Treatment for painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic treatment: a randomised controlled trial. Gut. 2007;56:545–52.
6. Morrow CE, Cohen JI, Sutherland DE, et al. Chronic pancreatitis: long-term surgical results of pancreatic duct drainage, pancreatic resection, and near-total pancreatectomy and islet autotransplantation. Surgery. 1984;96:608–16.
7. Ito K, Igarashi Y, Okano N, et al. Efficacy of combined endoscopic lithotomy and extracorporeal shock wave lithotripsy, and additional electrohydraulic lithotripsy using the SpyGlass direct visualization system or X-ray guided EHL as needed, for pancreatic lithiasis. Biomed Res Int. 2014;2014:732781. https://doi.org/10.1155/2014/732781.
8. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2012;44:784–800.
9. Platonov MA, Gillis AM, Kavanagh KM, et al. Pacemakers, implantable cardioverter/defibrillators, and extracorporeal shockwave lithotripsy: evidence-based guidelines for the modern era. J Endourol. 2008;22:243–7.
10. Nguyen-Tang T, Dumonceau JM. Endoscopic treatment in chronic pancreatitis, timing, duration and type of intervention. Best Pract Res Clin Gastroenterol. 2010;24:281–98.
11. Tandan M, Reddy DN, Santosh D, et al. Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi-a large single center experience. Indian J Gastroenterol. 2010;29:143–8.
12. Joo YW, Yoon JH, Cho SC, et al. Endoscopic pancreatic sphincterotomy: indications and complications. Korean J Intern Med. 2009;24:190–5.
13. Hirai T, Goto H, Hirooka Y, et al. Pilot study of pancreatoscopic lithotripsy using a 5-fr instrument: selected patients may benefit. Endoscopy. 2004;36:212–6.
14. Rios GA, Adams DB. Does intraoperative electrohydraulic lithotripsy improve outcome in the surgical management of chronic pancreatitis? Am Surg. 2001;67:533–7; discussion 537–8

15. Attwell AR, Brauer BC, Chen YK, et al. Endoscopic retrograde cholangiopancreatography with per oral pancreatoscopy for calcific chronic pancreatitis using endoscope and catheter-based pancreatoscopes: a 10-year single-center experience. Pancreas. 2014;43:268–74.
16. Sherman S, Lehman GA, Hawes RH, et al. Pancreatic ductal stones: frequency of successful endoscopic removal and improvement in symptoms. Gastrointest Endosc. 1991;37:511–7.
17. Delhaye M, Matos C, Deviere J. Endoscopic technique for the management of pancreatitis and its complications. Best Pract Res Clin Gastroenterol. 2004;18:155–81.
18. Shah RJ, Langer DA, Antillon MR, et al. Cholangioscopy and cholangioscopic forceps biopsy in patients with indeterminate pancreaticobiliary pathology. Clin Gastroenterol Hepatol. 2006;4:219–25.
19. Itoi T, Moon JH, Waxman I, et al. Current status of direct peroral cholangioscopy. Dig Endosc. 2011;23(Suppl 1):154–7.
20. Nguyen NQ, Shah JN, Binmoeller KF, et al. Diagnostic cholangioscopy with SpyGlass probe through an endoscopic retrograde cholangiopancreatography cannula. Endoscopy. 2010;42(Suppl 2):E288–9.
21. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc. 2007;65:832–41.
22. Moon JH, Cha SW, Ryu CB, et al. Endoscopic treatment of retained bile-duct stones by using a balloon catheter for electrohydraulic lithotripsy without cholangioscopy. Gastrointest Endosc. 2004;60:562–6.
23. Papachristou GI, Baron TH. Endoscopic treatment of an impacted pancreatic duct stone using a balloon catheter for electrohydraulic lithotripsy without pancreatoscopy. J Clin Gastroenterol. 2006;40:753–6.

Chapter 23
Endoscopic Lithotomy and ESWL for Pancreatic Stones

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Abstract The indication for the treatment of pancreatic stones is stone location in the main pancreatic duct (MPD) or Santorini duct and the presence of abdominal symptoms. If the diameter of the stone is >5 mm, the initial therapy is extracorporeal shock wave lithotripsy (ESWL), which is safe and minimally invasive. ESWL achieves adequate fragmentation and improves abdominal symptoms. Before ESWL, we usually perform endoscopic pancreatic sphincterotomy (EPST) because it prevents the impaction of crushed stones, acute pancreatitis, and acute cholangitis. However, if the stone is large or multiple stones are present, the success rate of ESWL alone is low, and endoscopic lithotomy is needed. If the size of the stone becomes ˂4 mm after ESWL, endoscopic lithotomy can be performed safely using basket forceps and a balloon catheter. We perform electrohydraulic lithotripsy (EHL) under peroral pancreatoscopy if ESWL fails to fragment the stone. If the stenosis of the MPD is present on the duodenum side of the stone, we perform endoscopic dilation using a dilation catheter and balloon followed by endoscopic pancreatic stenting. Endoscopic treatment is safer if these techniques are used.

Keywords Chronic pancreatitis • Pancreatic stone • Endoscopic treatments Endoscopic lithotomy

23.1 Introduction

Endoscopic treatments for pancreatobiliary disorders include newly developed endoscopic sphincterotomy (EST) and endoscopic transpapillary treatment for bile duct stones [1–3]. EST followed by stone removal with basket forceps has also been reported for small pancreatic stones [4], but removal of large pancreatic stones in

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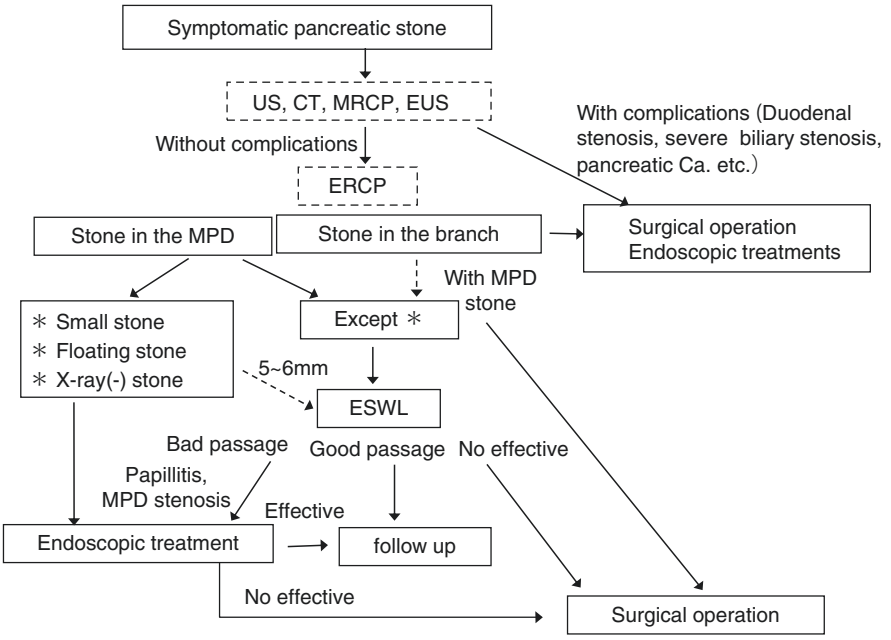
the main pancreatic duct (MPD) using basket forceps is difficult. The proven efficacy of extracorporeal shock wave lithotripsy (ESWL) in treating pancreatic stones, as well as renal stones and gallstones [5], has led to the introduction of endoscopic pancreatic lithotomy with ESWL as a safe treatment option for pancreatic stones.

This report describes endoscopic pancreatic lithotomy with ESWL for pancreatic stone removal.

23.2 Indications

We usually perform treatment in accordance with the clinical practice guidelines for pancreatic stones (Table 23.1) [6]. The current technique is indicated for patients with chronic pancreatitis with a pancreatic stone in the MPD or Santorini duct causing abdominal pain [7]. A pancreatic stone impacted in the MPD causing dilation and increased internal pressure of the caudal pancreatic duct and resulting in recurrent pancreatitis is a good indication for the technique. Some asymptomatic patients are also good candidates, such as young patients and those in whom removal of a pancreatic stone is likely to lead to preserved pancreatic function. Fragmentation of a pancreatic stone by ESWL into fragments of ≤4 mm in size will enable safe stone removal. However, chronic inflammatory changes of the main papilla or stenosis of the MPD may prevent clearance of stone fragments, which causes acute pancreatitis

Table 23.1 Indication of endoscopic treatment for pancreatic stone



and papillitis. In such cases, we perform endoscopic pancreatic sphincterotomy (EPST) or endoscopic pancreatic duct balloon dilation as pretreatment.

23.2.1 Endoscopic Pancreatic Sphincterotomy (EPST)

After selective cannulation of the MPD, a wire-guided papillotome (CleverCut 3, with a 7-mm tip and a 20-mm cutting wire; Olympus Medical Systems Co., Tokyo, Japan) is inserted over a guidewire (Fig. 23.1a, b). An incision is made at the 12 o'clock position while preserving the upper edge of the papilla. After incision, the papilla usually appears whitish due to fibrosis associated with papillitis.

23.2.2 Endoscopic Lithotomy for Pancreatic Stones

23.2.2.1 Pancreatic Stones Sized <5 mm

EPST is performed as a pretreatment to resolve stenosis of the papilla. The MPD is then selectively cannulated with a guidewire (Fig. 23.2a, b), followed by the insertion of a 6- or 8-mm biliary balloon dilator over the guidewire to gently

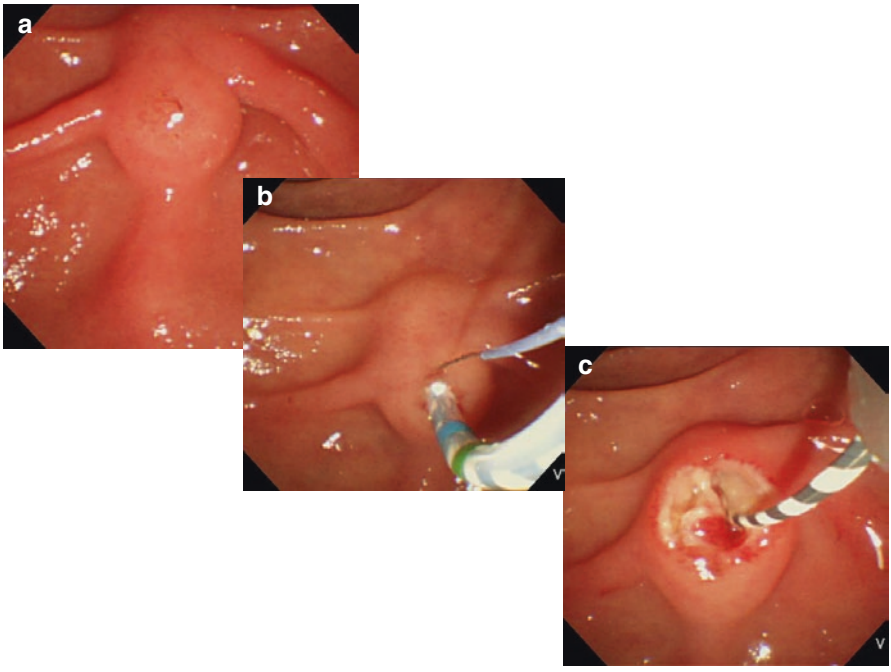


Fig. 23.1 (**a**–**c**) Endoscopic pancreatic sphincterotomy (EPST)

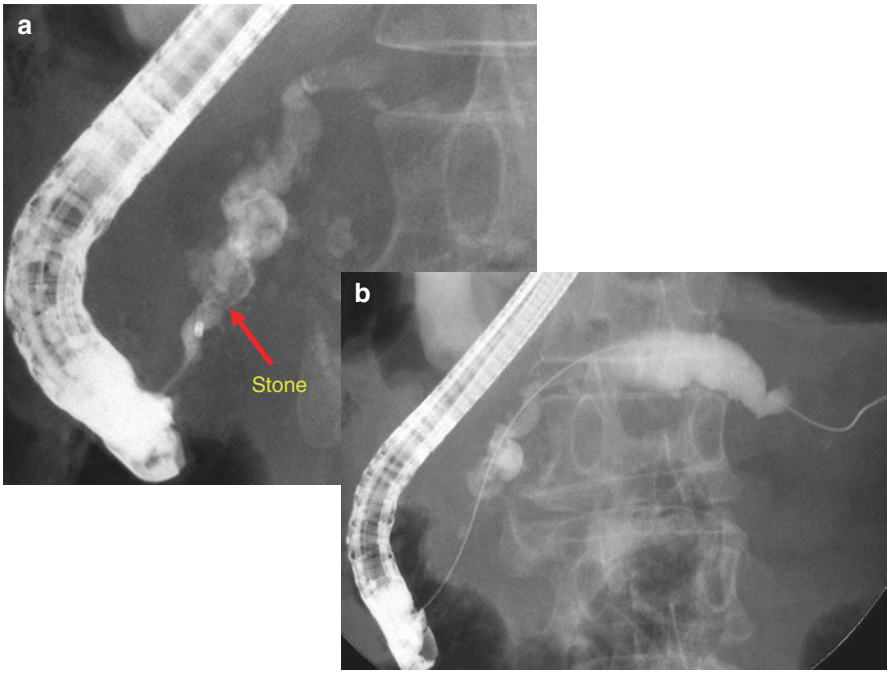


Fig. 23.2 A guidewire passed through the tail of the pancreas

dilate the main papilla and the MPD at the pancreatic head until the notch disappears (Fig. 23.3a, b). The stone is then removed with 4 or 8 wire-type wire-guided basket forceps (Olympus Medical Systems) (Fig. 23.4a, b). In order to avoid balloon rupture by a hard pancreatic stone, we use a balloon catheter for biliary dilation to remove a small pancreatic stone. Drawing the catheter with the balloon inflated up to 80% will enable safe removal of a small stone (Fig. 23.5a, b).

23.2.2.2 Pancreatic Stones Sized ≥5 mm

Fragmentation by ESWL is performed as pretreatment. An endoscopic mechanical lithotriptor should not be used, as its use for a pancreatic stone, which is harder than a gallstone, is associated with a high risk of impaction of the basket forceps [7]. ESWL is performed to crush the stone into small fragments. For an X-ray-negative stone, an endoscopic nasopancreatic drainage tube should be inserted and used for stone fragmentation by ESWL. ESWL for pancreatic stones is successful in about 70% of cases, but it fails in some cases with stones impacted in the MPD. In such cases, we perform electrohydraulic lithotripsy (EHL) under peroral pancreatoscopy.

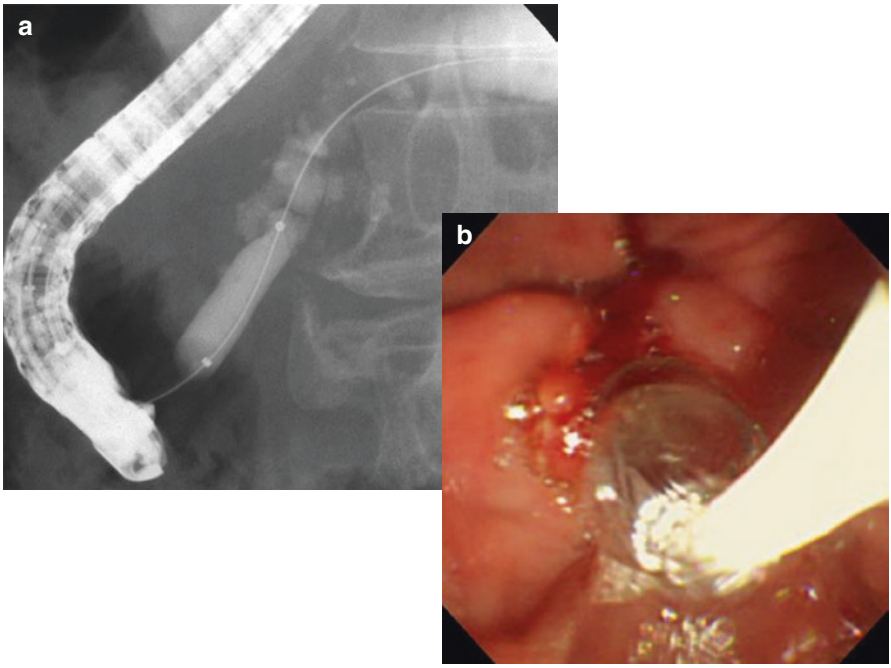


Fig. 23.3 The balloon dilated the main papilla

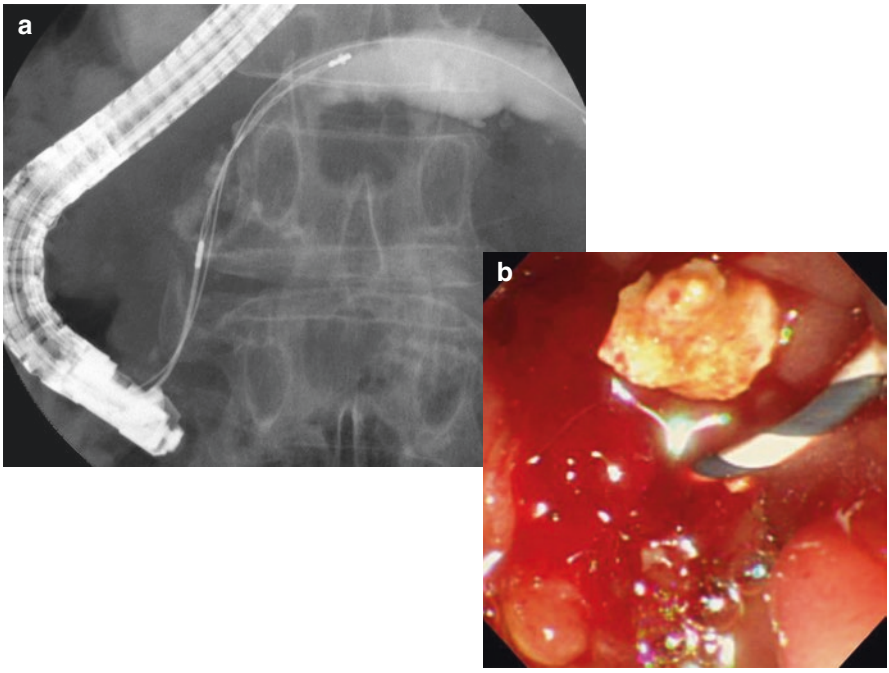


Fig. 23.4 The pancreatic stone removed by basket forceps

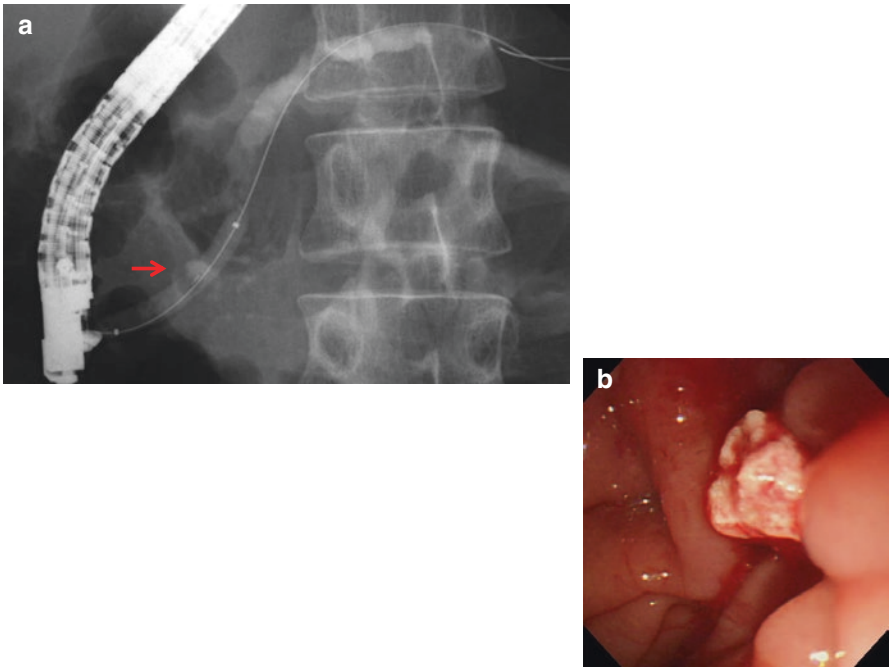


Fig. 23.5 (**a**, **b**) The pancreatic stone (→) removed by balloon catheter

23.2.2.3 EHL Under Peroral Pancreatoscopy

Prior to the introduction of the SpyGlass system (Boston Scientific Co., Marlborough, MA) in 2011 (Fig. 23.6a–c), we had performed EHL under pancreatoscopy guidance with a videoscope or fiberscope (Fig. 23.6d–g) [8]. The SpyGlass system has a 10-Fr plastic tube (spy scope) that allows for four-directional angulation of the tip. A 1.9-Fr EHL probe is inserted for endoscopic lithotripsy of the pancreatic stone under observation with a 0.8-mm optical fiber and water supply through an infusion channel. Securing a direct view of the stone leads to successful fragmentation, whereas a stone located at a winding portion of the pancreatic duct may lead to failure of fragmentation. Crushed pancreatic stone fragments can be removed with basket forceps or other tools.

Since EHL probes are currently not commercially available, we will be unable to use this technique once we use up all the previously purchased probes. We hope that the probe will be reintroduced for clinical use in the near future.

23.2.2.4 Pancreatic Stones with Stenosis of the MPD

In the presence of MPD stenosis on the duodenal side of a pancreatic stone, the stone cannot be removed without additional procedures, such as endoscopic dilation of the stenosis by a balloon or a catheter. If a guidewire can be inserted through the duct, a biliary dilation catheter (5, 6, or 7 Fr, Hanako Medical Co., Saitama, Japan; 6, 7, 9,

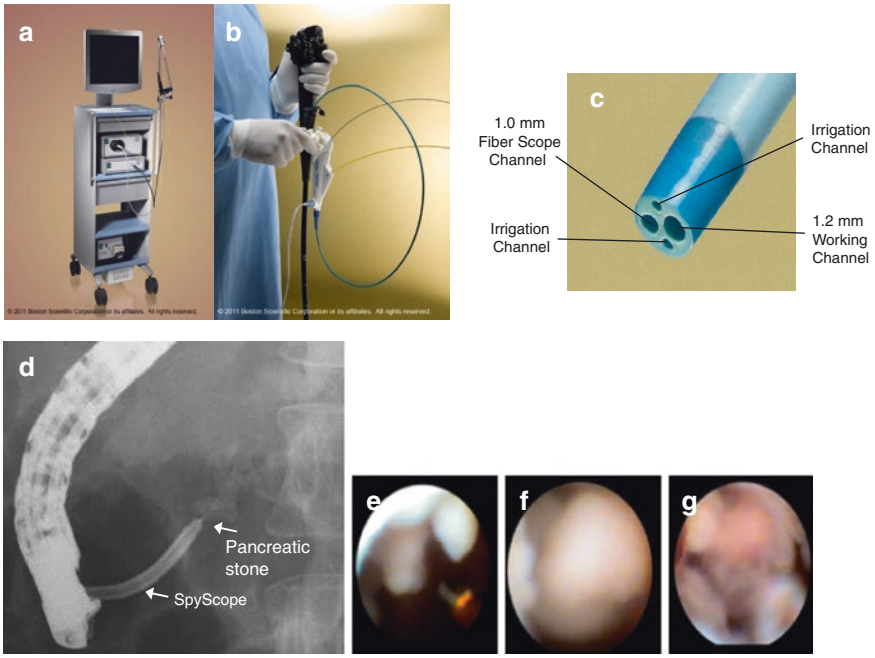


Fig. 23.6 (**a**–**g**) EHL by SpyGlass system

or 10 Fr, Cook Medical Co., Bloomington, IN) or biliary balloon dilator (4, 6, or 8 mm, Olympus Medical Systems) is used to dilate the duct. If there is a severe stenosis, the Soehendra stent retriever (7, 8.5, or 10 Fr, Cook Medical Co.) should be used with a 0.035-in. REVOWAVE guidewire (PIOLAX. Yokohama, Japan). Other guidewires should not be used as the Soehendra stent retriever (Cook Medical Co.) has a screw-like tip, which may cause loss of surface coating and breakage of the guidewire. After temporary dilation of stenosis has been achieved, S-type pancreatic stents (Olympus Medical Systems) [9] of increasing size are inserted sequentially, starting from 7 Fr, then 8.5 Fr, and eventually 10 Fr, over 2 weeks to 1 month to fully dilate the stenosis, followed by stone removal. The long-term placement of an S-type pancreatic stent also leads to improved stenosis and prevention of recurrent pancreatic stones. It is also important to strongly advise patients to abstain from alcohol.

In conclusion, stone fragmentation by ESWL and the proper use of various devices enable the safe removal of pancreatic stones.

References

1. Sohma S, Tatekawa I, Okamoto Y, et al. Endoscpic papillotomy: a new approach for extraction of residual stones. Gastroenterol Endosc. 1974;16:446–53. (Japanese with English abstract).
2. Kawai K, Akasaka Y, Hashimoto Y, et al. Endoscopical sphincterotomy of the ampulla of vater. Gastrointest Endosc. 1974;20:148–51.

3. Classen M, Demling L. Endoskopische sphinkterotomie der papilla vateri und steinextraktion aus dem ductus choledochus. Dtsch Med Wochenschr. 1974;99:496–7.
4. Inui K, Nakae Y, Nakamura J, et al. A case of non-calcified pancreatolithiasis which was removed by endoscopic sphincterotomy of the pancreatic duct. Gastroenterol Endosc. 1983;25:1246–53. (Japanese with English abstract).
5. Sauerbruch T, Holl J, Sackmann M, et al. Disintegration of a pancreatic duct stone with extracorporeal shock waves in a patient with chronic pancreatitis. Endoscopy. 1987;19:207–8.
6. Inui K, Tazuma S, Yamaguchi T, et al. Treatment of pancreatic stone with extracorporeal shock wave lithotripsy. Pancreas. 2005;30:26–30.
7. Thomas M, Howell DA, Carr-Locke D, et al. Mechanical lithotripsy of pancreatic and biliary stones: complications and available treatment options collected from expert centers. Am J Gastroenterol. 2007;102:1896–902.
8. Draqanov PV, Lin T, Chauhan S, et al. Prospective evaluation of the clinical utility of ERCP-guided cholangiopancreatoscopy with a new direct visualization system. Gastrointest Endosc. 2011;73:971–9.
9. Igarashi Y, Ito K, Mimura T, et al. Endoscopic pancreatic stenting using S-type stent for the benign stricture in the patient with chronic pancreatitis-concept of pioneering and usefulness of endoscopic treatments. Tan to Sui. 2012;33:847–51. (Japanese).

Part VII
Biliary Drainage

Chapter 24
Endoscopic Nasobiliary Drainage

Yoshiaki Kawaguchi

Abstract Four approaches are available for biliary drainage, including the surgical approach, percutaneous transhepatic approach, approach through the digestive tract, and transpapillary approach. Of these approaches, the transpapillary biliary drainage is often selected because of low invasiveness. There are two routes for this drainage: external drainage and internal drainage. The stents used include plastic stent and self-expandable metallic stent (SEMS). Depending on the stenotic lesion of the biliary tract, the bile duct is divided into the hilar bile duct and distal bile duct.

Endoscopic nasobiliary drainage (ENBD) is a transpapillary external biliary drainage technique, which was first performed in endoscopic retrograde cholangiopancreatography (ERCP) by Cotton et al. in 1979 (Gut 20:285–287, 1979). This technique is useful for examining the volume and color of the discharged bile, for identifying the etiologic bacterium in cholangitis, and for pathological examination. At present, ENBD is widely used for biliary decompression in patients with obstructive jaundice, for the treatment of acute cholangitis and biliary fistula after biliary tract surgery, and for the cytological examination of tumorous lesions in the biliary tract (Leung and Cotton, Am J Gatroenterol 86:389–394, 1991; Kawakami et al., J Gastroenterol 46:242–248, 2011; Lai et al., N Engl J Med 326:1582–1586, 1992; Yagioka et al., J Hepatobiliary Pancreat Sci 18:211–215, 2011; Uchida et al., J Gastroenterol Hepatol 23:1501–1504, 2008; Foutch et al., Gastrointest Endosc 39:416–421, 1993).

Keywords Endoscopic nasobiliary drainage • ENBD • Preoperative drainage External drainage • Hilar bile duct cancer

24.1 Advantages and Disadvantages of ENBD

Endoscopic biliary drainage (EBD) can be divided into (1) endoscopic biliary stenting (EBS), i.e., internal drainage with a plastic or self-expandable metallic stent (SEMS) (Fig. 24.1), and (2) ENBD, i.e., external drainage with a transnasal tube (Fig. 24.2)

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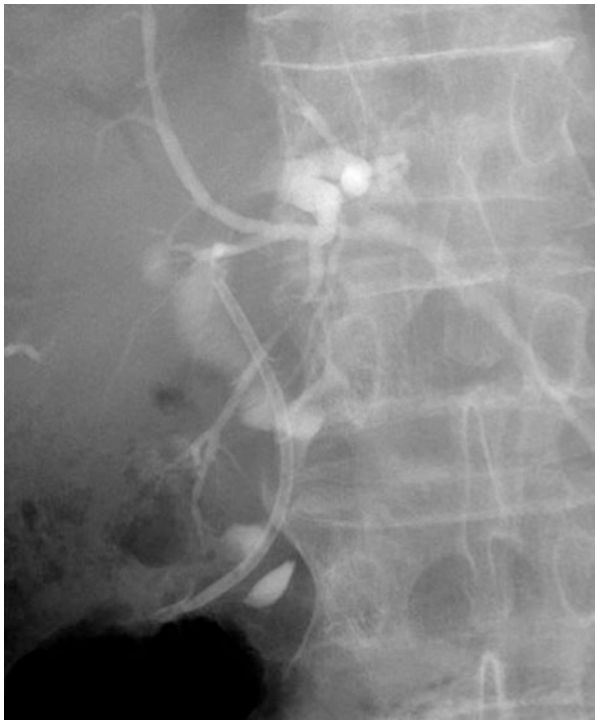

Fig. 24.1 Endoscopic biliary stenting (EBS), i.e., internal drainage. A plastic stent was inserted for pancreatic head cancer

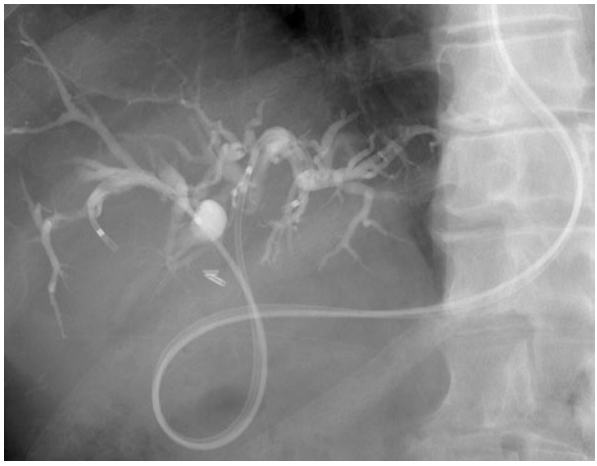

Fig. 24.2 Endoscopic nasobiliary drainage (ENBD), i.e., external drainage. Two ENBD tubes were inserted for hilar bile duct cancer

[1–7]. In previous studies, comparisons between these two EBD techniques showed that the visual analogue scale score of tube insertion was significantly higher in the ENBD group, but there were no differences in any of the following indicators of drainage treatment: procedure success rate, response rate, incidence of complications, and death rate [8–10]. Each drainage technique has its advantages and disadvantages, and therefore, the technique should be chosen depending on the patient condition. In patients who have severe cholangitis and require reliable drainage, ENBD is

performed because it allows (1) the assessment of the response to treatment of cholangitis by the precise evaluation of bile volume and color, (2) bile duct washing at the appropriate time, (3) repeated cytological examination, and (3) repeated cholangiography [2–9]. On the other hand, since ENBD involves guiding a tube out of the nose, patients may experience some pain and behavioral restrictions. Therefore, ENBD is used for temporary drainage (for a relatively short period of time) before surgery or SEMS insertion. Elderly patients often attempt self-removal of the tube when this technique is performed. In patients with a long-term indwelling tube, care needs to be taken to avoid aspiration pneumonia.

24.2 Indications for ENBD

ENBD is indicated in patients with acute cholangitis or obstructive jaundice because of bile duct stones or benign/malignant biliary tract stenosis and in patients requiring cytological examination or cholangiography for the evaluation of biliary tract disease. In cases of acute cholangitis, ENBD is shifted to EBS after the alleviation of inflammation. In cases of hilar bile duct cancer with no communication between the right and left bile ducts, multiple tubes need to be inserted during ENBD (Fig. 24.3). In recent years, the number of patients undergoing portal vein

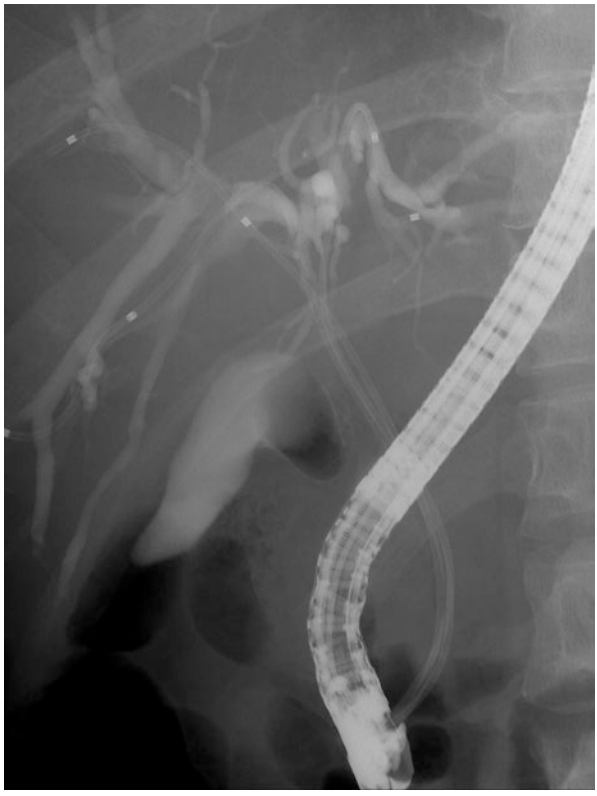

Fig. 24.3 In cases of hilar bile duct cancer with no communication among the right anterior branch, right posterior branch, and left bile ducts, three ENBD tubes were inserted

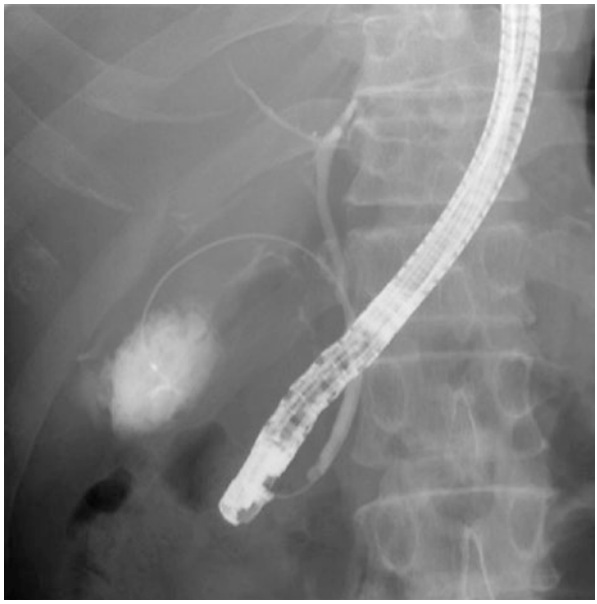

Fig. 24.4 Endoscopic nasogallbladder drainage (ENGBD) was performed for gallbladder drainage in patients with acute cholecystitis

embolization (PE) before hepatectomy has increased. In such cases, bile duct washing can be performed in ENBD, whenever needed at the onset of cholangitis, and therefore, ENBD is more convenient than EBS, in which tube exchange is necessary in case of cholangitis.

Endoscopic nasogallbladder drainage (ENGBD) has been performed for gallbladder drainage in patients with acute cholecystitis (Fig. 24.4). Particularly in patients using anticoagulants, ENGBD can be performed more safely than percutaneous transhepatic gallbladder drainage, although attention should be paid to avoid post-ERCP pancreatitis. Similarly, endoscopic naso-pancreatic drainage (ENPD) of the pancreatic duct is performed for pancreatic duct decompression for treating pancreatitis caused by disturbed pancreatic juice flow due to pancreatic stones or pancreatic duct stenosis. This technique improves the diagnosis of pancreatic cancer by the repeated collection of pancreatic juice. ENPD is also useful for the drainage of infectious pancreatic cysts.

24.3 Types and Selection of ENBD Tubes

Depending on the shape of the tip, ENBD tubes can be divided into the short α, long α, reverse long α, and pigtail types. Usually, the short α type is used for insertion into the extrahepatic bile duct (Fig. 24.5a), the long α type for insertion into the right intrahepatic bile duct (Fig. 24.5b), and the reverse long α type for insertion into the left intrahepatic bile duct (Fig. 24.5c). The pigtail type can be inserted regardless of the location of stenosis but can cause injury to the bile duct mucosa by hooking the

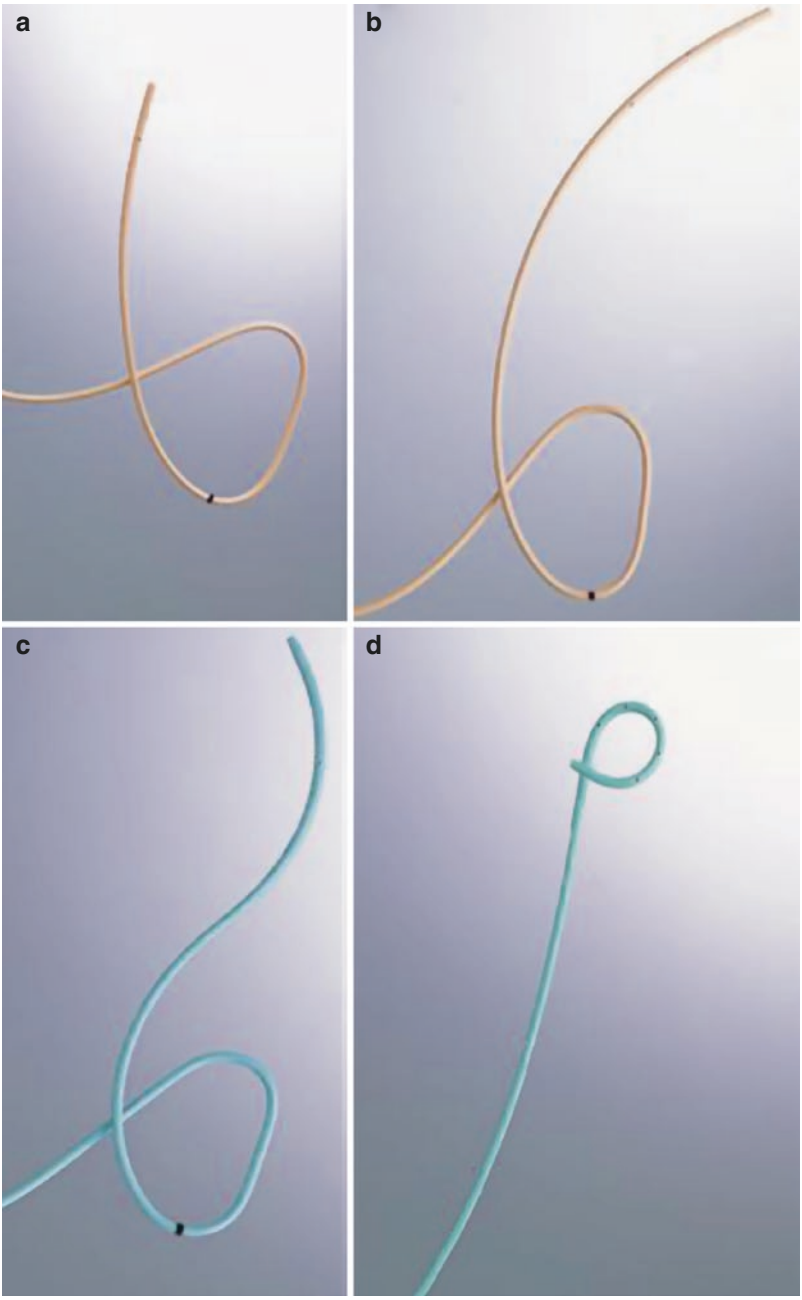

Fig. 24.5 Depending on the shape of the tip, ENBD tubes can be divided into the short α, long α, reverse long α, and pigtail types. The short α type is used for insertion into the extrahepatic bile duct (**a**), the long α type for insertion into the right intrahepatic bile duct (**b**), and the reverse long α type for insertion into the left intrahepatic bile duct (**c**). The pigtail type can be inserted regardless of the location of stenosis (**d**)

bile duct wall (this possibility should be considered if patients experience pain) (Fig. 24.5d). We often use the pigtail type.

The available tube sizes are 5, 6, and 7 Fr. Use of large diameter tubes is expected to lead to better drainage effects, but in patients with a history of pancreatitis or small papillae, it is advisable to perform endoscopic sphincterotomy (EST) or use small diameter tubes to prevent post-ERCP pancreatitis. If multiple ENBD tubes need to be inserted, a scope with a 4.2-mm diameter forceps channel (TJF-200, 230, 240, 260V, Olympus Corporation) should be used, and before insertion, EST should be performed to prevent post-ERCP pancreatitis.

24.4 Techniques of ENBD Tube Insertion [11]

First, ERCP is performed to obtain contrast-enhanced images of the bile duct. Then, deep cannulation into the bile duct is performed by advancing the guidewire to the target bile duct segment. If cholangitis is present, excessive radiography should be avoided because it can lead to the exacerbation of cholangitis. Using the guidewire, the bile duct segment at which the inserted tube forms a natural angle is selected. After the guidewire is inserted, the catheter is removed, and the ENBD tube is inserted. In this step, the tip of the tube may bend during passage through the stenotic site of the bile duct, particularly when a pigtail tube is used. Therefore, it is important that the operator manipulates the scope while keeping it close to the papilla and the assistant pulls the guidewire in accordance with the operator's manipulation. When the tube reaches the target site, the guidewire is removed, and the bile is aspirated to check the effects of the drainage. Finally, the scope is removed while keeping the ENBD tube inserted. To avoid dislocation of the ENBD tube after insertion, it is essential to avoid curving the tube in the direction from the papilla to the anal side.

The tube extending out from the mouth should be guided into the nasal cavity. In general, a Nelaton tube is inserted into the nasal cavity, and its tip is caught at the pharynx using a laryngoscope and forceps and guided out of the mouth. Next, the tip of the ENBD tube extending out from the mouth is inserted into the Nelaton tube, and the Nelaton tube extending out from the nasal cavity is pulled. In this way, the ENBD tube can be guided into the nasal cavity. Compared with the use of this technique, the use of the roping technique with a guidewire helps alleviate the patient's pain to some extent. In the roping technique, the tip of the guidewire is inserted into the nasal cavity, and a ring is formed using another part of the guidewire and inserted into the oral cavity. Under fluoroscopic guidance, the guidewire inserted through the nasal cavity is passed through the ring formed by the guidewire inserted through the oral cavity (Fig. 24.6a). The guidewire inserted through the nasal cavity is then guided into the oral cavity (Fig. 24.6b). The ENBD tube tip is inserted into the guidewire extending out from the oral cavity and then guided into the nasal cavity.

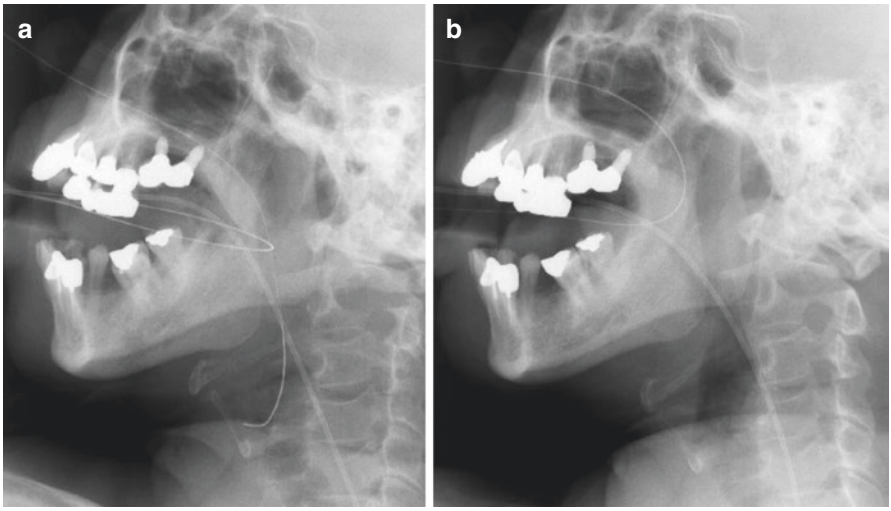

Fig. 24.6 Roping technique. Under fluoroscopic guidance, the guidewire inserted through the nasal cavity is passed through the ring formed by the guidewire inserted through the oral cavity (**a**). The guidewire inserted through the nasal cavity is then guided into the oral cavity (**b**)

24.5 Preoperative ENBD

24.5.1 Preoperative Biliary Drainage in Patients with Malignant Distal Biliary Tract Obstruction

In cases complicated by acute cholangitis, internal drainage presents the risk of early stent obstruction due to bile sludge and food residue, and therefore, external drainage is often performed. However, both internal and external drainage showed similar effects in a previous randomized controlled trial [10]. A retrospective study in Japan also showed similar results [12]. Therefore, if the preoperative waiting period is short, internal drainage with a plastic stent should be the first-choice therapy. However, if early obstructions repeatedly occur after plastic stent insertion, switching to ENBD or SEMS insertion should be considered.

Recently, a multicenter randomized controlled trial on preoperative transpapillary biliary drainage in patients with pancreatic head cancer was conducted by a European study group [13]. This study reported a surprising finding that preoperative biliary drainage is not needed in patients with pancreatic head cancer. However, in Japan, surgical treatment is generally avoided in jaundiced patients, and drainage is usually performed in such patients. This is because progression of jaundice during the waiting period (including the detailed preoperative examination period) can adversely affect patient tolerance to surgery. There exists some controversy regarding whether a strategy that reported for pancreatic head cancer is effective similarly for distal bile duct cancer.

24.5.2 Preoperative Biliary Drainage in Patients with Malignant Hilar Biliary Tract Obstruction

In the past, complete liver drainage was considered important, and insertion of multiple biliary drainage tubes was often needed. Under such circumstances, percutaneous transhepatic biliary drainage (PTBD) was generally the procedure of choice.

However, in the 1970s, PE was developed. The frequency of hepatic failure after extended hepatectomy markedly reduced, because PE for resected liver area before hepatectomy can induce enlargement of the unresected one. Thus, lobectomy after PE became a standard treatment procedure for hilar bile duct cancer, and the frequency of liver segmentectomy decreased. Currently, in the age of extended hepatectomy, there is less need to make detailed diagnosis of each bile duct branch of each liver segment by using percutaneous transhepatic cholangiography or percutaneous transhepatic cholangioscopy, and there is no need to adhere to the conventional complete liver drainage strategy.

The major problems involved in PTBD include early complications (i.e., bleeding, bile peritonitis); the risk of iatrogenic portal branch injury, which requires the switching of the operative procedure; and the risk of disseminated lesions as late complications [3, 14]. In a previous study, disseminated lesions were observed in 5.6% of the patients who had hilar bile duct cancer and underwent PTBD [15], and the indications for PTBD are considered to be limited because the prognosis is poor even after the active resection of such disseminated lesions [15].

Following the establishment of a standard operative procedure involving preoperative PE and simplification of the diagnostic management using multidetector computed tomography, it is considered that unilateral lobe drainage of the residual side of the liver is sufficient for preoperative biliary drainage, and it is recommended that the transpapillary approach should be used to perform the drainage. Transpapillary biliary drainage can be divided into EBS (internal drainage) and ENBD (external drainage). Because EBS can lead to stent obstruction in a short period [3, 14], ENBD is recommended in patients with hilar bile duct cancer in Japan (primarily at high-volume centers) [3, 14, 16].

Thus, ENBD is the technique of choice for preoperative biliary drainage in patients with hilar bile duct cancer [3, 14, 16]. However, the insertion of long period needed for ENBD is problematical, and there is no consensus regarding patient tolerance to this technique, particularly in Western countries. Considering the prevention of recurrence of cholangitis and early obstruction in EBS, long-lasting ENBD insertion is needed during the preoperative waiting period. To improve patient tolerance to ENBD and overcome the shortcomings of EBS (e.g., early obstruction due to food residue), insertion of inside EBS has begun to be applied (Fig. 24.7). Therefore, more data on inside EBS insertion are required, and further modifications of transpapillary stenting are expected.

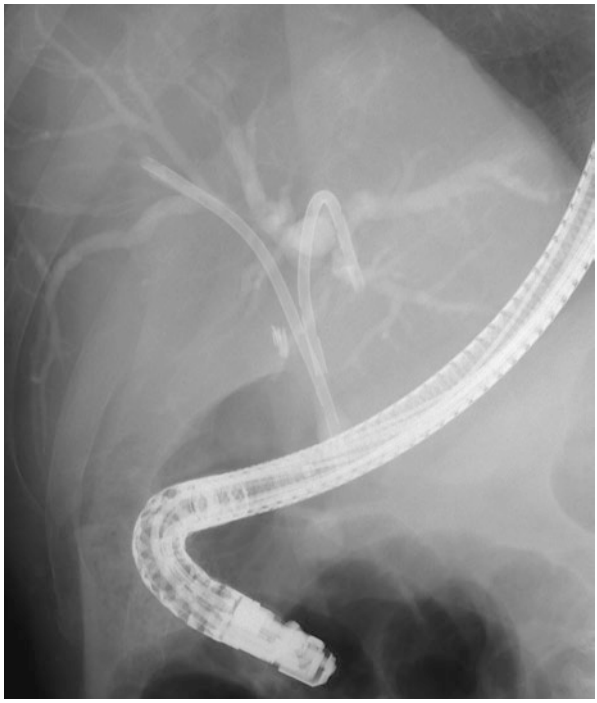

Fig. 24.7 In cases of hilar bile duct cancer with no communication between the right and left bile ducts, two inside EBS were inserted

24.6 Complications

24.6.1 Poor Drainage

If bile outflow is poor, the possibility of tube kinking should be considered. When small diameter tubes are used, attention needs to be paid for the possibility of bending. Bending of the tube often occurs in the area from the nasal cavity to the oral cavity, at the fixed sites of the body, and at the site of connection to the bag. First, the extracorporeal parts should be visually checked. If the bending of tube is observed at an extracorporeal part, it should be straightened or fixed using tape (because bending tends to recur). If there is a sufficient safety margin for the tube, the tube should be cut shorter including a bending part. If no problems are found in the extracorporeal parts, then the other parts should be checked using fluoroscopy. If kinking is detected, it should be corrected using a guidewire, or if the tube inside the stomach is highly bended, then it should be pulled out to straighten the curve. If the tube tip penetrates deep into the periphery, the tube should be pulled out and adjusted.

24.6.2 Abdominal Pain

First, pancreatitis due to pancreatic juice retention caused by the compression of the pancreatic duct opening by the tube should be suspected. Care should be taken particularly in the case of untreated papillae [17–19]. If pancreatitis is confirmed by a blood test, then the tube should be removed immediately. Contact with the tube can rarely cause gastroduodenal mucosal injury, and the use of H2 blocker or proton pump inhibitor is desirable.

24.6.3 Dehydration

In fasting patients with massive discharge, dehydration can lead to prerenal renal failure. Sufficient fluid therapy is needed in such cases. If inflammation or pancreatitis is absent, water and food intake should be resumed without delay.

24.6.4 Tube Dislocation and Self-Removal

If the tube is inappropriately inserted, its dislocation can be caused by digestive tract peristalsis. If the volume of discharge sharply decreases, then tube dislocation should be suspected and checked using radiography. Patients with poor compliance, such as elderly patients, may remove the tubes themselves. Therefore, with sufficient informed consent, the use of suppression bands should be considered. In addition, EBD, instead of ENBD, should be considered. A reason for self-removal of the tube by the patient is nose/throat discomfort during the tube insertion period. A previous study showed that the use of small diameter (4-Fr) tubes in ENBD for reducing discomfort had favorable outcomes and helped reduce the onset of pancreatitis [16].

References

1. Cotton PB, Burney PG, Mason RR. Transnasal bile duct catheterisation after endoscopic sphincterotomy: method for biliary drainage, perfusion, and sequential cholangiography. Gut. 1979;20:285–7.
2. Leung JW, Cotton PB. Endoscopic nasobiliary catheter drainage in biliary and pancreatic disease. Am J Gatroenterol. 1991;86:389–94.
3. Kawakami H, Kuwatani M, Onodera M, et al. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. J Gastroenterol. 2011;46:242–8.
4. Lai EC, Mok FP, Tan ES, et al. Endoscopic biliary drainage for severe acute cholangitis. N Engl J Med. 1992;326:1582–6.

5. Yagioka H, Hirano K, Isayama H, et al. Clinical significance of bile cytology via an endoscopic nasobiliary drainage tube for pathological diagnosis of malignant biliary strictures. J Hepatobiliary Pancreat Sci. 2011;18:211–5.
6. Uchida N, Kamada H, Ono M, et al. How many cytological examinations should be performed for the diagnosis of malignant biliary stricture via an endoscopic nasobiliary drainage tube? J Gastroenterol Hepatol. 2008;23:1501–4.
7. Foutch PG, Harlan JR, Hoefer M. Endoscopic therapy for patients with a post-operative biliary leak. Gastrointest Endosc. 1993;39:416–21.
8. Lee DW, Chan AC, Lam YH, Ng EK, Lau JY, Law BK, et al. Biliary decompression by nasobiliary catheter or biliary stent in acute suppurative cholangitis: a prospective randomized trial. Gastrointest Endosc. 2002;56:361–5.
9. Sharma BC, Kumar R, Agarwal N, Sarin SK. Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis. Endoscopy. 2005;37:439–43.
10. Park SY, Park CH, Cho SB, Yoon KW, Lee WS, Kim HS, et al. The safety and effectiveness of endoscopic biliary decompression by plastic stent placement in acute suppurative cholangitis compared with nasobiliary drainage. Gastrointest Endosc. 2008;68:1076–80.
11. Tsuyuguchi T, Takada T, Kawarada Y, Nimura Y, Wada K, Nagino M, et al. Techniques of biliary drainage for acute cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:35–45.
12. Sugiyama H, Tsuyuguchi T, Sakai Y, et al. Preoperative drainage for distal biliary obstruction: endoscopic stenting or nasobiliary drainage? Hepatogastroenterology. 2013;60:231–4.
13. van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362:129–37.
14. Kawakami H, Kondo S, Kuwatani M, et al. Preoperative biliary drainage for hilar cholangiocarcinoma: which stent should be selected? J Hepatobiliary Pancreat Sci. 2011;18:630–5.
15. Takahashi Y, Nagino M, Nishio H, et al. Percutaneous transhepatic biliary drainage catheter tract recurrence in cholangiocarcinoma. Br J Surg. 2010;97:1860–6.
16. Kawashima H, Itoh A, Ohno E, et al. Preoperative endoscopic nasobiliary drainage in 164 consecutive patients with suspected perihilar cholangiocarcinoma: a retrospective study of efficacy and risk factors related to complications. Ann Surg. 2013;257:121–7.
17. Pedersen FM. Endoscopic management of malignant biliary obstruction. Is stent size of 10 French gauge better than 7 French gauge? Scand J Gastroenterol. 1993;28:185–9.
18. Kadakia SC, Starnes E. Comparison of 10 French gauge stent with 11.5 French gauge stent in patients with biliary tract diseases. Gastrointest Endosc. 1992;38:454–9.
19. Katsinelos P, Kountouras J, Paroutoglou G, et al. A comparative study of 10-Fr vs. 7-Fr straight plastic stents in the treatment of postcholecystectomy bile leak. Surg Endosc. 2008;22:101–6.

Chapter 25
Plastic (Tube) Stent Drainage

Masatsugu Nagahama

Abstract Endoscopic biliary drainage using a plastic stent (PS) has been widely performed for endoscopic treatment of cholangitis and jaundice due to biliary obstruction. However, subsequent studies comparing PS and self-expandable metallic stent (SEMS) demonstrated the superiority of SEMS in the treatment of unresectable malignant biliary obstruction. Thus, good candidates for endoscopic biliary drainage with a PS are now considered to include emergency drainage for acute cholangitis, drainage for benign biliary stricture, temporary drainage for obstructive jaundice during diagnostic differentiation of benign from malignant lesions, and stent-in-stent placement for SEMS obstruction. On the other hand, a new effort to place a stent that is called "inside stent" has been reported. The "inside-stent" technique has recently been reported to be useful for the treatment of benign biliary stricture after hepatic transplantation and unresectable malignant hilar biliary obstruction. Future studies on the "inside-stent" technique are warranted.

Keywords Plastic stent • EBS • Inside stent

25.1 Introduction

Since endoscopic biliary stenting (EBS) was first reported by Soehendra et al. in 1980 [1], endoscopic biliary drainage using a plastic stent (PS) has been widely performed for endoscopic treatment of cholangitis and jaundice due to biliary obstruction. A self-expandable metallic stent (SEMS) was introduced in the 1990s and came to be used for EBS. Subsequent studies comparing PS and SEMS demonstrated the superiority of SEMS in the treatment of middle and lower biliary obstruction associated with unresectable malignancy [2–6]. Other comparative studies have also shown that SEMS is more beneficial than PS in the treatment of unresectable malignant hilar obstruction [7–9]. Thus, SEMS has come to be more commonly used as the first choice of endoscopic biliary drainage for unresectable malignant biliary obstruction. Furthermore, because there are more than a few cases of preoperative

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biliary drainage with a PS in which stent obstruction occurs during the waiting period, SEMS placement is reportedly worthy for consideration as the preoperative treatment, particularly for malignant middle and lower biliary obstruction [10–15].

As described above, good candidates for endoscopic biliary drainage with a PS are now considered, because of inexpensive and removable application, to include emergency drainage for acute cholangitis, drainage for benign biliary stricture, temporary drainage for obstructive jaundice during diagnostic differentiation of benign from malignant lesions, and stent-in-stent placement for SEMS obstruction. In recent years, PS has also been used for endoscopic ultrasound (EUS)-guided pancreatic pseudocyst drainage and EUS-guided biliary drainage.

A new effort to place a stent that is called "inside stent" has been reported [16]. With this technique, a PS is placed in the bile duct without protruding the lower end of the stent on the duodenal side from the papilla. Because the device dedicated for the "inside stent" is commercially available, results of future studies are awaited.

In this review, we first introduce the currently available PS types and, then, describe PS placement according to the following diseases: drainage for acute cholangitis, long-term PS placement for common bile duct stones difficult to extract, benign biliary stricture, postoperative biliary fistula, and malignant hilar obstruction. The details of EUS-guided drainage and the stent-in-stent technique for SEMS obstruction are reported elsewhere.

25.2 PS Types

PS can be classified, according to the tip shape, as the straight type, single-pigtail type, or double-pigtail type (Fig. 25.1). Moreover, the straight-type PS is subdivided into the Tannenbaum type (Fig. 25.2), which is attached with flaps but has no side

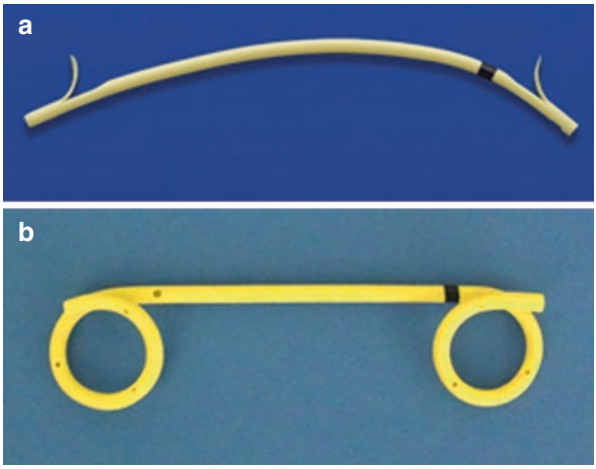

Fig. 25.1 (**a**) Straight-type plastic stent, (**b**) double-pigtail-type plastic stent

Fig. 25.2 Tannenbaum-type straight plastic stent

Fig. 25.3 Amsterdam-type straight plastic stent

holes, and the Amsterdam type (Fig. 25.3), which has large side holes. In particular, the pigtail-type PS is less likely to migrate.

In recent years, a preloaded PS that combines the guiding and pushing catheter has been sold by various manufacturers, which allows accurate and safe PS placement (Fig. 25.4).

Fig. 25.4 A preloaded straight plastic stent

25.2.1 Endoscopic Biliary Drainage with a PS for Acute Cholangitis

As for biliary drainage for acute cholangitis, endoscopic drainage is the first choice of procedure because of its less invasiveness than percutaneous and surgical drainages [17–20]. Endoscopic biliary drainage is of two types: external drainage (endoscopic nasobiliary drainage [ENBD]) and internal drainage (EBS with a PS). Both types of drainage are applicable because there are no differences in success rate, response rate, complication rate, or mortality between them [21–23]. However, EBS appears to be more useful for the treatment of patients with nasal cavity disorders and elderly patients in whom self-removal of the stent is a concern. Although there have been no reports concerning differences in the outcomes depending on PS type, the pigtail type is considered to be associated with a lower risk of migration compared to the straight type.

25.2.2 Long-Term PS Placement for Common Bile Duct Stones Difficult to Extract

Several reports have shown that long-term PS placement is useful for the treatment of common bile duct stones difficult to extract [23, 24], while there is also a report describing that stenting resulted in a decrease in stone diameter [25]. However, other studies have shown that long-term PS placement is associated with a high incidence of acute cholangitis due to stent obstruction [26–28]. The recent arrival of aging society has increased the number of high-risk patients with common bile duct stones due to their extreme old age or comorbidities. At present, it seems preferable to apply long-term PS placement after careful consideration of the indications, for instance, to only patients with a short prognosis predicted by old age or comorbidities (Fig. 25.5).

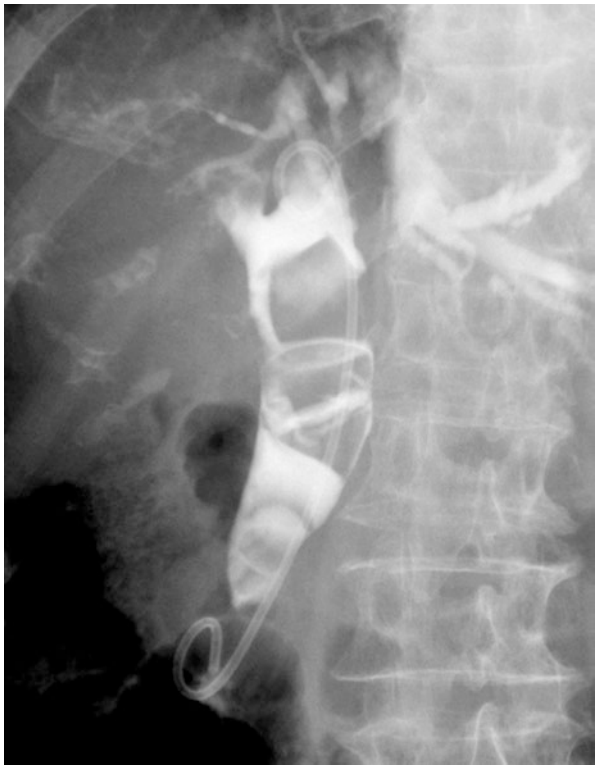

Fig. 25.5 A fluoroscopic view of common bile duct. This patient was a 90-year-old female, and numerous calculi were found in the common bile duct and accumulated. As this patient declined endoscopic lithotripsy, she replaced the pigtail-type plastic stent every 6 months

25.2.3 Benign Biliary Stricture

For the treatment of lower biliary stricture complicating chronic pancreatitis or benign biliary stricture associated with postoperative biliary anastomosis, removable PS has been selected because of benign conditions. However, when one PS is placed, it needs to be replaced every 2–3 months. Thus, since a technique to insert multiple PSs was reported [29, 30], multiple PS placement has widely been performed (Fig. 25.6). Meanwhile, sporadic reports have been published on the use of SEMS, which has a larger diameter than PS; that is, there are reports describing the use of fully covered SEMS which can be theoretically removed after placement [31, 32], a systematic review compared uncovered SEMS placement with single and multiple PS placement [33], and there is another report describing the use of partially covered SEMS [34]. All previous studies have shown that although SEMS remained patent for a longer period of time than PS and could be removed in 80–90% of all cases, the development of early and late complications, particularly migration soon after placement, was recognized as an SEMS problem. The improvement of SEMS is desired to avoid the migration.

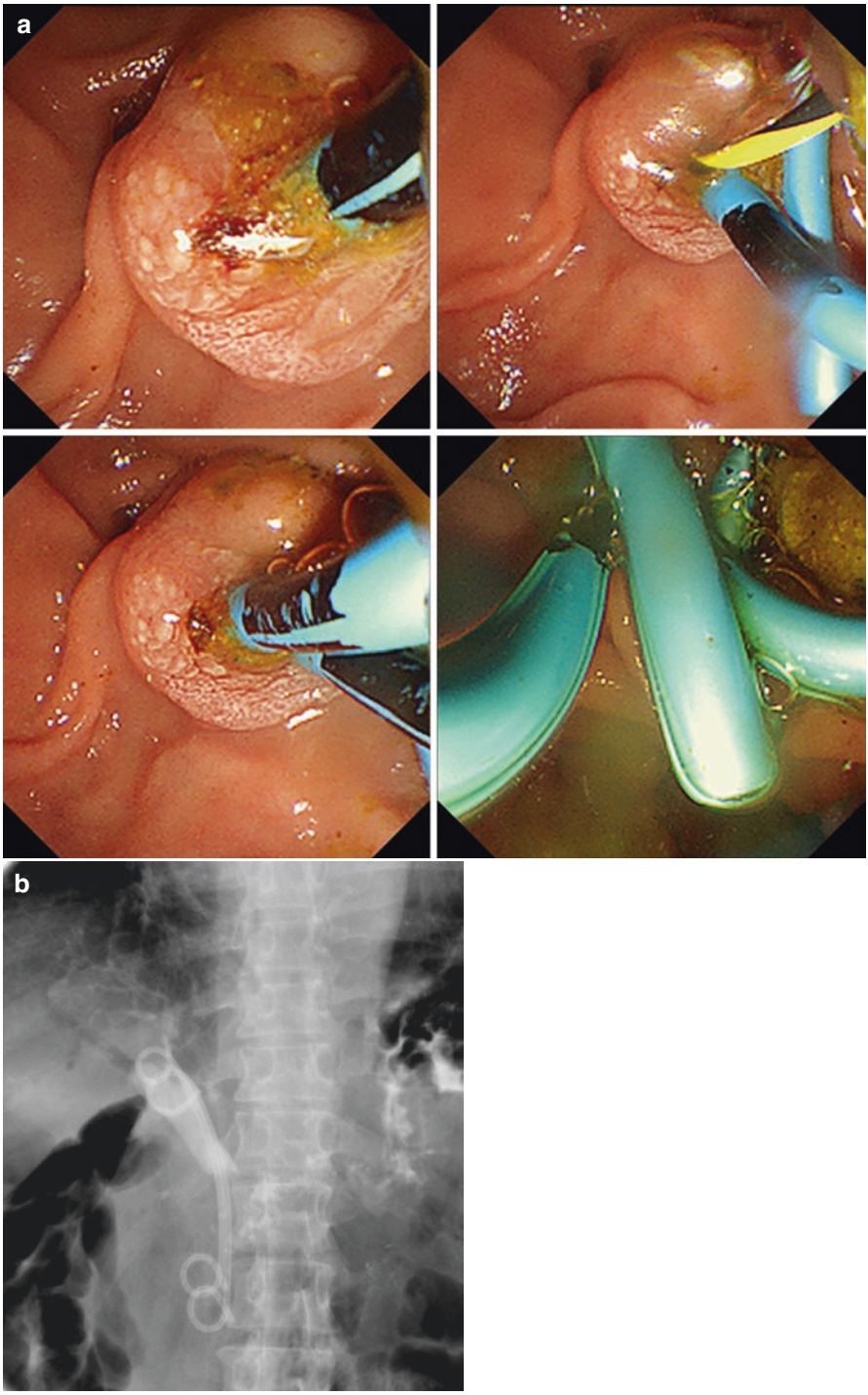

Fig. 25.6 A case of benign lower biliary duct stenosis due to chronic pancreatitis. Two pigtail stents were placed in the bile duct. (**a**) Endoscopic view, (**b**) fluoroscopic view

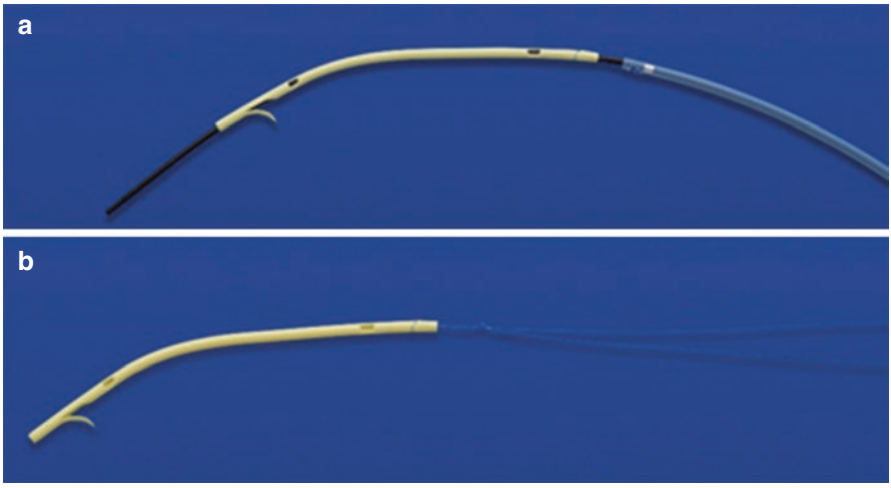

Fig. 25.7 Photograph of the device dedicated for the inside stent. (**a**) A preloaded straight plastic stent. (**b**) A nylon thread is attached to the distal side to aid removal of the stent, when necessary

Furthermore, there are reports describing that the "inside-stent" technique is useful for the treatment of benign biliary stricture after hepatic transplantation [35, 36]. This technique is expected to extend the duration of stent patency by placing the duodenal side of the PS within the bile duct [16, 37]. Because the device dedicated for the "inside stent" is commercially available (Fig. 25.7), future studies on the "inside-stent" technique are warranted.

25.2.4 Postoperative Biliary Fistula

For biliary fistula, surgical treatment has often been performed; however, the usefulness of endoscopic drainage has recently been reported. Removable PS is often used for endoscopic drainage, and the success rate of endoscopic treatment is reportedly 75% after hepatectomy [38] and 87–100% after laparoscopic cholecystectomy (LC) [39]. Katshnelos et al. [40] studied the effects of PS diameter by dividing 63 patients with post-LC biliary fistula into the 7-Fr stent group and the 10-Fr stent group, reporting that there was no difference in therapeutic outcomes between the two types of stent. When biliary fistula after hepatectomy was examined in terms of positional relationship between PS placement and leak, bridging was possible by placing the PS to cover the leak site in more patients successfully treated with endoscopy, as compared to those with unsuccessful endoscopic treatment, although the difference between the groups did not reach statistical significance [40]. Thus, when PS is placed for biliary fistula, the PS placement site and the leak are considered more important than the stent diameter (Fig. 25.8).

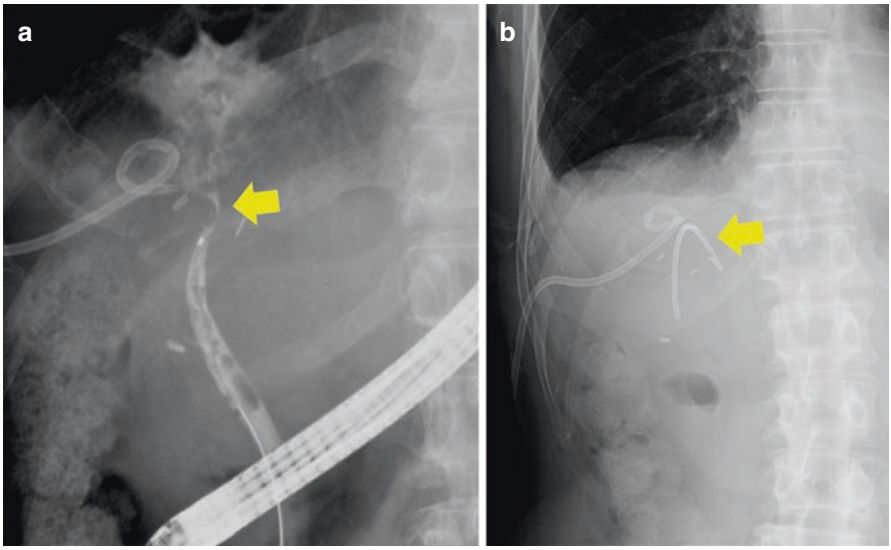

Fig. 25.8 A case of rectal cancer metastasis to the right lobe of the liver. (**a**) Bile leakage (*yellow arrow*) occurred from the left hepatic duct after hepatic right lobectomy and partial hepatectomy S4. (**b**) A 7Fr plastic stent was placed as a "inside stent" to cover the leakage portion of the left hepatic duct

25.2.5 Malignant Hilar Biliary Obstruction

In Japan, total biliary drainage (the method by which multiple percutaneous transhepatic biliary drainage [PTBD] catheters are placed) has conventionally been recommended as the preoperative drainage for malignant hilar biliary obstruction [41]. However, a subsequent study has reported that postoperative PTBD fistula recurred in 5.2% of cases and that placement of one ENBD catheter for the planned residual liver was sufficiently effective for reducing jaundice in preoperative cases with Bismuth type I, II, or III [42]. Furthermore, in a study comparing PTBD, EBS, and ENBD as a preoperative drainage for hilar cholangiocarcinoma, ENBD was found to be the most efficient drainage technique [43]. However, in cases with malignant hilar biliary obstruction, long-term placement of an ENBD catheter may be inevitable as the preoperative waiting period becomes longer because of preoperative portal vein embolism or preoperative chemotherapy. Although internal drainage (EBS) from ENBD may be considered in such a case, conventional EBS with a PS is associated with a short patency period and a high risk of developing obstruction and inflammation during the preoperative waiting period. A recent study on preoperative drainage for malignant biliary obstruction has shown that the "inside-stent" technique yielded a longer patency period and was more useful than conventional stenting [44]. In that study, patients with malignant hilar obstruction were included for analysis. In the future, the "inside-stent" technique may be a promising method of temporary internal drainage from ENBD in preoperative cases with malignant hilar obstruction.

In cases with unresectable malignant hilar biliary obstruction, SEMS is considered to have more advantages than PS because SEMS is expected to remain patent for a longer period and to thereby reduce the obstruction rate, the number of treatment sessions, hospital stay length, and treatment cost [7–9]. However, the "inside-stent" technique has recently been reported to be useful for the treatment of unresectable malignant hilar biliary obstruction [45, 46]. Because a stent placed by this technique remains patent for a longer period and can be more easily removed and replaced than that placed by conventional EBS, the "inside-stent" technique appears to be a useful drainage technique for initial treatment of malignant hilar biliary obstruction (Fig. 25.9). This technique would be useful in the treatment of patients diagnosed with unresectable hilar cholangiocarcinoma in whom the degrees

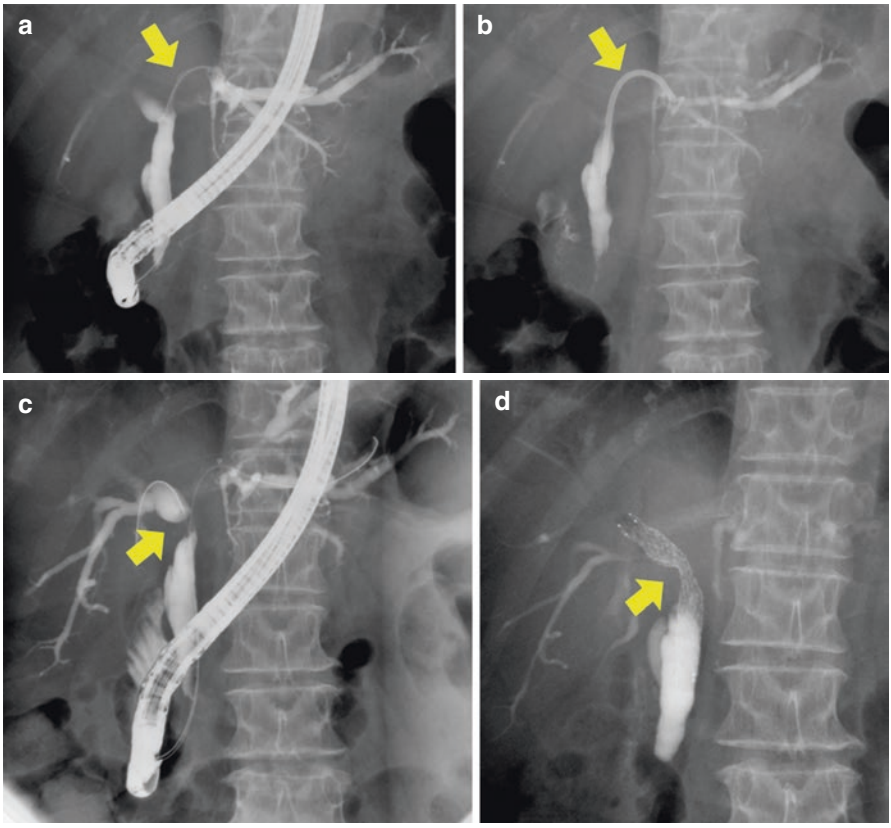

Fig. 25.9 A case of unresectable hilar bile duct cancer. (**a**) The left hepatic duct is stenotic (*yellow arrow*) due to cancer. (**b**) A 7Fr plastic stent (*yellow arrow*) was inserted as an "inside stent" into the stenosis of the left hepatic duct. After inserting stent and improving jaundice, we started chemotherapy. (**c**) One hundred and forty-five days after inserting stent into the left hepatic duct, obstructive jaundice occurred due to right hepatic duct stenosis (*yellow arrow*). (**d**) The plastic stent of the left hepatic duct was removed, and an uncovered self-expandable metallic stent (*yellow arrow*) was inserted into the right hepatic duct. Drainage of the left hepatic duct was unnecessary, because the left lobe of the liver was atrophied due to the portal vein invasion

of stricture or obstruction are changed due to chemotherapy or radiotherapy and those who may become indicated for surgery after down staging. Future studies are thus awaited.

References

1. Soehendra N, Reynders-Frederix V. Palliative bile duct drainage - a new endoscopic method of introducing a transpapillary drain. Endoscopy. 1980;12(1):8–11.
2. Davids PH, Groen AK, Rauws EA, et al. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet. 1992;340(8834–8835):1488–92.
3. Knyrim K, Wagner HJ, Pausch J, et al. A prospective, randomized, controlled trial of metal stents for malignant obstruction of the common bile duct. Endoscopy. 1993;25(3):207–12.
4. Prat F, Chapat O, Ducot B, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. Gastrointest Endosc. 1998;47(1):1–7.
5. Kaassis M, Boyer J, Dumas R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc. 2003;57(2):178–82.
6. Moss AC, Morris E, Leyden J, et al. Do the benefits of metal stents justify the costs? A systematic review and meta-analysis of trials comparing endoscopic stents for malignant biliary obstruction. Eur J Gastroenterol Hepatol. 2007;19(12):1119–24.
7. Wagner HJ, Knyrim K, Vakil N, et al. Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. Endoscopy. 1993;25(3):213–8.
8. Perdue DG, Freeman ML, DiSario JA, et al. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. J Clin Gastroenterol. 2008;42(9):1040–6.
9. Mukai T, Yasuda I, Nakashima M, et al. Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. J Hepatobiliary Pancreat Sci. 2013;20(2):214–22.
10. Mullen JT, Lee JH, Gomez HF, et al. Pancreaticoduodenectomy after placement of endobiliary metal stents. J Gastrointest Surg. 2005;9(8):1094–104. discussion 1104-5
11. Wasan SM, Ross WA, Staerkel GA, et al. Use of expandable metallic biliary stents in resectable pancreatic cancer. Am J Gastroenterol. 2005;100(9):2056–61.
12. Lawrence C, Howell DA, Conklin DE, et al. Delayed pancreaticoduodenectomy for cancer patients with prior ERCP-placed, nonforeshortening, self-expanding metal stents: a positive outcome. Gastrointest Endosc. 2006;63(6):804–7.
13. Singal AK, Ross WA, Guturu P, et al. Self-expanding metal stents for biliary drainage in patients with resectable pancreatic cancer: single-center experience with 79 cases. Dig Dis Sci. 2011;56(12):3678–84.
14. Decker C, Christein JD, Phadnis MA, et al. Biliary metal stents are superior to plastic stents for preoperative biliary decompression in pancreatic cancer. Surg Endosc. 2011;25(7):2364–7.
15. Aadam AA, Evans DB, Khan A, et al. Efficacy and safety of self-expandable metal stents for biliary decompression in patients receiving neoadjuvant therapy for pancreatic cancer: a prospective study. Gastrointest Endosc. 2012;76(1):67–75.
16. Liu Q, Khay G, Cotton PB. Feasibility of stent placement above the sphincter of Oddi ("inside-stent") for patients with malignant biliary obstruction. Endoscopy. 1998;30(8):687–90.
17. Lai EC, Mok FP, Tan ES, et al. Endoscopic biliary drainage for severe acute cholangitis. N Engl J Med. 1992;326(24):1582–6.

18. Leung JW, Chung SC, Sung JJ, et al. Urgent endoscopic drainage for acute suppurative cholangitis. Lancet. 1989;1(8650):1307–9.
19. Boender J, Nix GA, de Ridder MA, et al. Endoscopic sphincterotomy and biliary drainage in patients with cholangitis due to common bile duct stones. Am J Gastroenterol. 1995;90(2):233–8.
20. Lau JY, Chung SC, Leung JW, et al. Endoscopic drainage aborts endotoxaemia in acute cholangitis. Br J Surg. 1996;83(2):181–4.
21. Lee DW, Chan AC, Lam YH, et al. Biliary decompression by nasobiliary catheter or biliary stent in acute suppurative cholangitis: a prospective randomized trial. Gastrointest Endosc. 2002;56(3):361–5.
22. Sharma BC, Kumar R, Agarwal N, et al. Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis. Endoscopy. 2005;37(5):439–43.
23. Park SY, Park CH, Cho SB, et al. The safety and effectiveness of endoscopic biliary decompression by plastic stent placement in acute suppurative cholangitis compared with nasobiliary drainage. Gastrointest Endosc. 2008;68(6):1076–80.
24. Soomers AJ, Nagengast FM, Yap SH. Endoscopic placement of biliary endoprostheses in patients with endoscopically unextractable common bile duct stones. A long-term follow up study of 26 patients. Endoscopy. 1990;22(1):24–6.
25. Chan AC, Ng EK, Chung SC, et al. Common bile duct stones become smaller after endoscopic biliary stenting. Endoscopy. 1998;30(4):356–9.
26. Cotton PB. Stents for stones: short-term good, long-term uncertain. Gastrointest Endosc. 1995;42(3):272–3.
27. Bergman JJ, Rauws EA, Tijssen JG, et al. Biliary endoprostheses in elderly patients with endoscopically irretrievable common bile duct stones: report on 117 patients. Gastrointest Endosc. 1995;42(3):195–201.
28. Chopra KB, Peters RA, O'Toole PA, et al. Randomised study of endoscopic biliary endoprosthesis versus duct clearance for bileduct stones in high-risk patients. Lancet. 1996;348(9030):791–3.
29. Costamagna G, Pandolfi M, Mutignani M, et al. Long-term results of endoscopic management of postoperative bile duct strictures with increasing numbers of stents. Gastrointest Endosc. 2001;54(2):162–8.
30. Catalano MF, Linder JD, George S, et al. Treatment of symptomatic distal common bile duct stenosis secondary to chronic pancreatitis: comparison of single vs. multiple simultaneous stents. Gastrointest Endosc. 2004;60(6):945–52.
31. Kahaleh M, Behm B, Clarke BW, et al. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? (With video). Gastrointest Endosc. 2008;67(3):446–54.
32. Devière J, Nageshwar Reddy D, Püspök A, et al. Successful management of benign biliary strictures with fully covered self-expanding metal stents. Gastroenterology. 2014;147(2):385–95.
33. van Boeckel PG, Vleggaar FP, Siersema PD. Plastic or metal stents for benign extrahepatic biliary strictures: a systematic review. BMC Gastroenterol. 2009;9:96.
34. Behm B, Brock A, Clarke BW, et al. Partially covered self-expandable metallic stents for benign biliary strictures due to chronic pancreatitis. Endoscopy. 2009;41(6):547–51.
35. Tsujino T, Isayama H, Sugawara Y, et al. Endoscopic management of biliary complications after adult living donor liver transplantation. Am J Gastroenterol. 2006;101:2230–6.
36. Kurita A, Kodama Y, Minami R, et al. Endoscopic stent placement above the intact sphincter of Oddi for biliary strictures after living donor liver transplantation. J Gastroenterol. 2013;48(9):1097–104.
37. Uchida N, Tsutsui K, Ezaki T, et al. Estimation of the stent placement above the intact sphincter of Oddi against malignant bile duct obstruction. J Gastroenterol. 2005;40(3):291–6.
38. Dechêne A, Jochum C, Fingas C, et al. Endoscopic management is the treatment of choice for bile leaks after liver resection. Gastrointest Endosc. 2014;80(4):626–33.

39. Canena J, Horta D, Coimbra J, et al. Outcomes of endoscopic management of primary and refractory postcholecystectomy biliary leaks in a multicentre review of 178 patients. BMC Gastroenterol. 2015;15:105.
40. Katsinelos P, Kountouras J, Paroutoglou G, et al. A comparative study of 10-Fr vs. 7-Fr straight plastic stents in the treatment of postcholecystectomy bile leak. Surg Endosc. 2008;22(1):101–6.
41. Nimura Y. Preoperative biliary drainage before resection for cholangiocarcinoma (Pro). HPB (Oxford). 2008;10(2):130–3.
42. Arakura N, Takayama M, Ozaki Y, et al. Efficacy of preoperative endoscopic nasobiliary drainage for hilar cholangiocarcinoma. J Hepato-Biliary-Pancreat Surg. 2009;16(4):473–7.
43. Kawakami H, Kuwatani M, Onodera M, et al. Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. J Gastroenterol. 2011;46(2):242–8.
44. Kobayashi N, Watanabe S, Hosono K, et al. Endoscopic inside stent placement is suitable as a bridging treatment for preoperative biliary tract cancer. BMC Gastroenterol. 2015;15:8.
45. Ishiwatari H, Hayashi T, Ono M, et al. Newly designed plastic stent for endoscopic placement above the sphincter of Oddi in patients with malignant hilar biliary obstruction. Dig Endosc. 2013;25:94–9.
46. Kaneko T, Sugimori K, Shimizu Y, et al. Efficacy of plastic stent placement inside bile ducts for the treatment of unresectable malignant hilar obstruction (with videos). J Hepatobiliary Pancreat Sci. 2014;21(5):349–55.

Chapter 26
Hilar Malignant Strictures

Anand Singla and Richard A. Kozarek

Abstract When it comes to endoscopic management, a malignant stricture at the biliary confluence poses a significant challenge to the therapeutic endoscopist both diagnostically and therapeutically. The diagnostic goal is to determine malignant or benign etiology of a biliary stricture and to determine resectability. In addition to proper imaging of the biliary hilum with computed tomography (CT) and magnetic resonance (MR), endoscopic tissue acquisition is an extremely important component to determining the etiology of a biliary stricture, specifically to differentiate between malignant and benign process. Brushings for cytology, intraductal biopsies, and even endoluminal fine-needle aspiration can all be performed at the time of endoscopic retrograde cholangiography (ERC), while endoscopic ultrasound (EUS) offers additional opportunity for fine-needle aspiration. Peroral cholangioscopy is an emerging technique that can directly visualize a malignant hilar stricture and allow for directed biopsies. Therapeutically, the ultimate goal is palliative biliary drainage to relieve biliary obstruction. This can be accomplished endoscopically with the placement of plastic or metal biliary stents to drain the most obstructed lobe of the liver, with uncovered self-expanding metal stents (SEMS) being preferred. Photodynamic therapy and radiofrequency ablation are emerging endoscopic techniques that allow for localized destruction of tumor cells, potentially improving biliary drainage, quality of life, and survival in most patients, but require further randomized, controlled studies.

Keywords Malignant hilar stricture • Biliary stricture • Cholangiocarcinoma Endoscopic retrograde cholangiography (ERC) • Cholangioscopy • Biliary stent Photodynamic therapy

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26.1 Introduction

The malignant hilar stricture poses a difficult management challenge to the endoscopist, with complex and varied endoscopic techniques for diagnosis and treatment. The etiology of a hilar stricture itself can be benign or malignant, with malignant strictures being primary tumors (cholangiocarcinoma), local extension of other tumors (gallbladder cancer, pancreatic adenocarcinoma, hepatocellular carcinoma), and rarely lymph node metastases (breast, colon, stomach, ovaries, lymphoma, and melanoma), with cholangiocarcinoma being the most common [1]. Hilar cholangiocarcinoma (HCCA) was first described by Klatskin in 1965 and accounts for 60–70% of diagnosed cholangiocarcinomas [2].

Biliary papillomatosis (BP) is a rare disease characterized by multiple papillary adenomas of variable distribution and extent in the intrahepatic and/or extrahepatic biliary tree, manifesting as recurrent abdominal pain, jaundice, and cholangitis [3]. In a review of 58 patients with BP over 8 years, 83% went on to develop papillary adenocarcinoma [3]. BP is thus considered a premalignant disease with high malignant potential and a potential cause of stricture at the hilum (Fig. 26.1).

While most patients when diagnosed do not have risk factors, there are some known risk factors for the development of cholangiocarcinoma [2, 4]. These include general risk factors such as age, smoking, obesity, and diabetes, as well as chronic inflammatory diseases such as primary sclerosing cholangitis. *Opisthorchis viverrini* and *Clonorchis sinensis* are two parasites common in Asia that infect the bile ducts and have been classified by the International Agency for Research on Cancer as group I carcinogens for the development of cholangiocarcinoma [5, 6].

HCCA typically presents in an insidious manner with early disease manifesting as nonspecific symptoms of nausea, vomiting, weight loss, abdominal pain, and low-grade fevers. More advanced disease usually signifies complete biliary obstruction with manifestations of obstructive jaundice (80–90%) [2]. Only about 1/3 of patients have surgically resectable disease at the time of presentation, with an overall survival of less than 1 year in patients with non-resectable disease (Fig. 26.2) [7–9].

Given this, the endoscopist plays an important role in establishing the diagnosis of malignant hilar stricture, which in most cases is unresectable advanced hilar cholangiocarcinoma, typically requiring endoscopic palliative therapy.

26.2 Diagnosis of Malignant Hilar Strictures

The diagnostic imperative when encountering a hilar stricture, be it from the clinical presentation or an imaging study, is to determine malignant vs benign etiology and to determine potential surgical resectability [1]. This is easier said than done, however. A small study of 24 patients comparing 12 patients with benign biliary strictures and 12 patients with malignant biliary strictures found some potential utility in combining laboratory results with imaging and cholangiographic findings [10]. However, even in patients with elevated plasma bilirubin/alkaline phosphatase,

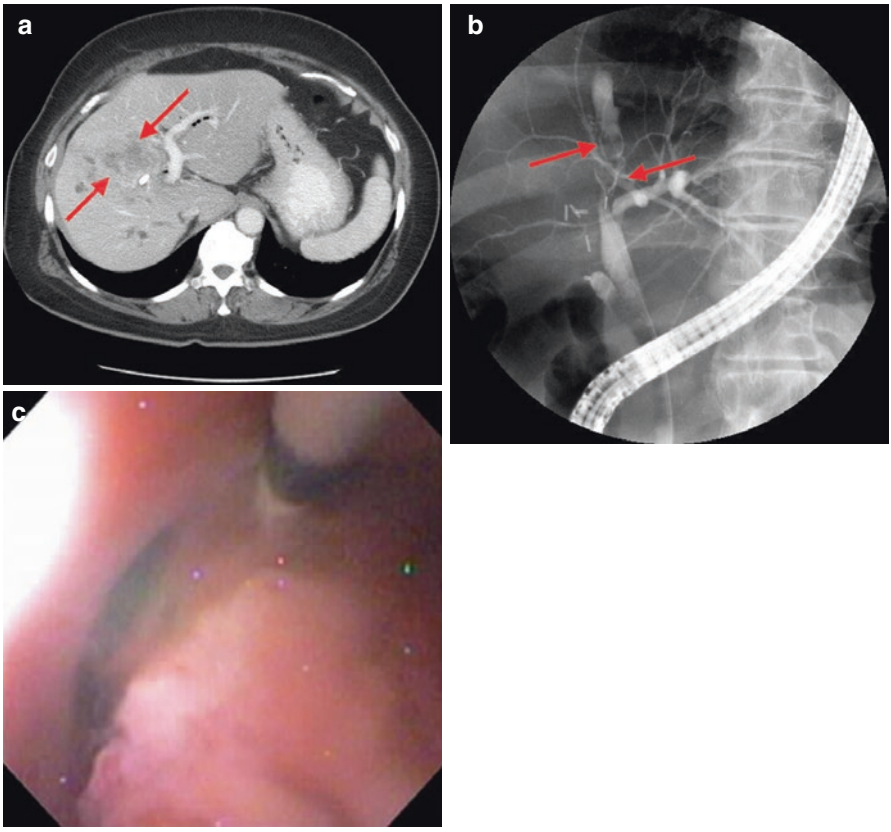

Fig. 26.1 Bile duct adenomas seen in a patient with biliary papillomatosis. (**a**) In this CT image, note incomplete obstruction of the right intrahepatic system with biliary adenomas (arrows). (**b**) Findings at cholangiography show lack of contrast through the right intrahepatic duct and multiple adenomas leading to filling defects in the right duct and dilation of the left intrahepatic system (arrows). (**c**) Cholangioscopic view of biliary adenoma after wire access obtained in the left intrahepatic system

elevated carcinoembryonic antigen (CEA)/CA 19–9 levels, suspicious imaging findings, and direct cholangiographic findings showing an irregular hilar stricture, up to 20% can have benign disease at the time of surgical resection [11]. Thus, adequate tissue acquisition for cytology and histology is essential to diagnostic management of the hilar stricture.

26.2.1 Classification of Malignant Hilar Stricture

Specific to malignant obstruction at the hilum, the Bismuth-Corlette system provides preoperative or preprocedural assessment of local tumor spread and can be used to determine extent or feasibility of surgical resection (Fig. 26.3) [12, 13]. In

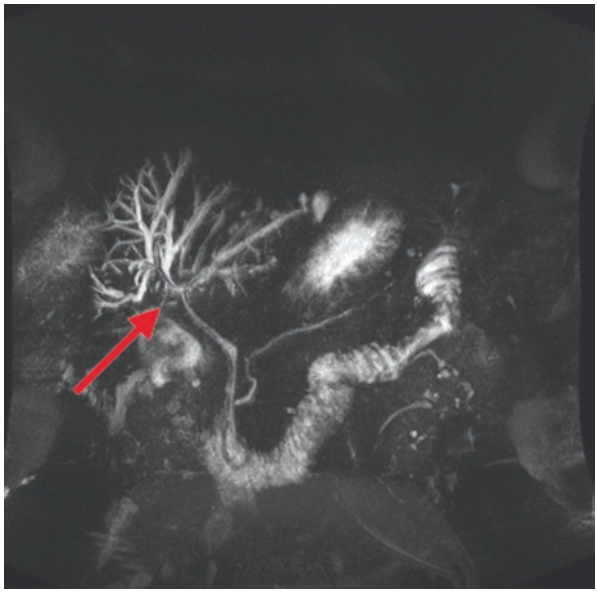

Fig. 26.2 MR cholangiography of a patient with malignant obstruction due to mass at the biliary hilum (arrow)

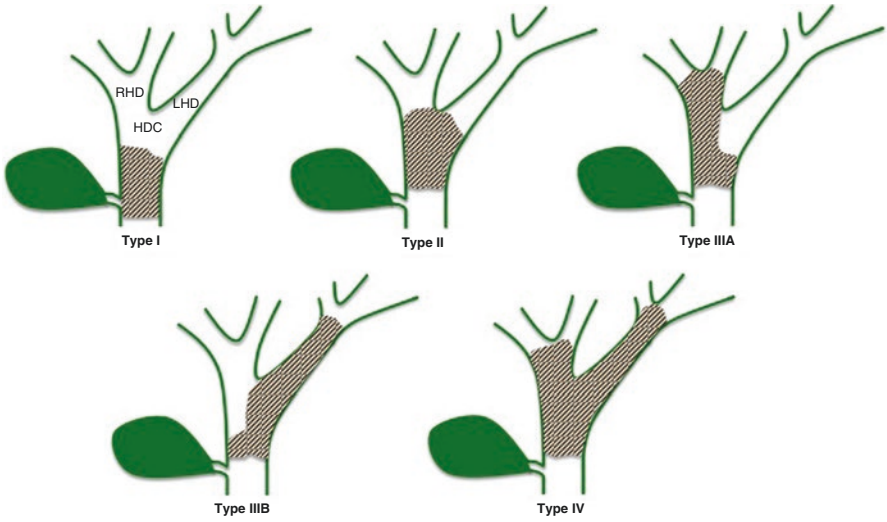

Fig. 26.3 The Bismuth-Corlette classification of hilar cholangiocarcinoma. Type I tumors are distal to the hepatic duct confluence (HDC), while type II tumors extend to and involve the HDC but do not extend into the left or right intrahepatic ducts. Type III tumors involve the HDC and either the right intrahepatic duct (type IIIA) or the left intrahepatic duct (type IIIB), while type IV tumors extend into both the left and right intrahepatic duct systems. Reused with permission from AME Publishing Company; Soares KC, Kamel I, Cosgrove DP, Herman JM, Pawlik TM (2014) Hilar cholangiocarcinoma: diagnosis, treatment options, and management. *Hepatobiliary Surg Nutr* 3:18–34

this classification, there are four types of malignant hilar strictures. Type I tumors are distal to the hepatic duct confluence, while type II neoplasms extend to and involve the confluence but do not extend into either the left or right intrahepatic duct system. Type III tumors involve either the proximal right hepatic duct (type IIIA) or the proximal left hepatic duct (type IIIB), while type IV tumors extend into both the proximal left and right intrahepatic system [14].

While this system can provide some knowledge regarding the overall anatomy of the malignant hilar stricture, it does not provide information regarding vascular encasement or metastatic disease, and, in addition, studies have shown that it may have little prognostic value [13, 15]. Understanding the extent of local tumor spread can, however, aid in determination of optimal endoscopic approach [16].

26.2.2 Endoscopic Tissue Acquisition

There are multiple endoscopic techniques for tissue acquisition in a suspected malignant hilar stricture, which are generally done at the time of endoscopic retrograde cholangiography (ERC) or sampling lymph nodes with endoscopic ultrasound (EUS). These include brush cytology, intraductal biopsies, endoluminal fine-needle aspiration (FNA), and targeted biopsies through direct cholangioscopy (Table 26.1). It should be noted, however, that studies specific to hilar strictures are very limited, and most of the studies examining tissue acquisition techniques include all types of biliary strictures.

Brush cytology at the time of ERC is easy to perform and routinely done when evaluating suspicious biliary strictures, but the diagnostic yield is limited by an overall low sensitivity. In this technique, the brush and catheter are inserted into the bile duct, the brush advanced through the stricture 5–10 times and then removed along with the catheter from the endoscope [17]. The sensitivity of brush cytology alone in diagnosing malignant biliary strictures ranges between 30% and 70% in various small studies [17–19]. Specific to hilar strictures, brush cytology alone has been shown to detect malignancy in only 24 of 58 patients (41%) [20]. In a recent systematic review and meta-analysis, the pooled sensitivity in 730 patients of brushings for the diagnosis of malignant biliary strictures was 45%, though with a high specificity of 99% [17, 21].

Intraductal biopsies with endobiliary forceps performed under fluoroscopy can be difficult in narrow bile ducts and would typically require a sphincterotomy. Usually, a minimum of three specimens is obtained from two passes (Fig. 26.4). The sensitivity of

Table 26.1 Endoscopic diagnostic modalities for malignant hilar strictures

Brush cytology
Intraductal biopsy
Endoluminal fine-needle aspiration
Endoscopic ultrasound with fine-needle aspiration
Peroral cholangioscopy
Probe-based confocal laser endomicroscopy

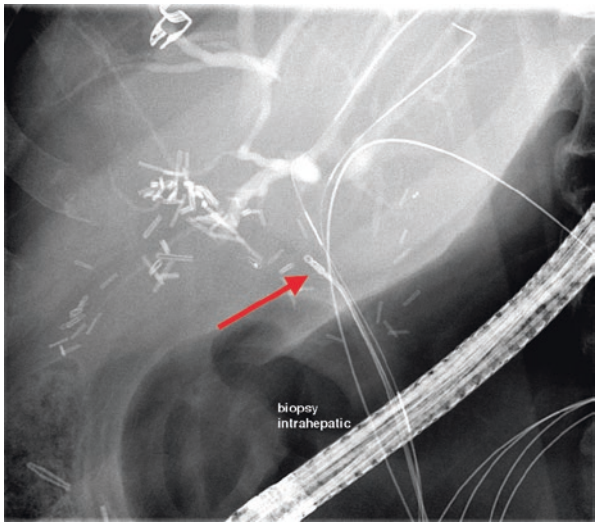

Fig. 26.4 Intraductal biopsy of a malignant biliary stricture using endobiliary forceps (arrow) in a patient who is status post prior cholecystectomy for gallbladder cancer

this technique ranges between 43% and 81%, with a very high specificity (97–100%) [17–19]. With regard to hilar strictures, intraductal forceps biopsy successfully detected malignancy in 31/58 patients (53%) [20]. In the most recent systematic review and meta-analysis, the pooled sensitivity and specificity for intraductal biopsies for the diagnosis of malignant biliary strictures were 48% and 99%, respectively [21].

With the overall low diagnostic yield of brush cytology and intraductal biopsies on an individual basis, a multimodal approach combining the two techniques could potentially be more effective. When specifically examining cholangiocarcinoma, Ponchon et al. found that the combination of brushings and intraductal biopsy increased the sensitivity to 86%, though the overall sensitivity for malignant biliary strictures was only 63%, which was still improved from either technique alone [19]. Specific to hilar cholangiocarcinoma, Weber et al. found that the multimodal approach of brushing and biopsy yielded a sensitivity of 60.3%, a minor increase from either technique individually [20]. In a meta-analysis of nine studies comparing the two techniques, the combination of both modalities modestly increased the sensitivity to 59%, again higher than either technique alone, consistent with prior pooled analyses [17, 21].

Endoluminal FNA is a difficult technique to perform, with insertion of the needle into the biliary system and aspirating several areas of stricture under fluoroscopic guidance. The overall sensitivity for this technique was approximately in 38% in 30 patients with cholangiocarcinoma; however, when three modalities were used (brushings, biopsy, FNA), sensitivity rose to 73% [18]. Endoscopic ultrasound (EUS) with FNA (EUS-FNA) is technically easier and has been shown to have a sensitivity of 77% in proximal biliary strictures, which had negative brush cytology results; however the negative predictive value is too low to allow exclusion of malignancy following a negative biopsy [22]. Moreover, EUS-FNA of a malignant hilar stricture can be associated with disease dissemination of cholangiocarcinoma and is

thus not routinely recommended if surgical resection or liver transplant is being considered [23]. With that in mind, the Asia-Pacific Working Group on hepatobiliary disorders recommends at least a combination of two techniques such as brushings and forceps biopsy for all suspicious strictures [24].

In patients with primary sclerosing cholangitis (PSC), the distinction between malignant and inflammatory strictures is especially difficult, as the bile ducts can be narrow, making tissue acquisition difficult, and the inflammation may complicate the cytology results [25]. Fluorescence in situ hybridization (FISH) and digital image analysis (DIA) are two techniques that may enhance cytological and tissue evaluation in patients with indeterminate biliary strictures. FISH utilizes fluorescently labeled DNA probes to examine cells for chromosomal abnormalities, while DIA uses DNA content of cells to assess for aneuploidy. In a study of 66 patients with confirmed malignancy, FISH was significantly more sensitive than cytology alone for the diagnosis of malignancy (34% vs 15%) [26]. In a larger study, FISH and DIA detected more patients with malignancy and had higher sensitivity than routine cytology alone [27]. In patients with PSC, FISH polysomy notably had a sensitivity of 46% with similar long-term outcomes as patients with cholangiocarcinoma [28]. In a pooled meta-analysis of 828 patients from eight studies, sensitivity and specificity of FISH for diagnosis of cholangiocarcinoma in patients with PSC were 68% and 70%, respectively [29]. Thus, while the role of FISH and DIA is currently limited, they may provide another data point in those patients with PSC.

As is now clear, there are significant limitations to endoscopy in diagnosis of malignant biliary strictures, and thus, imaging plays a very significant role in the workup of obstructive jaundice. Spiral computed tomography (CT) scan and magnetic resonance-magnetic resonance cholangiopancreatography (MR-MRCP) show high accuracy for assessment of biliary strictures when compared to direct cholangiography, with the added benefit of not having to inject contrast into an obstructed biliary system [30]. Cross-sectional imaging allows for accurate determination of the extent of ductal involvement and thus can guide endoscopic or surgical treatment [31]. Moreover, CT/MR-MRCP can further determine resectability by assessing vascular encasement, lymph node, and distant metastasis.

26.2.3 Peroral Cholangioscopy and Laser Endomicroscopy

The role of peroral cholangioscopy (POC) in the diagnosis of biliary strictures is evolving, especially with the new SpyGlass Direct Visualization System (Boston Scientific Corp., Natick, MA). POC allows for direct visualization of the biliary system as well as targeted biopsies with a mini-forceps through the cholangioscope (Fig. 26.5) [32]. Currently, the availability of this system is limited due to cost and maintenance to specialized, tertiary care centers. In evaluation of patients with indeterminate biliary lesions, visual interpretation alone was successful in differentiating malignant vs benign lesions in 89% of patients ($n = 36$), with biopsies successful in 82% of patients who had inconclusive ERC evaluations [33]. Visual

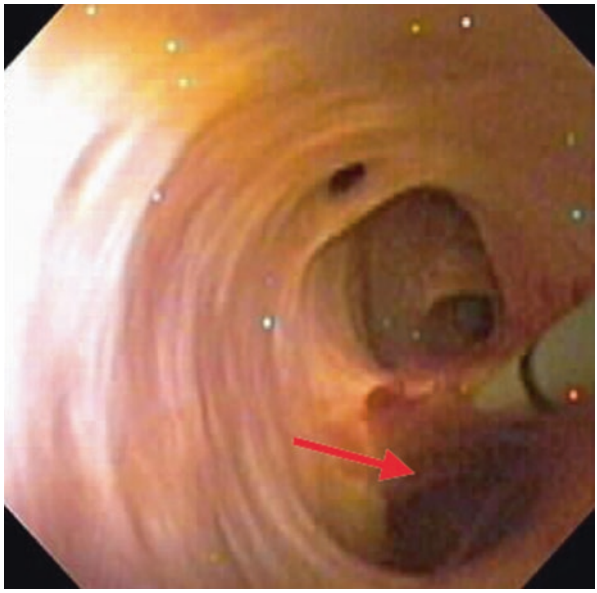

Fig. 26.5 Cholangioscopic view of malignancy, with guidewire in place. Note erythema, friability, and easy bleeding of the malignant area (arrow)

characteristics of malignancy included visible mass, dilated tortuous vessels, papillary or villous projections, and intraductal nodules. When compared to brushing and intraductal biopsy, mini-forceps biopsy provided significantly better sensitivity and overall accuracy (76.5%) [34]. In a recent meta-analysis of POC with biopsies of indeterminate biliary strictures, the pooled sensitivity and specificity to detect cholangiocarcinomas were 66% and 97%, respectively [32].

Probe-based confocal laser endomicroscopy (pCLE) using the CholangioFlex probe (Mauna Kea Tech) enables real-time microscopic visualization of biliary strictures during an ongoing ERCP or cholangioscopy. The Miami classification has been developed in a multicenter study of 89 patients, laying out specific findings with pCLE for predicting neoplasia. These include thick dark bands, thin white bands, dark clumps, fluorescein leakage, and a visualized epithelium (Fig. 26.6). Combining individual characteristics can improve sensitivity [35]. A proof of concept study in 14 patients showed that completely normal findings on pCLE could potentially rule out malignancy [36]. In a prospective study of 89 patients, 40 of whom were proven to have cancer, pCLE had a sensitivity of 98%, but specificity of only 67%, significantly higher than ERCP with tissue acquisition alone [37].

26.3 Treatment of Malignant Hilar Strictures

Given that 70–90% of patients presenting with malignant biliary obstruction have unresectable disease with poor overall prognosis, the ultimate goal of therapy is palliation with relief of biliary obstruction. Surgical biliary-enteric bypass was the

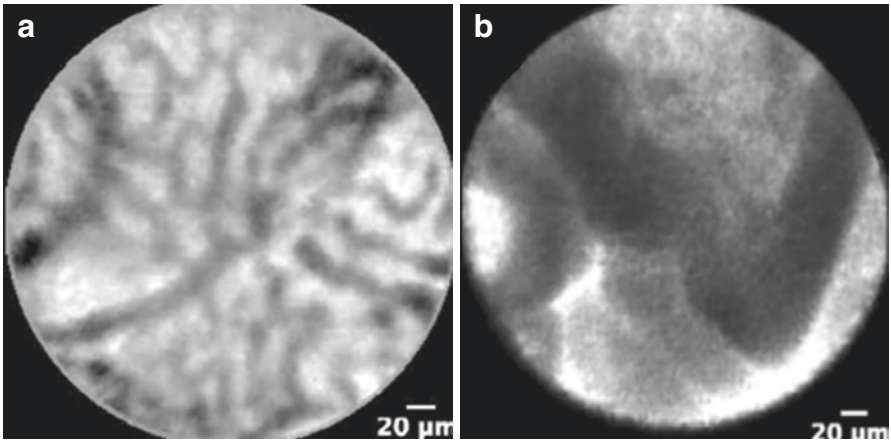

Fig. 26.6 Probe-based confocal laser endomicroscopy (pCLE) images of bile duct mucosa. (**a**) Reticular pattern with thin dark bands resembling benign mucosa. (**b**) Epithelial structures with thick dark bands consistent with malignancy. Reprinted from *Gastrointestinal Endoscopy*, 74(5), Meining A, Chen YK, Pleskow D, Stevens P, Shah RJ, Chuttani R, Michalek J, Slivka A, Direct visualization of indeterminate pancreaticobiliary strictures with probe-based confocal laser endomicroscopy: a multicenter experience, 961–968 (2011) with permission from Elsevier

treatment of choice in patients with malignant pancreaticobiliary disease up until the 1980s, with high morbidity and mortality [38, 39]. Over the last 20 years, endoscopic decompression has emerged as the preferred treatment option with lower complication rates, lower morbidity, lower overall cost, and shorter hospitalization [38]. Specifically, endoscopic stenting of hilar cholangiocarcinoma can offer relief of biliary obstruction and alleviate symptoms of pain, intractable pruritus, and cholangitis [40]. While biliary stenting does not improve overall mortality, photodynamic therapy (PDT) is an emerging endoscopic treatment modality that offers the possibility of remodeling the tumor mass and may actually improve survival in patients with non-resectable cholangiocarcinoma [41, 42]. Endoscopic modalities for therapeutic management of malignant hilar strictures are summarized in Table 26.2.

26.3.1 Endoscopic Stenting

With regard to endoscopic stenting, there are two main considerations: plastic vs metal stent and unilateral vs bilateral stenting of the hepatic ducts [39, 43]. Regardless of the type of stent used or the segments drained, drainage of adequate liver volume (>30%) is needed to relieve jaundice [44]. In fact, in a recent retrospective study of 107 patients, the main factor determining effective drainage (decrease in serum bilirubin by 50% at day 30) and longer survival was a decrease in liver volume by >50% following stenting of malignant hilar strictures [45]. Procedural complications for stenting in general can include occlusion (tissue overgrowth, ingrowth, debris), migration, and infection (cholangitis, cholecystitis) [39].

Table 26.2 Therapeutic modalities for malignant hilar strictures

Endoscopic retrograde cholangiopancreatography (ERCP) with stenting
Plastic stent
Self-expanding metal stent (straight, side-by-side, or Y-shaped)
Endoscopic ultrasound-guided biliary drainage
Hepaticogastrostomy
Photodynamic therapy
Radiofrequency ablation

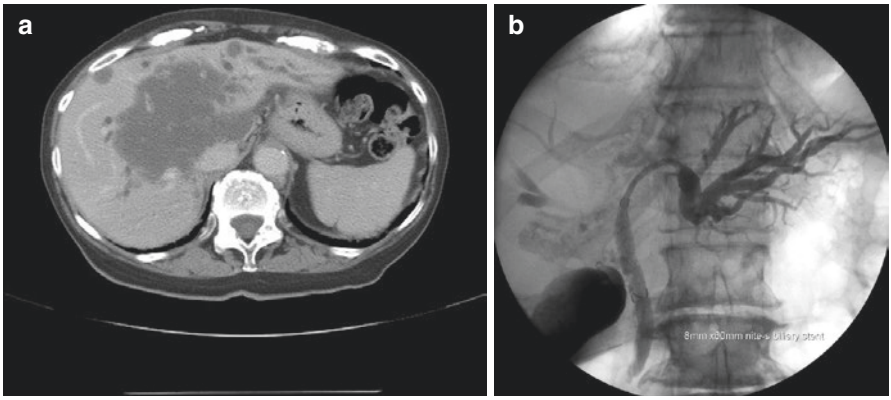

Fig. 26.7 (**a**) CT image of intrahepatic cholangiocarcinoma presenting as a major mass in a patient with weight loss and jaundice. (**b**) Palliation with placement of single self-expanding metal stent into the dominant left intrahepatic duct. NITI-S SEMS (TaeWoong Inc., Seoul, Korea). Reprinted from *Clinical Gastroenterology and Hepatology*, 7, Kozarek RA, Inflammation and Carcinogenesis of the Biliary Tract: Update On Endoscopic Treatment, s89–94 (2009), with permission from Elsevier

Plastic stents (PS) are made from materials including Teflon, polyurethane, or polyethylene that have various diameters and lengths, with options including straight stents with end flaps, single-pigtail stent, or double-pigtail stent for anchoring purposes [46]. Self-expandable metal stents (SEMS) are made of various metal alloys configured into a cylinder by interwoven wires and constructed to achieve adequate radial expandable force without sacrificing flexibility and conformability to the duct [47, 48]. SEMS can be either uncovered or covered with material to prevent tumor overgrowth, though uncovered are preferred in strictures at the hilum as to not occlude drainage from the contralateral biliary system or the cystic duct (Fig. 26.7) [39]. The details of plastic and metal stents and their placement are discussed in other chapters in this section.

Both PS and SEMS have been used for malignant hilar strictures, with recent prospective studies comparing the two methods ranging between 60 and 100 patients [49–51]. Although PS are less expensive than SEMS, the duration of their patency is low, typically about 3 months [52, 53]. In contrast, SEMS are patent for much longer, around 6–12 months [51, 53, 54]. Moreover, one study showed overall higher rates of

successful drainage and longer overall survival with SEMS when compared to PS [50]. Rates of late complications such as migration, stent failure, and cholangitis have also been shown to be lower with SEMS as opposed to PS in patients with malignant hilar stricture [55]. In a recent pooled meta-analysis comparing SEMS and PS for malignant hilar obstruction, SEMS had a lower 30-day occlusion rate, lower long-term occlusion rate, higher rate of successful stent insertion, lower rate of therapeutic failure, and lower rate of cholangitis [47]. Given this, SEMS are overall more cost-effective when compared to PS in malignant hilar obstruction [56]. Therefore, two consensus statements from separate groups in Asia prefer metallic stenting when palliating malignant hilar strictures, particularly in patients with a predicted survival of longer than 3 months and Bismuth II-IV HCCA lesions [24, 57].

There is still some debate as to whether unilateral stenting should be performed versus bilateral stenting in malignant hilar obstruction. In one randomized controlled trial of 157 patients in Italy, unilateral drainage had a higher rate of successful stent insertion, lower rate of complications, and lower rate of early cholangitis, with no difference in mortality, in an intention to treat analysis [58]. In a pooled meta-analysis of seven studies comprising a total of 574 patients, there was no statistically significant difference in occlusion rate, therapeutic failure, cholangitis, and mortality between unilateral and bilateral stenting [47]. Bilateral stenting may be needed if both ductular systems become contaminated with contrast injection, in which case parallel stents can be placed side-by-side or a newly available Y-shaped stent can be deployed with reasonable success (Fig. 26.8) [59].

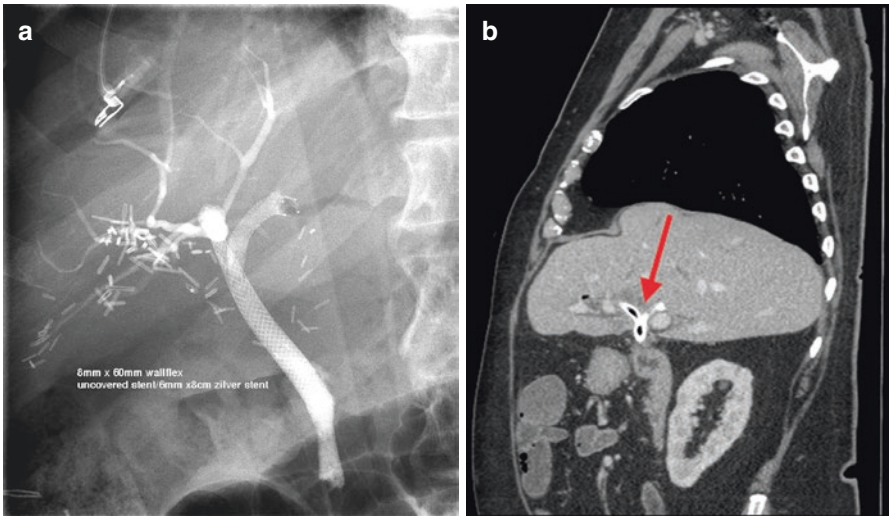

Fig. 26.8 (**a**) Patient with malignant biliary stricture who had inadequate drainage with prior percutaneous transhepatic biliary drain, contaminating the left intrahepatic ductular system, necessitating bilateral endoscopic drainage with two self-expanding metal stents (SEMS) in Y-configuration. (**b**) Sagittal view on cross-sectional imaging of two SEMS in Y-configuration (arrow)

It should be mentioned that percutaneous stenting of the biliary system by interventional radiology can also be performed and may even be beneficial in more complex hilar lesions (Bismuth III and IV). A retrospective study of 85 patients in Korea with advanced hilar cholangiocarcinoma noted that the percutaneous approach had a higher rate of initial procedural success and low level of procedure-related cholangitis, but once successful biliary decompression was achieved, there was no difference in median survival between endoscopic and percutaneous placement of stents [60].

Therefore, in patients with a lesion at the hilum, placement of a single SEMS potentially affords equal palliation and survival statistics compared with bilateral stenting, and endoscopists should plan their drainage strategy based on CT or magnetic resonance cholangiopancreatography findings, with selective wire-guided cannulation of the desired side and placement of a single SEMS to drain at least 30–50% of the total liver volume [31, 43, 45].

26.3.2 Endoscopic Ultrasound-Guided Biliary Drainage

There are times when both endoscopic and percutaneous access fail or when neither procedure is possible, making EUS-guided biliary drainage a potential alternative. This technique is very challenging from a technical standpoint and is fraught with complications, and thus the Asia-Pacific Working Group considers this an "experimental" approach for now [24]. EUS-guided biliary drainage stems from EUS-guided cholangiopancreatography and has evolved therapeutically [61].

The technique involves beginning with EUS-guided puncture of the left intrahepatic duct from the stomach, followed by guidewire insertion into the bile duct, advancing to the distal common bile duct and duodenum. If this is achieved, a rendezvous ERC can be attempted, with subsequent stenting as above [62]. If, however, there is a distal bile duct obstruction or the wire cannot pass into the duodenum, then EUS-guided stent placement can be attempted across the hilar stricture [63]. If the guidewire cannot pass across the hilar stricture, then EUS-guided hepaticogastrostomy is the option left [64].

There have been many different types of stents ranging from plastic stents to fully covered SEMS in prior reports of EUS-guided stent placement, but a new hybrid metal stent that is partially covered with distal anti-migrating flaps has recently been developed and has shown promising results for hepaticogastrostomy and choledochoduodenostomy [65]. While most studies demonstrate a high overall success rate, the overall complication rates can still approximate 20% and include bleeding, bile leakage, self-limited pneumoperitoneum, and peritonitis [64–68]. Therefore, this technique is still evolving with the development of new instruments, necessitating performance only at high volume, tertiary care centers.

26.3.3 Photodynamic Therapy (PDT)

PDT is an emerging and evolving technology in the management of unresectable cholangiocarcinoma. PDT uses a photosensitizing agent (such as a derivative of hematoporphyrin), which is administered intravenously and selectively accumulates within malignant cells. Subsequently, 2–4 days after administration of the agent, a transpapillary or percutaneous directed light at a specific wavelength activates the photosensitizing agent leading to local ablation of tumor tissue via the formation of free oxygen radicals [41, 69, 70]. This light activation is performed using a quartz fiber mounted with a cylindrical diffuser tip of 1–7 cm in length, coupled with diode laser emitting a wavelength of 630 nm [39, 71].

Since the first successful case report of PDT being used to treat a tumor of the extrahepatic biliary ducts in 1991 [72], there have been studies demonstrating the ability of PDT to locally control tumor, improve stent patency, improve quality of life, and even improve survival in patients with unresectable cholangiocarcinoma [9, 42, 73–77]. Ortner and colleagues performed the first randomized controlled trial in 2003 comparing PDT plus stenting with stenting alone in a total of 39 patients. PDT resulted in a median survival of 493 days compared to 98 days in patients who underwent stenting alone, a difference so significant that the study was terminated prematurely [42]. Kahaleh and colleagues treated 48 patients over 5 years with unresectable cholangiocarcinoma with either plastic biliary stents or PDT plus plastic stents, showing a statistically improved survival in the PDT group at 3 and 6 months, but not at 12 months [77]. Three meta-analyses confirmed that palliative treatment of cholangiocarcinoma with PDT is associated with improved biliary drainage, better quality of life, and increased survival, though all noted that the overall quality of evidence is low with few randomized trials and low number of patients [78–80].

Chemotherapy for hilar cholangiocarcinoma typically involves the combination of platinum and gemcitabine [12]. Trials and reviews have shown only a small improvement in survival with varying combinations of these regimens, with median survival approximating 8 months to 11 months [81–83]. In a prospective trial of 74 patients, 16 patients were treated with PDT and gemcitabine, while 58 were treated with PDT alone. Median survival in the combination group was 538 days compared to 335 days in the chemotherapy alone group [74]. Other chemotherapy agents have been investigated as well in combination with PDT. In a randomized trial of 43 patients with advanced hilar cholangiocarcinoma, 21 patients received PDT plus an oral fluoropyrimidine and 22 patients received PDT alone. The combination group showed a higher 1-year survival rate, with a median of 17 months vs 8 months, and longer progression-free survival [84].

The main complications of PDT noted in all studies were cholangitis (almost 30%) and phototoxicity, which can occur in 10–15% of patients [43, 78, 80]. This suggests that PDT still needs to be further studied and developed in larger, better quality studies, as it is only currently available in highly specialized centers.

26.3.4 Radiofrequency Ablation (RFA)

A new technology emerging just this decade is endoscopic RFA, which also allows for localized, targeted destruction of tumor cells. This technique involves the introduction of a catheter with a bipolar probe into the biliary system which is then activated at 10 W of energy for 60–90 s at a time, producing localized coagulation necrosis of the tumor [39, 85, 86]. The catheter is then removed with subsequent stent insertion.

One open-label prospective pilot study demonstrated successful RFA of the biliary system in 21 of 22 patients, but only six had cholangiocarcinoma. By day 90, one patient had died and only three had stent occlusions. Complications included pancreatitis, need for percutaneous cholecystostomy, and rigors, but neither hemorrhage nor abscess formation was seen in this study [86]. This is a technology still in its infancy, and further studies will be needed to evaluate the efficacy, durability, and safety of this technique, particularly with regard to the malignant hilar stricture.

26.4 Conclusion

Endoscopic management of the malignant hilar stricture remains a diagnostic and therapeutic challenge for the therapeutic endoscopist, but there are a growing number of tools and techniques available and many opportunities for comparative effectiveness studies. Cross- sectional imaging can guide endoscopic evaluation and treatment and should always be performed as part of the workup of malignant biliary obstruction. At least two modes of tissue acquisition should be performed endoscopically for cytological and histological analysis in order to increase the diagnostic yield for malignancy. The goal for endoscopic treatment remains adequate biliary drainage and can be performed with the placement of a single, unilateral self-expanding metal stent, draining the dominant, obstructed lobe. In most patients, endoscopic ablation of malignant hilar tumor is emerging with photodynamic therapy and radiofrequency ablation and holds promise to improve stent function, quality of life, and overall survival in patients with advanced, unresectable disease.

Reference

1. Larghi A, Tringali A, Lecca PG, et al. Management of hilar biliary strictures. Am J Gastroenterol. 2008;103:458–73.
2. Aljiffry M, Abdulelah A, Walsh M, et al. Evidence-based approach to cholangiocarcinoma: a systematic review of the current literature. J Am Coll Surg. 2009;208:134–47.
3. Lee SS, Kim MH, Lee SK, et al. Clinicopathologic review of 58 patients with biliary papillomatosis. Cancer. 2004;100:783–93.
4. Broomé U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut. 1996;38:610–5.

5. Shin HR, JK O, Masuyer E, et al. Epidemiology of cholangiocarcinoma: an update focusing on risk factors. Cancer Sci. 2010;101:579–85.
6. Bouvard V, Baan R, Straif K, et al. A review of human carcinogens—part B: biological agents. Lancet Oncol. 2009;10:321–2.
7. Nakeeb A, Pitt HA, Sohn TA, et al. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg. 1996;224:463–73. discussion 473–475
8. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg. 2001;234:507–17. discussion 517–519
9. Witzigmann H, Berr F, Ringel U, et al. Surgical and palliative management and outcome in 184 patients with hilar cholangiocarcinoma: palliative photodynamic therapy plus stenting is comparable to r1/r2 resection. Ann Surg. 2006;244:230–9.
10. Kim HJ, Lee KT, Kim SH, et al. Differential diagnosis of intrahepatic bile duct dilatation without demonstrable mass on ultrasonography or CT: benign versus malignancy. J Gastroenterol Hepatol. 2003;18:1287–92.
11. Koea J, Holden A, Chau K, McCall J. Differential diagnosis of stenosing lesions at the hepatic hilus. World J Surg. 2004;28:466–70.
12. Soares KC, Kamel I, Cosgrove DP, et al. Hilar cholangiocarcinoma: diagnosis, treatment options, and management. Hepatobiliary Surg Nutr. 2014;3:18–34.
13. Bismuth H, Majno PE. Biliary strictures: classification based on the principles of surgical treatment. World J Surg. 2001;25:1241–4.
14. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilus of the liver. Surg Gynecol Obstet. 1975;140:170–8.
15. Paul A, Kaiser GM, Molmenti EP, et al. Klatskin tumors and the accuracy of the Bismuth-Corlette classification. Am Surg. 2011;77:1695–9.
16. Bulajic M, Panic N, Radunovic M, et al. Clinical outcome in patients with hilar malignant strictures type II Bismuth-Corlette treated by minimally invasive unilateral versus bilateral endoscopic biliary drainage. Hepatobiliary Pancreat Dis Int HBPD Int. 2012;11:209–14.
17. de Bellis M, Sherman S, Fogel EL, et al. Tissue sampling at ERCP in suspected malignant biliary strictures (Part 2). Gastrointest Endosc. 2002;56:720–30.
18. Jailwala J, Fogel EL, Sherman S, et al. Triple-tissue sampling at ERCP in malignant biliary obstruction. Gastrointest Endosc. 2000;51:383–90.
19. Ponchon T, Gagnon P, Berger F, et al. Value of endobiliary brush cytology and biopsies for the diagnosis of malignant bile duct stenosis: results of a prospective study. Gastrointest Endosc. 1995;42:565–72.
20. Weber A, von Weyhem C, Fend F, et al. Endoscopic transpapillary brush cytology and forceps biopsy in patients with hilar cholangiocarcinoma. World J Gastroenterol. 2008;14:1097–101.
21. Navaneethan U, Njei B, Lourdusamy V, et al. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis. Gastrointest Endosc. 2015;81:168–76.
22. DeWitt J, Misra VL, Leblanc JK, et al. EUS-guided FNA of proximal biliary strictures after negative ERCP brush cytology results. Gastrointest Endosc. 2006;64:325–33.
23. Heimbach JK, Sanchez W, Rosen CB, et al. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. HPB. 2011;13:356–60.
24. Rerknimitr R, Angsuwatcharakon P, Ratanachu-ek T, et al. Asia-Pacific consensus recommendations for endoscopic and interventional management of hilar cholangiocarcinoma: consensus for hilar cholangiocarcinoma. J Gastroenterol Hepatol. 2013;28:593–607.
25. Charatcharoenwitthaya P, Enders FB, Halling KC, Lindor KD. Utility of serum tumor markers, imaging, and biliary cytology for detecting cholangiocarcinoma in primary sclerosing cholangitis. Hepatology. 2008;48:1106–17.
26. Kipp BR, Stadheim LM, Halling SA, et al. A comparison of routine cytology and fluorescence in situ hybridization for the detection of malignant bile duct strictures. Am J Gastroenterol. 2004;99:1675–81.
27. Fritcher EG, Kipp BR, Halling KC, et al. A multivariable model using advanced cytologic methods for the evaluation of indeterminate pancreatobiliary strictures. Gastroenterology. 2009;136:2180–6.

28. Bangarulingam SY, Bjornsson E, Enders F, et al. Long-term outcomes of positive fluorescence in situ hybridization tests in primary sclerosing cholangitis. Hepatology. 2010;51:174–80.
29. Navaneethan U, Njei B, Venkatesh PG, et al. Fluorescence in situ hybridization for diagnosis of cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. Gastrointest Endosc. 2014;79:943–950.e3.
30. Park HS, Lee JM, Choi JY, et al. Preoperative evaluation of bile duct cancer: MRI combined with MR cholangiopancreatography versus MDCT with direct cholangiography. AJR Am J Roentgenol. 2008;190:396–405.
31. Freeman ML, Overby C. Selective MRCP and CT-targeted drainage of malignant hilar biliary obstruction with self-expanding metallic stents. Gastrointest Endosc. 2003;58:41–9.
32. Navaneethan U, Hasan MK, Lourdusamy V, et al. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review. Gastrointest Endosc. 2015. https://doi.org/10.1016/j.gie.2015.04.030.
33. Ramchandani M, Reddy DN, Gupta R, et al. Role of single-operator peroral cholangioscopy in the diagnosis of indeterminate biliary lesions: a single-center, prospective study. Gastrointest Endosc. 2011;74:511–9.
34. Draganov PV, Chauhan S, Wagh MS, et al. Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study. Gastrointest Endosc. 2012;75:347–53.
35. Meining A, Shah RJ, Slivka A, et al. Classification of probe-based confocal laser endomicroscopy findings in pancreaticobiliary strictures. Endoscopy. 2012;44:251–7.
36. Loeser CS, Robert ME, Mennone A, et al. Confocal endomicroscopic examination of malignant biliary strictures and histologic correlation with lymphatics. J Clin Gastroenterol. 2011;45:246–52.
37. Meining A, Chen YK, Pleskow D, et al. Direct visualization of indeterminate pancreaticobiliary strictures with probe-based confocal laser endomicroscopy: a multicenter experience. Gastrointest Endosc. 2011;74:961–8.
38. Moss AC, Morris E, Leyden J, MacMathuna P. Malignant distal biliary obstruction: a systematic review and meta-analysis of endoscopic and surgical bypass results. Cancer Treat Rev. 2007;33:213–21.
39. Webb K, Saunders M. Endoscopic management of malignant bile duct strictures. Gastrointest Endosc Clin N Am. 2013;23:313–31.
40. Goenka MK, Goenka U. Palliation: Hilar cholangiocarcinoma. World J Hepatol. 2014;6:559–69.
41. Berr F, Tannapfel A, Lamesch P, et al. Neoadjuvant photodynamic therapy before curative resection of proximal bile duct carcinoma. J Hepatol. 2000;32:352–7.
42. Ortner ME, Caca K, Berr F, et al. Successful photodynamic therapy for nonresectable cholangiocarcinoma: a randomized prospective study. Gastroenterology. 2003;125:1355–63.
43. Kozarek RA. Inflammation and carcinogenesis of the biliary tract: update on endoscopic treatment. Clin Gastroenterol Hepatol. 2009;7:S89–94.
44. Dowsett JF, Vaira D, Hatfield AR, et al. Endoscopic biliary therapy using the combined percutaneous and endoscopic technique. Gastroenterology. 1989;96:1180–6.
45. Vienne A, Hobeika E, Gouya H, et al. Prediction of drainage effectiveness during endoscopic stenting of malignant hilar strictures: the role of liver volume assessment. Gastrointest Endosc. 2010;72:728–35.
46. Ferreira LE, Baron TH. Endoscopic stenting for palliation of malignant biliary obstruction. Expert Rev Med Devices. 2010;7:681–91.
47. Sawas T, Al Halabi S, Parsi MA, Vargo JJ. Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis. Gastrointest Endosc. 2015;82:256–267.e7.
48. ASGE Technology Assessment Committee, Pfau PR, Pleskow DK, et al. Pancreatic and biliary stents. Gastrointest Endosc. 2013;77:319–27.
49. Perdue DG, Freeman ML, DiSario JA, et al. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. J Clin Gastroenterol. 2008;42:1040–6.

50. Sangchan A, Kongkasame W, Pugkhem A, et al. Efficacy of metal and plastic stents in unresectable complex hilar cholangiocarcinoma: a randomized controlled trial. Gastrointest Endosc. 2012;76:93–9.
51. Mukai T, Yasuda I, Nakashima M, et al. Metallic stents are more efficacious than plastic stents in unresectable malignant hilar biliary strictures: a randomized controlled trial. J Hepatobiliary Pancreat Sci. 2013;20:214–22.
52. Donelli G, Guaglianone E, Di Rosa R, et al. Plastic biliary stent occlusion: factors involved and possible preventive approaches. Clin Med Res. 2007;5:53–60.
53. Raju RP, Jaganmohan SR, Ross WA, et al. Optimum palliation of inoperable hilar cholangiocarcinoma: comparative assessment of the efficacy of plastic and self-expanding metal stents. Dig Dis Sci. 2011;56:1557–64.
54. Cheng JL, Bruno MJ, Bergman JJ, et al. Endoscopic palliation of patients with biliary obstruction caused by nonresectable hilar cholangiocarcinoma: efficacy of self-expandable metallic Wallstents. Gastrointest Endosc. 2002;56:33–9.
55. Liberato MJ, Canena JM. Endoscopic stenting for hilar cholangiocarcinoma: efficacy of unilateral and bilateral placement of plastic and metal stents in a retrospective review of 480 patients. BMC Gastroenterol. 2012;12:103.
56. Sangchan A, Chaiyakunapruk N, Supakankunti S, et al. Cost utility analysis of endoscopic biliary stent in unresectable hilar cholangiocarcinoma: decision analytic modeling approach. Hepato-Gastroenterology. 2014;61:1175–81.
57. Katanuma A, Irisawa A, Itoi T. Otaru consensus on biliary stenting for unresectable malignant hilar biliary obstruction. Dig Endosc. 2013;25(Suppl 2):58–62.
58. De Palma GD, Galloro G, Siciliano S, et al. Unilateral versus bilateral endoscopic hepatic duct drainage in patients with malignant hilar biliary obstruction: results of a prospective, randomized, and controlled study. Gastrointest Endosc. 2001;53:547–53.
59. Lee JH, Kang DH, Kim JY, et al. Endoscopic bilateral metal stent placement for advanced hilar cholangiocarcinoma: a pilot study of a newly designed Y stent. Gastrointest Endosc. 2007;66:364–9.
60. Paik WH, Park YS, Hwang JH, et al. Palliative treatment with self-expandable metallic stents in patients with advanced type III or IV hilar cholangiocarcinoma: a percutaneous versus endoscopic approach. Gastrointest Endosc. 2009;69:55–62.
61. Binmoeller KF, Nguyen-Tang T. Endoscopic ultrasound-guided anterograde cholangiopancreatography. J Hepatobiliary Pancreat Sci. 2011;18:319–31.
62. Shami VM, Kahaleh M. Endoscopic ultrasound-guided cholangiopancreatography and rendezvous techniques. Dig Liver Dis. 2010;42:419–24.
63. Nguyen-Tang T, Binmoeller KF, Sanchez-Yague A, Shah JN. Endoscopic ultrasound (EUS)-guided transhepatic anterograde self-expandable metal stent (SEMS) placement across malignant biliary obstruction. Endoscopy. 2010;42:232–6.
64. Park DH, Song TJ, Eum J, 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). Gastrointest Endosc. 2010;71:413–9.
65. Song TJ, Lee SS, Park do H, et al. Preliminary report on a new hybrid metal stent for EUS-guided biliary drainage (with videos). Gastrointest Endosc. 2014;80:707–11.
66. Kahaleh M, Hernandez AJ, Tokar J, et al. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. Gastrointest Endosc. 2006;64:52–9.
67. Hara K, Yamao K. Is endoscopic ultrasonography-guided biliary drainage really that wonderful? Dig Endosc. 2014;26:333–4.
68. Yamao K, Hara K, Mizuno N, et al. EUS-guided biliary drainage. Gut Liver. 2010;4(Suppl 1):S67–75.
69. Abels C. Targeting of the vascular system of solid tumours by photodynamic therapy (PDT). Photochem Photobiol Sci. 2004;3:765–71.
70. Dougherty TJ, Gomer CJ, Henderson BW, et al. Photodynamic therapy. J Natl Cancer Inst. 1998;90:889–905.

71. Zoepf T. Photodynamic therapy of cholangiocarcinoma. HPB (Oxford). 2008;10:161–3.
72. McCaughan JS, Mertens BF, Cho C, et al. Photodynamic therapy to treat tumors of the extrahepatic biliary ducts. A case report. Arch Surg. 1991;126:111–3.
73. Cheon YK, Lee TY, Lee SM, et al. Long term outcome of photodynamic therapy compared with biliary stenting alone in patients with advanced hilar cholangiocarcinoma. HPB (Oxford). 2012;14:185–93.
74. Hong MJ, Cheon YK, Lee EJ, et al. Long-term outcome of photodynamic therapy with systemic chemotherapy compared to photodynamic therapy alone in patients with advanced hilar cholangiocarcinoma. Gut Liver. 2014;8:318–23.
75. Lee TY, Cheon YK, Shim CS, Cho YD. Photodynamic therapy prolongs metal stent patency in patients with unresectable hilar cholangiocarcinoma. World J Gastroenterol. 2012;18:5589–94.
76. Zoepf T, Jakobs R, Arnold JC, et al. Palliation of nonresectable bile duct cancer: improved survival after photodynamic therapy. Am J Gastroenterol. 2005;100:2426–30.
77. Kahaleh M, Mishra R, Shami VM, et al. Unresectable cholangiocarcinoma: comparison of survival in biliary stenting alone versus stenting with photodynamic therapy. Clin Gastroenterol Hepatol. 2008;6:290–7.
78. Lu Y, Liu L, Wu JC, et al. Efficacy and safety of photodynamic therapy for unresectable cholangiocarcinoma: a meta-analysis. Clin Res Hepatol Gastroenterol. 2015. https://doi.org/10.1016/j.clinre.2014.10.015.
79. Leggett CL, Gorospe EC, Murad MH, et al. Photodynamic therapy for unresectable cholangiocarcinoma: a comparative effectiveness systematic review and meta-analyses. Photodiagn Photodyn Ther. 2012;9:189–95.
80. Gao F, Bai Y, Ma SR, et al. Systematic review: photodynamic therapy for unresectable cholangiocarcinoma. J Hepatobliary Pancreat Sci. 2010;17:125–31.
81. Fiteni F, Nguyen T, Vernerey D, et al. Cisplatin/gemcitabine or oxaliplatin/gemcitabine in the treatment of advanced biliary tract cancer: a systematic review. Cancer Med. 2014;3:1502–11.
82. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362:1273–81.
83. Liu H, Zhang QD, Li ZH, et al. Efficacy and safety of gemcitabine-based chemotherapies in biliary tract cancer: a meta-analysis. World J Gastroenterol. 2014;20:18001–12.
84. Park DH, Lee SS, Park SE, et al. Randomised phase II trial of photodynamic therapy plus oral fluoropyrimidine, S-1, versus photodynamic therapy alone for unresectable hilar cholangiocarcinoma. Eur J Cancer. 2014;50:1259–68.
85. Monga A, Gupta R, Ramchandani M, et al. Endoscopic radiofrequency ablation of cholangiocarcinoma: new palliative treatment modality (with videos). Gastrointest Endosc. 2011;74:935–7.
86. Steel AW, Postgate AJ, Khorsandi S, et al. Endoscopically applied radiofrequency ablation appears to be safe in the treatment of malignant biliary obstruction. Gastrointest Endosc. 2011;73:149–53.

Chapter 27
Uncovered Metallic Stenting

Sung-Hoon Moon

Abstract Uncovered metallic stenting is typically used for unresectable distal or hilar malignant biliary obstruction. This chapter describes the approach, mechanical properties, and stenting techniques, as well as the outcome of uncovered metallic stenting in "distal" malignant biliary obstruction. Endoscopic biliary metal stenting is recommended for unresectable distal malignant biliary obstruction when patient life expectancy is longer than 4 months because the outcomes with metal stenting are superior to both surgical drainage and plastic stenting. The self-expandable metal stent is a metallic stent with a small predeployment diameter constrained by a sheath and a large post-deployment diameter when expanded. The mechanical properties of the metal stent are imparted by the stent material, stent mesh design, radial force, axial flexibility, foreshortening, radiopacity, covering membrane, and the anchoring mechanism. The adequate stent length can be measured using a graduated guidewire or the catheter distance measured outside the endoscope. During metal stent deployment, the position of the stent can be adjusted by applying additional traction or recapturing the metal stent. Reintervention for an occluded or migrated stent is also discussed at the end of this chapter.

Keywords Endoscopic stenting • Biliary stent • Metal stent • Self-expandable metal stent

27.1 Introduction

Endoscopic biliary stent placement is commonly used for relief of unresectable malignant biliary obstruction (distal or hilar), benign biliary stricture, bile leakage (e.g., postoperative), temporary stenting for biliary stones, and preoperative biliary drainage. The biliary stents used for endoscopic procedures include plastic stents and self-expandable metal stents (SEMSs). The SEMSs are classified into

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uncovered SEMSs (USEMSs) and covered SEMSs (CSEMSs); the latter are further subclassified into partially covered SEMSs (PCSEMSs) and fully covered SEMSs (FCSEMSs). Due to the extreme difficulty in removal of USEMSs, they are presently used exclusively for unresectable malignant biliary obstruction. This chapter describes the approach, mechanical properties, and stenting techniques, as well as the outcomes of USEMS use in distal malignant biliary obstruction.

27.2 Approach of Biliary Drainage in Distal Malignant Biliary Obstruction

Common causes of distal malignant biliary obstruction include pancreatic carcinoma, cholangiocarcinoma, ampullary cancer, and metastatic lymphadenopathy of metastatic lesions [1, 2]. The mechanisms of malignant biliary obstruction by these tumors are direct tumor infiltration, extrinsic compression, adjacent inflammation, desmoplastic reaction, or a combination of these factors [3]. Malignant biliary obstruction can present with jaundice and requires palliative drainages if it is unresectable. Restoration of biliary flow, together with relief of jaundice and pruritus, is the primary goal in the palliation of malignant biliary obstruction, and it also prevents biliary obstruction-related complications such as cholangitis, coagulopathy, malabsorption, and hepatocellular dysfunction [2, 4]. Drainage can be approached in three ways, including surgical bypass (e.g., hepaticojejunostomy or choledochojejunostomy), percutaneous transhepatic biliary drainage, and endoscopic stenting [1, 4].

Cipolletta et al. [1], in a systematic review, reported no significant difference between endoscopic stenting and surgery groups in terms of overall patient survival, relief of jaundice, and improvement in quality of life. However, morbidity, mortality, and hospital stay were significantly greater in the surgery group than in the endoscopic group [1, 5, 6]. A meta-analysis of endoscopic and surgical bypass outcomes in malignant distal biliary obstruction demonstrated the same technical and therapeutic success for endoscopic stenting as for surgical drainage procedures, with similar quality of life and overall survival but with a reduced risk of complications, albeit with an increased risk of recurrent biliary obstruction for endoscopic stenting [7–9]. More treatment sessions are needed after endoscopic stenting than after surgical bypass, but endoscopic stenting still continues to be the most cost-effective approach [10]. Percutaneous transhepatic biliary drainage is associated with considerable morbidity, patient discomfort, and the need for repeated intervention [9].

Endoscopic biliary stenting is presently the standard of care for the palliation of distal malignant biliary obstruction [1, 8, 9]. It provides effective palliation and may offer lower morbidity and mortality, shorter hospital stay, and diminished overall cost when compared with surgical or radiological approaches [1]. Percutaneous transhepatic biliary drainage is most often used when endoscopic biliary stenting has failed [9]. Endoscopic ultrasound-guided biliary drainage can be an effective

alternative for percutaneous transhepatic biliary drainage after failed endoscopic retrograde cholangiopancreatography (ERCP) [11]. Surgical bypass is usually reserved for unsuccessful or unfeasible endoscopic/percutaneous drainage [8].

27.3 Mechanical Properties of Biliary SEMS

An ideal stent is inexpensive, is easy to insert, does not occlude or create significant tissue irrigation, and is potentially removable [12]. Plastic stents are the initial biliary endoprosthesis choice and are available in a variety of materials (polyethylene or Teflon), sizes, shapes, and designs. The mechanisms of occlusion for plastic stents are bacterial biofilm, plant materials, and sludge [1, 13]. The patency of the plastic stents differs mainly according to diameter but is limited by the accessory channel of the endoscope to 12 F [14].

The USEMSs were developed to expand the stent diameter. This metal stent has a small diameter constrained by a sheath. Upon delivery into the bile duct, it expands, with a large post-deployment diameter of up to 10 mm [1, 14]. The expanded metal stent then becomes embedded into the bile duct wall. This embedding by expansion may prevent stent migration and reduce sludge accumulation because little of the metal wire is exposed in the bile duct [14].

Most biliary SEMS models are available in several nominal lengths, ranging from 4 to 12 cm, with several nominal diameters, ranging from 6 to 10 mm when expanded [15, 16]. The main features that differentiate the different types of SEMSs are the stent material, stent mesh design, size of the open cells of the mesh, radial force, axial flexibility, shortening ratio, radiopacity, covering membrane, and anchoring mechanism [15].

27.3.1 Stent Material and Geometry

Biliary SEMSs are constructed of a variety of metal alloys such as stainless steel or nitinol; either a mesh is cut from a metal cylinder or metal wires are braided (hooking, crossing, or both) [15]. Nitinol, a metal alloy of nickel and titanium, is a type of "memory metal" that can be constrained within a narrow delivery device and can resume its original conformation or predetermined shape after release [17]. During self-expansion, SEMSs shorten by 0–50%. This shortening ratio is an important characteristic that must be considered when positioning SEMS during deployment [17]. SEMS with a low shortening ratio is preferable in some circumstances (e.g., long SEMS in the long tight strictures) [15]. When a SEMS with a high shortening ratio is deployed in a long tight stricture, its actual length may be significantly longer than its nominal length [15]. The biliary SEMSs have a small mesh size because large open cells in the mesh could allow tissue to protrude into the SEMS lumen, making it ineffective for biliary drainage either immediately after insertion or during follow-up (due to tumor ingrowth) [15].

27.3.2 Radial Force and Axial flexibility

The radial force is an expansion force that overcomes the compression forces exerted by the stenosis and those related to dilation of the stricture and maintaining luminal patency [14]. A high radial force may be preferable for biliary SEMS, as long-term patency is higher if expansion of the SEMS reaches 70% at 24 h [15].

Axial force (returning force) is the recovery or straightening force when the expanded SEMS is bent and related to its flexibility and conformability in the bile duct [14]. When a SEMS is fixed in the bile duct, both sides of SEMS compress the biliary wall, cystic duct, and pancreatitis [14]. A low axial force might be preferable for biliary SEMS, as compression along the longitudinal axis of the stent by an axial force may cause inflammation of the bile duct epithelium, cholecystitis, and pancreatitis [14]. A SEMS should achieve adequate radial expansile force without sacrificing flexibility and conformability in the ducts [16].

27.3.3 Radiopacity and Design of the Ends

Deployment of a biliary SEMS is performed under fluoroscopic guidance. The radiopacity (clear fluoroscopic traceability) of the SEMS is essential for its accurate delivery to its intended location [17]. The radiopacity of the different stent designs is a function of the inherent radiopacity of the alloys used in their construction and the filament size [17]. The metal alloy used for SEMS construction is radiopaque, but most models have additional proximal and distal markers made of a different metal, such as a gold- or platinum-based alloy [15–17].

The distal end of the SEMS may cause bleeding or perforation if the wires are sharp and not fused, as in the previous Wallstent model. Recent models of the SEMS have looped soft ends that reduce the risk of tissue trauma and flared ends to prevent migration (Fig. 27.1).

27.3.4 Delivery System

SEMS delivery systems incorporate some mechanism to constrain the stent until it is positioned, at which point the constraining force is removed and the stent is deployed, expanding in a distal to proximal direction of the catheter (toward the distal bile duct) [17]. The diameter of a SEMS delivery system ranges between 5.0 and 10.5 F [15]. A thin delivery catheter may be advantageous to facilitate the passage through strictures without prior dilation or for specific purposes, such as the simultaneous deployment of two SEMSs in the hilum (stent by stent) [15]. Most current delivery catheters are adequately kink-resistant and some are transparent to allow endoscopic visualization of the distal SEMS extremity during deployment

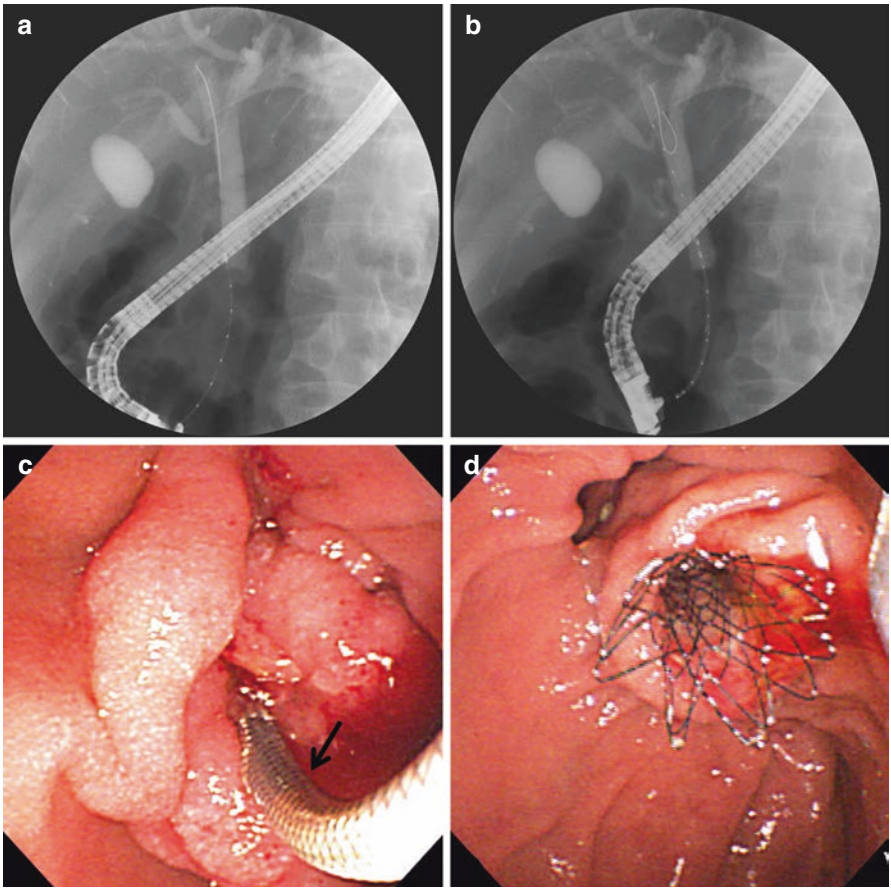

Fig. 27.1 A patient with distal malignant biliary obstruction. (**a**) An adequate stent length was measured using a dedicated guidewire that has radiopaque graduations at 1-cm intervals. (**b**) When the delivery catheter had been advanced into the desired location, the SEMS was deployed under fluoroscopic guidance. (**c**) An endoscopic view of the distal end of the SEMS through a transparent delivery system is also important during deployment. (**d**) The SEMS has looped soft ends that reduce the risk of tissue trauma and flared ends to prevent migration

[15]. Recapturing of the stent is possible in some SEMS delivery systems but only when partially deployed up to a certain point [9].

27.4 Stenting Techniques for USEMS

Before endoscopic stenting, endoscopists should meticulously review the available imaging studies such as computed tomography or magnetic resonance cholangiopancreatography (MRCP), focusing on identifying foci of biliary strictures, ductal

dilatation proximal to the stricture, intrahepatic ductal involvement, the nature of the biliary obstruction, and duodenal stricture [9]. The length of the stent is roughly estimated based on imaging studies before ERCP.

During ERCP, an adequate stent length may be measured using dedicated instruments, such as a graduated guidewire or a guiding catheter that has radiopaque graduations at 1-cm intervals (Fig. 27.1) [15]. A different way is to define the adequate stent length using the catheter (or sphincterotome) under fluoroscopy [9]. The proximal tip of the catheter is placed at the desired location for the proximal end of the stent (usually 1–2 cm above the proximal end of the stricture), and the catheter is grasped at the biopsy port [9, 15]. The catheter is then pulled back down to the desired location of the distal end of the stent (usually 1 cm below the papilla in trans-papillary stent placement or 1–2 cm below the stricture in supra-papillary stent placement) under fluoroscopic visualization. The distance of the catheter that was pulled back from the biopsy port is then measured using a ruler; this distance corresponds to the length of the stent [9]. The stated nominal length should be regarded with caution for SEMSs that have a high shortening ratio because if this type of SEMS is deployed in a tight stenosis, its actual length will be significantly longer than expected [15]. With regard to the issue of supra-papillary SEMS placement, one retrospective study suggested that disruption of the sphincter mechanism by trans-papillary stent placement may be the most important etiologic factor for cholangitis after SEMS placement for malignant biliary obstruction [18].

The required diameter of a SEMS is essentially tailored to the diameter of the nonstrictured portion of the bile duct [8]. A stent diameter that exceeds the diameter of the natural size of the bile duct would cause discomfort to the patients. However, SEMSs with nominal diameters of 10 mm are exclusively used for distal malignant biliary obstruction. The reasons are as follows: First, the diameter of the dilated bile duct proximal to the stricture is mostly greater than 10 mm in distal malignant biliary obstruction. Second, stent patency in unresectable distal malignant biliary obstruction is significantly longer in 10-mm SEMS than in 6-mm SEMS [19]. Third, the available nominal diameters of biliary SEMSs range from 6 to 10 mm when expanded.

The European Society of Gastrointestinal Endoscopy (ESGE) guideline stipulates that a biliary sphincterotomy is not necessary for insertion of a SEMS, but it may facilitate more complex stenting procedures [20]. The anticipated benefits of a pre-stenting biliary sphincterotomy should be weighed against its risks on a case-by-case basis. Proponents of sphincterotomy believe that the sphincterotomy allows expansion of the SEMS without causing compression of the pancreatic duct [8]. When a tumor involves the main pancreatic duct, diminished pancreatic function may protect against the pancreatitis after SEMS placement [21]. Biliary sphincterotomy may have the potential to prevent pancreatitis, especially when the pancreatic duct does not have tumor involvement.

After securing the position of the guidewire, the prepared SEMS delivery system is flushed with saline. If the malignant biliary stricture is firm and tight, the stricture

should be dilated to the size of the delivery catheter of the SEMS (usually 6–8.5 F). Placement of the biliary SEMSs is performed under both endoscopic guidance and fluoroscopic guidance. The delivery catheter is advanced over the guidewire into the bile duct with the aid of the radiopaque markers in the proximal and distal ends of SEMS [9]. The proximal markers should be placed well above the proximal end of the stricture, as a foreshortening of the SEMS expected [9]. When the delivery catheter has been advanced into the desired location, the SEMS is deployed under fluoroscopic guidance (Fig. 27.1). The outer sheath of the SEMS is slowly withdrawn by an assistant, as the endoscopist applies gentle pulling tension on the stent to compensate for the forward propelling force of the stent [9]. As the expanded stent covers the stricture area, the formation of a "waist" in the midportion of the stent should be confirmed.

During deployment, the position of the stent can be adjusted in the distal direction by applying more traction on the delivery catheter or in the proximal direction by reconstraining the SEMS and advancing the delivery catheter again [15]. An endoscopic view of the distal end of the SEMS through a transparent delivery system is also important during deployment (Fig. 27.1). Soon after a SEMS is deployed, its expansion can be confirmed by the flow of bile or by an air-biliarygram. If a SEMS fails to expand and poor drainage is observed, balloon dilation of the stricture within the stent can be performed to facilitate immediate drainage [9]. Biliary imaging or endoscopic revision should be considered when cholangitis develops, or the decrease in total bilirubin is less than 20% from baseline at 7 days after biliary stenting [20].

27.5 Outcome

A group of studies comparing between the use of plastic and metal stents in distal malignant biliary obstruction concluded that the patency periods of metal stents are approximately twice those of plastic stents, with a time to first obstruction of 6–10 months vs. 3–5 months, respectively [1, 9, 22–25]. SEMS placement is also associated with a lower therapeutic failure, less need for reintervention, lower cholangitis incidence, and decreased hospital readmission but shows no difference in patient survival [1, 20, 26]. The ESGE recommended initial insertion of a SEMS (preferably 10 mm) as it is more cost-effective if patient life expectancy is longer than 4 months [20]. Initial insertion of a plastic stent (preferably 10 F) is recommended if patient life expectancy is shorter than 4 months or the diagnosis of malignancy is not established.

The rate of biliary SEMS occlusion increases over time, even though SEMSs were originally designed to be permanent. The mechanisms of USEMS occlusion mostly involve tumor ingrowth [19, 27]. This tumor ingrowth can be reduced by covering the mesh of metal stents with a membrane, thereby converting the USEMS to a CSEMS. However, a meta-analysis of randomized trials of USEMS and CSEMS

demonstrated no differences in patency after 6 or 12 months, with similar rates of pancreatitis, cholecystitis, perforation, bleeding, or cholangitis [28]. Disadvantage of the CSEMS include the potential for migration and higher cost [20, 28]. The issue of comparison between USEMS and CSEMS is fully discussed in another chapter of this book.

27.6 Reintervention

Migration of SEMSs after placement occurs in 1% of USEMS placements, 5% of PCSEMS placements, and 20% of FCSEMS placements [20]. Patients with migrated stents undergo ERCP to remove stents that have not been spontaneously eliminated and to restore bile flow by another stent. If the migrated first stent is a CSEMS, a USEMS can be used as an alternative choice after removal of the covered model. If a USEMS undergoes a partial outward migration, the prolapsing part of the migrated stent at the duodenal side may be the cause of duodenal ulcer or bleeding [29]. Stent trimming with argon plasma coagulation (APC) has been reported as useful for the rescue of these cases. The reported settings of APC for stent trimming are a voltage at 60–85 W and gas flow at 0.8–2.0 L/min [29, 30].

The mechanisms of USEMS occlusion most commonly involve tumor ingrowth; other causes include overgrowth, sludge or debris, stones, blood clots, food material, and tissue hyperplasia (Fig. 27.2) [19, 27]. Tumor ingrowth is defined as growth of the tumor invading the body of the stent and occluding its lumen [31]. Tumor overgrowth is defined as growth of the tumor proximal or distal to the stent and leading to lumen occlusion with function loss [31]. Removal of an occluded USEMS is quite difficult due to tissue/tumor ingrowth through the stent meshwork; forcible removal may be associated with stent breakage or biliary hemorrhage [29, 30, 32].

Occlusion of a USEMS should be treated by insertion of a CSEMS as a second stent (Fig. 27.2) [20, 29]. Inserting a second SEMS within the occluded SEMS yields a longer biliary patency than is obtained by inserting a plastic stent [20]. Among patients who had received a second SEMS insertion as a stent-in-stent technique, cumulative biliary patency was longer in patients who had received at least one CSEMS (in the primary or secondary procedure) compared with those who had a USEMS inserted twice (Table 27.1) [20, 29, 33]. Although clogging by stones, sludge, or food impaction can be treated by simply cleaning the inside of the metal stent with a balloon or a basket, additional stent placement is still usually necessary because the predicted stent patency may be too short following mechanical cleaning alone [20, 29]. If a clear reason is evident for removal of an embedded USEMS, a new technique of temporary placement of an FCSEMS within an USEMS can be attempted [34].

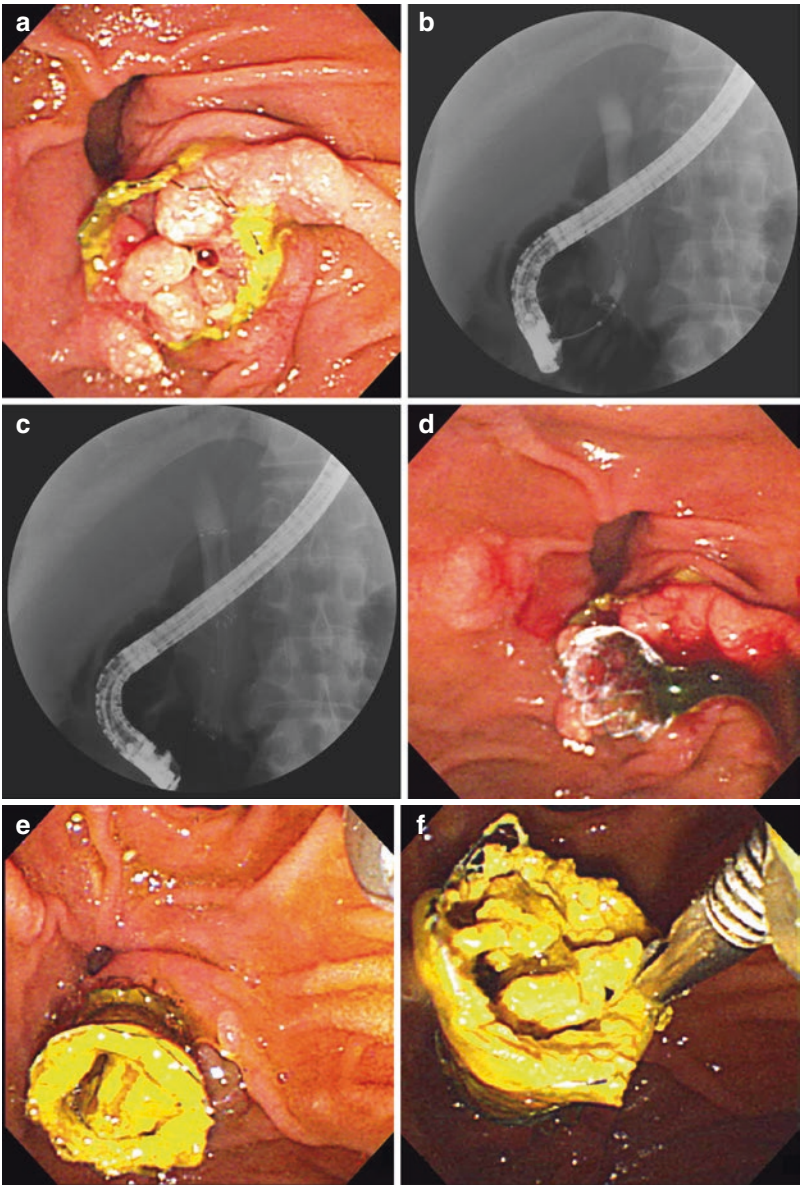

Fig. 27.2 Reintervention after occlusion of the SEMS. (**a**) Endoscopic view of occluded USEMS by tumor ingrowth/tissue hyperplasia. (**b**) Cholangiogram showed tumor ingrowth. (**c**) Insertion of the CSEMS as a second metal stent was performed for the treatment of USEMS occlusion (stent-in-stent technique). (**d**) The function of the second metal stent was confirmed by the flow of bile. (**e**) The second metal stent was occluded by sludge/stones. (**f**–**h**) This CSEMS was removed by rat-tooth forceps through working channel. (**i**) Because removal of first stent (USEMS) was not possible, (**j**) another CSEMS was inserted in the USEMS. *SEMS* self-expandable metal stent, *USEMS* uncovered self-expandable metal stent, *CSEMS* covered self-expandable metal stent, *PCSEMS* partially covered self-expandable metal stent, *FCSEMS* fully covered self-expandable metal stent, *ESGE* European Society of Gastrointestinal Endoscopy, *ERCP* endoscopic retrograde cholangiopancreatography, *APC* argon plasma coagulation

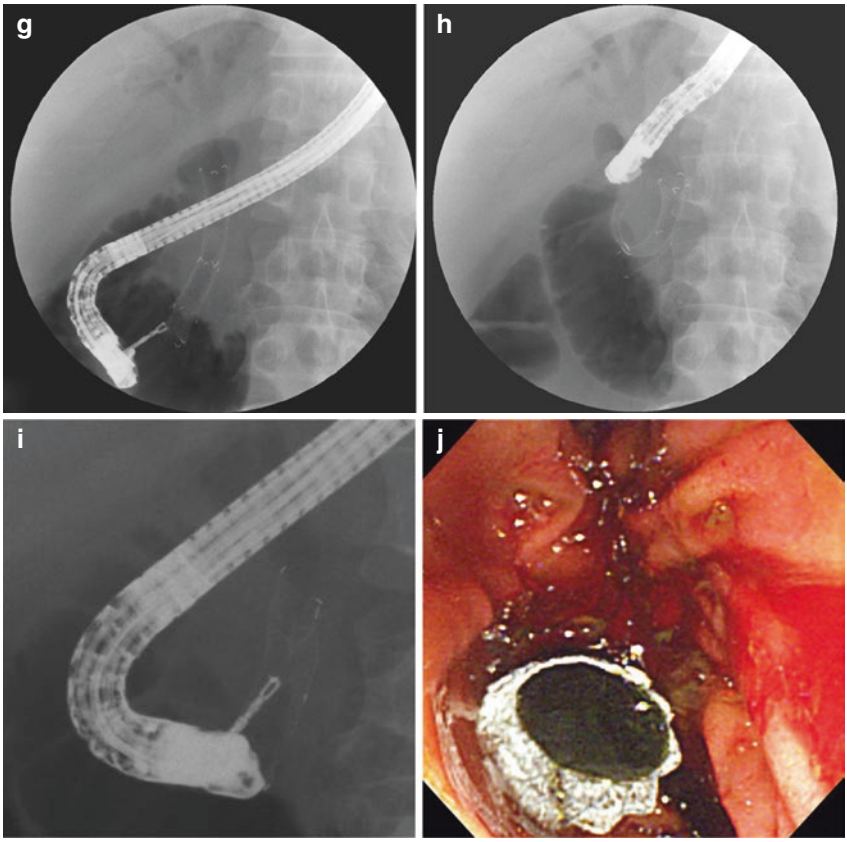

Fig. 27.2 (continued)

Table 27.1 Clinical pearls for adequate stenting using uncovered metallic stent in distal malignant biliary obstruction

1. Insertion of a SEMS with a 10-mm diameter is recommended when patient life expectancy is longer than 4 months. When the stent is occluded, the second stent should be a CSEMS if the first metal stent is an uncovered model
2. As a first stent, USEMS and CSEMS have similar stent patency rates at 6 or 12 months after stent placement
3. Good SEMSs have a high radial force and a low axial force
4. Remember that the removal of an uncovered metal stent is extremely difficult after embedding
5. The desired location of the stent is from 1–2 cm above the proximal end of the stricture to 1 cm below the papilla
6. Biliary sphincterotomy may not be necessary for insertion of a SEMS
7. Some delivery systems of the SEMS have a function for recapturing during deployment

References

1. Cipolletta L, Rotondano G, Marmo R, et al. Endoscopic palliation of malignant obstructive jaundice: an evidence-based review. Dig Liver Dis. 2007;39:375–88.
2. Stern N, Sturgess R. Endoscopic therapy in the management of malignant biliary obstruction. Eur J Surg Oncol. 2008;34:313–7.
3. Irisawa A, Katanuma A, Itoi T. Otaru consensus on biliary stenting for unresectable distal malignant biliary obstruction. Dig Endosc. 2013;25(Suppl 2):52–7.
4. Wassef W, Syed I. Designer stents: are we there yet? Gastrointest Endosc. 2007;66:804–8.
5. Smith AC, Dowsett JF, Russell RC, et al. Randomised trial of endoscopic stenting versus surgical bypass in malignant low bileduct obstruction. Lancet. 1994;344:1655–60.
6. Andersen JR, Sorensen SM, Kruse A, et al. Randomised trial of endoscopic endoprosthesis versus operative bypass in malignant obstructive jaundice. Gut. 1989;30:1132–5.
7. Moss AC, Morris E, Leyden J, et al. Malignant distal biliary obstruction: a systematic review and meta-analysis of endoscopic and surgical bypass results. Cancer Treat Rev. 2007;33:213–21.
8. Jaganmohan S, Lee JH. Self-expandable metal stents in malignant biliary obstruction. Expert Rev Gastroenterol Hepatol. 2012;6:105–14.
9. Lee JH. Self-expandable metal stents for malignant distal biliary strictures. Gastrointest Endosc Clin N Am. 2011;21:463–80. viii–ix
10. Artifon EL, Sakai P, Cunha JE, et al. Surgery or endoscopy for palliation of biliary obstruction due to metastatic pancreatic cancer. Am J Gastroenterol. 2006;101:2031–7.
11. Park do H, Jang JW, Lee SS, et al. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. Gastrointest Endosc. 2011;74:1276–84.
12. Raijman I. Biliary and pancreatic stents. Gastrointest Endosc Clin N Am. 2003;13:561–92. vii–viii
13. Moparty B, Carr-Locke DL. Metal or plastic stent for malignant biliary obstruction: what's got the most bang for your buck? Eur J Gastroenterol Hepatol. 2007;19:1041–2.
14. Isayama H, Nakai Y, Kogure H, et al. Biliary self-expandable metallic stent for unresectable malignant distal biliary obstruction: which is better: covered or uncovered? Dig Endosc. 2013;25(Suppl 2):71–4.
15. Dumonceau JM, Heresbach D, Deviere J, et al. Biliary stents: models and methods for endoscopic stenting. Endoscopy. 2011;43:617–26.
16. Pfau PR, Pleskow DK, Banerjee S, et al. Pancreatic and biliary stents. Gastrointest Endosc. 2013;77:319–27.
17. Nelson D. Expandable metal stents: physical properties and tissue responses. Tech Gastrointest Endosc. 2001;3:70–4.
18. Okamoto T, Fujioka S, Yanagisawa S, et al. Placement of a metallic stent across the main duodenal papilla may predispose to cholangitis. Gastrointest Endosc. 2006;63:792–6.
19. Loew BJ, Howell DA, Sanders MK, et al. Comparative performance of uncoated, self-expanding metal biliary stents of different designs in 2 diameters: final results of an international multicenter, randomized, controlled trial. Gastrointest Endosc. 2009;70:445–53.
20. Dumonceau JM, Tringali A, Blero D, et al. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2012;44:277–98.
21. Okano N, Igarashi Y, Kishimoto Y, et al. Necessity for endoscopic sphincterotomy for biliary stenting in cases of malignant biliary obstruction. Dig Endosc. 2013;25(Suppl 2):122–5.
22. Kaassis M, Boyer J, Dumas R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc. 2003;57:178–82.
23. Prat F, Chapat O, Ducot B, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. Gastrointest Endosc. 1998;47:1–7.

24. Schmassmann A, von Gunten E, Knuchel J, et al. Wallstents versus plastic stents in malignant biliary obstruction: effects of stent patency of the first and second stent on patient compliance and survival. Am J Gastroenterol. 1996;91:654–9.
25. Yeoh KG, Zimmerman MJ, Cunningham JT, et al. Comparative costs of metal versus plastic biliary stent strategies for malignant obstructive jaundice by decision analysis. Gastrointest Endosc. 1999;49:466–71.
26. Sawas T, Al Halabi S, Parsi MA, et al. Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis. Gastrointest Endosc. 2015;82:256–67. e257
27. Baron TH. Best endoscopic stents for the biliary tree and pancreas. Curr Opin Gastroenterol. 2014;30:453–6.
28. Almadi MA, Barkun AN, Martel M. No benefit of covered vs uncovered self-expandable metal stents in patients with malignant distal biliary obstruction: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11:27–37. e21
29. Ito K, Ogawa T, Horaguchi J, et al. Reintervention for occluded biliary metal stent for patients with malignant distal biliary stricture. Dig Endosc. 2013;25(Suppl 2):126–31.
30. Ishii K, Itoi T, Sofuni A, et al. Endoscopic removal and trimming of distal self-expandable metallic biliary stents. World J Gastroenterol. 2011;17:2652–7.
31. Yang Z, Wu Q, Wang F, et al. A systematic review and meta-analysis of randomized trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract. Int J Med Sci. 2013;10:825–35.
32. Shin HP, Kim MH, Jung SW, et al. Endoscopic removal of biliary self-expandable metallic stents: a prospective study. Endoscopy. 2006;38:1250–5.
33. Cho JH, Jeon TJ, Park JY, et al. Comparison of outcomes among secondary covered metallic, uncovered metallic, and plastic biliary stents in treating occluded primary metallic stents in malignant distal biliary obstruction. Surg Endosc. 2011;25:475–82.
34. Tan DM, Lillemoe KD, Fogel EL. A new technique for endoscopic removal of uncovered biliary self-expandable metal stents: stent-in-stent technique with a fully covered biliary stent. Gastrointest Endosc. 2012;75:923–5.

Chapter 28
Covered Metal Stenting

Nabi Zaheer, D. Nageshwar Reddy, and Sundeep Lakhtakia

Abstract Endoscopic biliary drainage is the mainstay of treatment for benign or malignant biliary obstruction. Endoprostheses for biliary drainage include plastic and metal stents. Uncovered metal stents are superior to plastic stents in terms of patency. However, tissue ingrowth and stent dysfunction are common through their bare wire mesh. Covered metal stents have been developed to overcome tissue ingrowth and prolong stent patency. Easy removability of covered metal stents makes them an attractive option for benign biliary obstructions. However, migration is an important drawback with covered stents. Currently available covered metal stents differ according to their structure, stent and covering material and mechanical properties. A number of studies have demonstrated their efficacy in benign as well as malignant biliary strictures. The safety, efficacy and ease of removability of covered metal stents have encouraged their use in non-stricture benign biliary diseases like bile leaks, perforation, bile duct stones and bleeding. The "battle of superiority" between covered and uncovered metal stents continues with contrasting results in recent studies. The choice of covered or uncovered metal stents should be individualized to the needs of each patient. Recent developments in covered metal stents include different antimigration designs, antireflux properties and drug-eluting capabilities.

Keywords Covered metal stents • Benign biliary strictures • Malignant biliary obstruction

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28.1 Background and Introduction

Endoscopic biliary drainage has revolutionized the management of benign as well as malignant biliary strictures. Endoprostheses for biliary drainage include plastic and self-expandable metallic stents (SEMS). Plastic stents have limited patency duration due to their smaller lumen and easily get occluded by biliary sludge. Moreover, the accessory channels of currently available endoscopes do not allow insertion of more than 12 Fr plastic stents. Therefore, there was an unmet need of stents with larger diameters and prolonged patency rates. SEMS have, more or less, overcome the shortcomings of plastic stents. They provide wider luminal diameters with longer patency rates and reduced recurrent obstruction.

Uncovered SEMS (UCSEMS) were developed initially with superior outcomes as compared to plastic biliary stents in various studies [1–3]. However, their main disadvantage is non-removability and stent occlusion due to tumour ingrowth through the wire mesh. To overcome these shortcomings, covered SEMS (CSEMS) were developed by coating them with various materials like polyurethane, silicone, polytetrafluoroethylene (PTFE), premalume etc. Since their initial introduction in the 1990s, they have undergone various modifications. In this chapter we will discuss the development of CSEMS and their utility and efficacy in biliary drainage.

28.2 Development of Covered Biliary SEMS

Expandable metal stents were introduced in the 1980s, when animal studies revealed the feasibility and safety of stainless steel wire stents. These uncovered metal stents could be introduced through a small delivery catheter and produce only mild inflammatory changes in the bile duct wall. Moreover, a small delivery catheter was required to introduce the stent [4]. However, the occlusion of UCSEMS due to tissue ingrowth somewhat dampened the initial enthusiasm. Evaluation of tissue responses to metal stents revealed that the wire of uncovered SEMS becomes deeply embedded in the bile duct epithelium, whereas that of CSEMS does not [5]. Subsequently, the development of CSEMS started by coating the uncovered stents with various non-porous polymeric membranes.

In one of the early animal studies, Alvarado and colleagues evaluated the utility of polymer-coated balloon-expandable stents in bile ducts. All the stents were patent at 24 weeks, but mucosal proliferation was most extensive with the uncoated stent [6].

28.3 Types of Covered SEMS

A variety of CSEMS are available for commercial use. These stents differ according to their structure (braided or specially braided, laser cut), stent material (steel, nitinol, Elgiloy, Platinol), covering material (silicone, polyurethane, expanded polytetrafluoroethylene, premalume), portion of the stent which is covered (fully covered

Table 28.1 Characteristics of the covered metallic stents (Adapted from ref. [10])

	PCD	SCW	ComVi	Viabil
Materials	Nitinol	Stainless	Nitinol	Nitinol
Covering material	Polyurethane	Silicone	PTFE	PTFE
Covering methods	Partial	Partial	Fully	Fully
AF (N)	0.46	0.95	0.04	0.14
RF (N)	6.67	3.41	7.67	9.67
Inner surface	Smooth	Smooth	Rough	Intermediate
Antimigration	None	+	+	Anchor fin

PCD polyurethane-covered diamond stent, *SCW* silicone-covered Wallstent, *ComVi* Niti-S stent, ComVi type, *Viabil* Viabil biliary stent, *AF* axial force, *RF* radial force, *N* newtons

or partially covered) and mechanical properties (axial and radial force). The characteristics of various types of CSEMS are summarized in Table 28.1.

28.4 Covered SEMS: Steel vs Nitinol

The currently available CSEMS are made of steel, nitinol (nickel and titanium alloy), Elgiloy (cobalt-chromium-nickel alloy) and Platinol (platinum and nitinol). Different alloys have difference in their flexibility, ability to conform to the shape of bile duct and expansion capacity. Initially the SEMS were made of steel (e.g. Wallstent). However, soon it was realized that the SEMS made of nitinol perform better than those made of steel. The distinct advantage of nitinol over steel is its shape memory effect and superelasticity. In a recent randomized controlled trial (RCT), steel alloy SEMS (Wallstent; Boston Scientific Nordic AB, Helsingborg, Sweden) was compared with the nitinol alloy SEMS (WallFlex; Boston Scientific Nordic AB) in patients with distal malignant biliary strictures. At 300 days, stent patency was significantly better (89% vs 77%), and stent migration rate was significantly lower (2% vs 7%) in the nitinol SEMS group [7]. Similar results were shown by Isayama and colleagues in a multicentre prospective study [8]. The authors attribute low migration to low axial force in SEMS made of nitinol (WallFlex and others) as compared to SEMS made of steel/Elgiloy (Wallstent). In facts, most of the currently available CSEMS are made of nitinol (ComVi, Niti-S, Nitinella, WallFlex).

28.5 Mechanical Properties: Radial Force and Axial Force

Axial force (AF) is the straightening force exerted when a stent is bent. Radial force (RF) is the outward expansion force exerted by the stent. High AF may lead to poor conformability, kinking, sludge formation and early migration of CSEMS. Low RF may result in inadequate expansion of SEMS. Therefore, a low AF and moderate RF are desirable for CSEMS. Isayama and colleagues measured the mechanical

properties (RF and AF) of various commercially available SEMS. Of all the available CSEMS, silicone-covered Wallstent was found to have the maximum AF and least RF, whereas ComVi SEMS had the least axial force. The mechanical characteristics of various types of CSEMS are summarized in Table 28.1 [9, 10].

28.6 Covering Material of CSEMS

Various types of stent coverings have been used in CSEMS including silicone, polyurethane, PTFE, Gore-Tex, etc. Polycaprolactone covering was not found biodurable in animal studies and therefore not developed further [11]. In contrast silicone and polyether-polyurethane membranes were resistant to hydrolysis [12].

Biodurability of the covering material is of paramount importance as degeneration of the membrane will lead to embedding of the stent and tissue ingrowth. Several studies have tested the biodurability of various covering materials [13–17]. In a recent study, biofilms and microcracks were observed in ePTFE on bile exposure [13]. However, this was an in vitro study, and multiple clinical trials using ePTFE-covered SEMS have not encountered the issue of tumour ingrowth (Tables 28.3 and 28.4). In another in vitro study, polyurethane was found bio-unstable, and degradation started at week 2 of bile exposure [14]. Tumour ingrowth was found in four patients who underwent polyurethane-covered stent (Wallstent) placement for malignant biliary obstruction in another study [15]. In contrast, an in vivo animal study and a randomized controlled trial found polyurethane coating to be biodurable [16, 17]. The authors of the latter study concluded that a membrane of sufficient thickness (50–60 μm) prevents tumour ingrowth, as compared to membranes with less thickness as used in some of the early studies. However, the polymeric covering in this study was handcrafted.

Contrasting results in these studies do not allow a definite conclusion to be drawn regarding the superiority of one covering material over the other. Most of the currently available CSEMS have either silicone or ePTFE covering (Tables 28.3, 28.4 and 28.6).

28.7 Commercially Available Covered SEMS

28.7.1 WallFlex™ Biliary RX Stent (Boston Scientific)

WallFlex biliary stents (Fig. 28.1a) are available in both partially and fully covered forms. These stents are made of Platinol (platinum core and nitinol encasement) and have a closed cell construction with a premalume covering to prevent tissue ingrowth. Platinol wires impart full-length radiopacity to aid visibility during stent placement. Antimigration system in these stents is provided by flared ends. The delivery system is reconstrainable up to 80% of deployment to aid in repositioning. These stents also have an integrated retrieval loop to facilitate removal (Fig. 28.1).

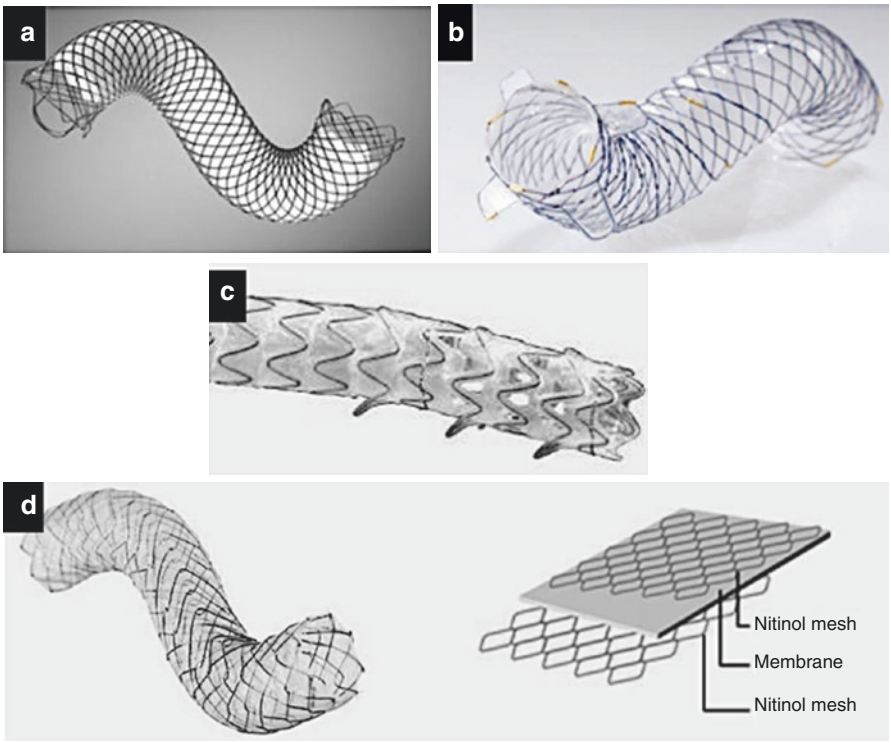

Fig. 28.1 Various commercially available covered biliary metal stents (**a**) WallFlex biliary stent (**b**) Hanarostent with anchoring flaps at the ends (**c**) Gore Viabil biliary stents (note the anchoring fins) (**d**) ComVi biliary stent with triple layered structure

28.7.2 Hanarostent® Biliary Stents

Covered Hanarostents (Fig. 28.1b) have four anchoring flaps either at the proximal end or at both proximal and distal ends to reduce stent migration (Fig. 28.1). The stents are also available without anchoring flaps (Hanarostent® SHCL), where both the ends are flared to minimize migration. Single or double lasso is provided to help the removal of these SEMS. In double-lasso SEMS (Hanarostent® BCT), the upper one goes through the stent and has a radiopaque marker (gold) to highlight it from the lower one. The proximal lasso may allow easy removal of SEMS in an inside-out fashion [18].

28.7.3 Gore® Viabil® Biliary Endoprosthesis

Viabil SEMS (Fig. 28.1c) are made of nitinol wire exoskeleton with an ultrathin ePTFE/FEP covering. These stents do not foreshorten on deployment. Atraumatic anchoring fins on this stent serve to prevent migration. Additional advantages of these stents include a high radial force and low axial force.

28.7.4 ComVi™ Stent (Taewoong Medical)

The ComVi stent (Fig. 28.1d) has a triple-layered structure in which an ePTFE membrane is sandwiched, but not fixed between two self-expandable wire meshes made of nitinol. This stent has an unfixed cell structure which provides conformability to the stent, an uncovered outer layer to reduce stent migration and a weak axial force to reduce the risk of kinking in the biliary tract. This stent is available in several different diameters (6, 8, 10 mm) and lengths (4–10 cm).

28.7.5 Niti-S™ Biliary Stent (Taewoong Medical)

This stent has atraumatic ends to reduce hyperplasia at edges and silicone covering on both inner and outer surface. A retrieval string is present to facilitate removal. A total of five radiopaque markers (three at the ends and two in the middle) are present.

28.7.6 KAFFES™ Biliary stent

This is a covered SEMS specially designed for anastomotic strictures after liver transplant. It has a characteristic waist (8 mm at the centre and 10 mm at the ends) at the centre which prevents migration. It is available in 5 lengths (4–8 cm) and 3 diameters (6, 8, 10 mm). A long platinum radiopaque retrieval string helps easy removal of short stent from high up location of the common bile duct.

28.7.7 Niti-S Biliary Bumpy Stent

The Niti-S biliary bumpy stent (Taewoong Medical) is made of nitinol. Irregular cell sizes with different magnitudes of segmental radial force and flared ends are meant to prevent migration. The stent is available in various (4–12 cm) lengths. It is fully covered with PTFE covering in body portion and silicone covering at both flared ends. There is a removal string at the proximal end for removal of stent. There are three radiopaque markers at both the ends and two in the middle.

28.7.8 SX-ELLA Stent Biliary: Nitinella Plus

Nitinella Plus biliary stents are braided nitinol SEMS with silicone covering (partially or fully covered). Stent deployment requires a 9 Fr delivery catheter. These stents come in 4 lengths (4–10 cm) and 2 diameters (8, 10 mm).

28.8 Covered SEMS for Benign Biliary Strictures (BBS)

Benign biliary strictures (BBS) usually result either postoperatively (cholecystectomy-related bile duct injury or post-liver transplant anastomotic stricture) or as a sequel to chronic pancreatitis. The standard of care in these patients is serial placement of multiple plastic stents (MPS) at present [19–21]. However, multiple sessions of stent exchanges are required with obvious implications on patient compliance and treatment cost. Recently, CSEMS have been utilized in several studies with good results [23, 24, 29–37]. CSEMS provide generous dilatation of biliary strictures in a single session (Fig. 28.2a-c). Recent data indicate that CSEMS have comparable efficacy to MPS in BBS and achieve stricture resolution in shorter time [22].

In a recent multicentre study, CSEMS (WallFlex Biliary RX Stent) were used for BBS [23]. About two-thirds of the study population consisted of chronic pancreatitis (CP) related to BBS, the remaining being post-liver transplant anastomotic stricture (OLT) and post-cholecystectomy (CCY) biliary strictures. The stricture resolution rate was maximum for CP patients (79.7%), followed by cholecystectomy (72.2%) and OLT (68.3%) related biliary strictures. The stent indwell time was 10–12 months for CP patients as compared to 4–6 months in OLT group in this study. This, along with lower migration rate in CP group, probably resulted in better outcomes. Kahaleh et al. noticed stricture resolution in 80.7% of CP-related biliary strictures. Absence of migration and longer indwell time (>90 days) were predictors of success in this study as well [24].

From the available data, it is clear that stent indwell time (>3 months for OLT and CCY strictures; 12 months for CP) and migration rates are critical factors which decide the outcomes with CSEMS in patients with BBS. Table 28.2 summarizes selected studies of CSEMS in benign biliary strictures.

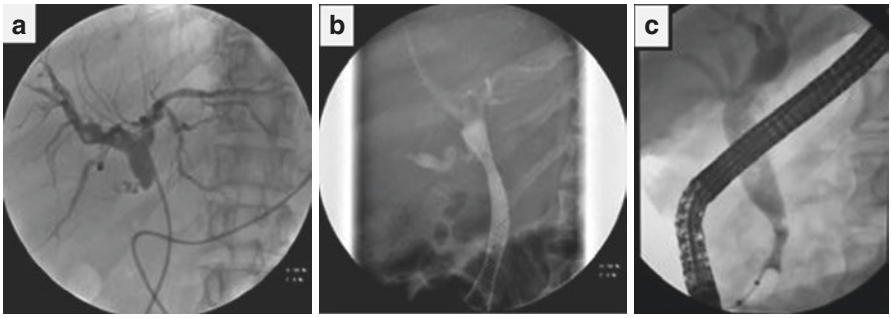

Fig. 28.2 Endotherapy in a case with benign biliary stricture (**a**) chronic pancreatitis related benign bilary stricture (**b**) covered metal stent placement across the stricture (**c**) complete resolution of stricture after removal of metal stent

Table 28.2 CSEMS in benign biliary strictures (selected studies)

Study	Type of stent	No.	Indication	Mean stent indwell duration (months)	Success, %	Recurrence, %	Migration, %	F/U (months)
Tarantino et al. [29]	Niti-S ComVi	62	Mixed	2	90.3	7.1	24.2	15.9
Park et al. [30]	AF: M.I Tech FE: Standard Sci-Tech Inc.	43	Mixed	6	84	16.3	16.3	4
Kahaleh et al. [31]	WallFlex (PC)	65	Mixed	4	90	NR	14	12
Mahajan et al. [32]	Conmed Viabil	44	Mixed	3.3	83	9	5	3.8
Walter et al. [33]	Niti-S biliary bumpy stent	38	Mixed	3	80	21	31	9
Irani et al. [34]	Wallstent, WallFlex, Viabil	125	Mixed	6	66	8	2.4	90 weeks
Tarantino et al. [35]	Niti-S ComVi	70	OLT	3	66	39	45.7	48
Rodriguez et al. [36]	Wallstent, Viabil, WallFlex	55	OLT	3–4	70	NA	7.3	V[a]
Saxena et al. [37]	WallFlex Viabil	123	Mixed	6	81	4.5	9.7	18.5
Devière et al. [23]	WallFlex	187	Mixed	4–12	76.3	14.8	29.4	20.3
Kahaleh et al. [24]	WallFlex	133	Mixed	3	78	NA	10.5	NA

[a]*V*-Wallstent = 38.9 ± 22.3 months, Viabil = 24.3 ± 9.5 months, WallFlex = 4.6 ± 3.4 months

28.9 Benign Biliary Strictures: CSEMS vs Multiple Plastic Stents (MPS)

The standard of care for BBS is placement of multiple large-bore plastic stents. Theoretically speaking, one SEMS (10 mm) is equivalent to six 10 Fr plastic stents. Encouraging results with covered SEMS demand comparison between the two strategies (CSEMS vs MPS). Unfortunately, there is a paucity of literature comparing these two approaches in randomized fashion. Till date three RCTs (one in abstract form) have been published (in English), which compared the efficacy of CSEMS with MPS [25, 26].

In a well-designed recent RCT, CSEMS (partially covered Wallstent and fully covered Hanarostent) were compared with MPS in patients with CP-related BBS. The stent indwell time in this study was 6 months. At 2 years, the absence of stricture recurrence was equal in both groups (MPS 90% vs CSEMS 92%, $P = 0.405$). Migration rate was low in CSEMS group (7%) [25]. In another RCT, Kaffes et al. compared the efficacy of MPS with CSEMS in a small number of OLT patients (10 patients in each arm). There was no difference in efficacy (CSEMS 100% vs MPS 80%) between the two arms. There was no incidence of SEMS migration and the stricture recurrence was equal in both the groups [26].

In a systemic review, comparing MPS (120 patients) with SEMS (200 patients) in OLT patients, the stricture resolution rates were inferior for SEMS group (80–95%) than MPS group (94–100%). However, this review was deficient in randomized trials, and therefore the results should be interpreted with caution [27].

In contrast, in another recently published systemic review, CSEMS faired better than MPS in CP-related BBS (77% vs 33%). However, in BBS of other aetiologies, there was no difference in efficacy among the two groups [28].

The available data shows promising results in patients with CP-related BBS [23, 25, 28]. However, the outcomes in OLT patients do not appear to be as good. In a long-term follow-up study, Trantino et al. evaluated the efficacy of CSEMS in refractory post-transplant anastomotic strictures. They found a high rate of stricture recurrence (39%) after initial resolution (66%) [35]. In another recent multicentre prospective study, stricture resolution in OLT patients was only 68% (vs 80% in CP patients) [23]. Therefore, good randomized trials are required before recommending the use of CSEMS in post-transplant anastomotic biliary strictures.

28.10 Use of CSEMS in Non-stricture Benign Biliary Disorders

The safety, efficacy and ease of removability of CSEMS have encouraged their use in other non-stricture benign biliary diseases like bile leaks, perforation, bile duct stones and bleeding.

The required stent indwell time is much less in this group of patients for obvious reasons. CSEMS with larger diameter can provide adequate compression at bleeding site and effectively close leaks/perforations in refractory cases. CSEMS are especially useful if bleeding fails to respond to conventional measures and the origin of bleed is from within the bile duct [38–40].

In a recent study, Irani et al. used partially and fully covered SEMS in non-stricture-related benign biliary diseases. Clinical success was achieved in all the patients with biliary perforations (100%) and more than 90% of patients with bile leaks and bleedings [41]. In another prospective study by Canena et al., closure of leak was accomplished in all the patients in CSEMS group as compared to only 65% in multiple plastic stent group [42].

CSEMS have also been used successfully in patients with complex biliary stones after failure of standard approach [43]. In a small study (10 patients), CSEMS were used as a primary modality (without prior sphincterotomy) to clear biliary stones in an attempt to preserve sphincter of Oddi (SO) function. Successful biliary clearance was achieved in all the cases, and SO function was preserved as evident by SO manometry [44]. By avoiding sphincterotomy and therefore reducing duodenobiliary reflux, should this strategy prevent the recurrence of stones remains to be seen.

From the available data, it appears that CSEMS may be useful in selected cases. However, randomized trials are required.

28.11 Covered SEMS in Malignant Biliary Obstruction

The efficacy and safety of CSEMS in distal malignant biliary obstruction (MBO) have been demonstrated in multiple trials [17, 62–66]. Ease of removability and prevention of tumour ingrowth are the major advantages with these stents. Therefore, these stents can be placed in patients with extrahepatic MBO, regardless of the resectability status [45, 46].

CSEMS appear to be cost-effective in the palliation of MBO. A recent multicentre randomized trial evaluated the cost efficacy of various stents (CSEMS or UCSEMS or plastic stents) in the palliation of extrahepatic MBO. Both CSEMS and UCSEMS had significantly longer patency than plastic stents (UCSEMS/CSEMS 288/299 days vs plastic 172 days). SEMS were equally cost-effective to plastic stents, irrespective of the survival time or presence of metastases [47]. Therefore, the conventional approach of using plastic stents if patient survival is less than 3–4 months needs to be scrutinized.

28.12 Pre-op Biliary Drainage: Role of Covered SEMS

With the advancements in chemotherapeutic agents, survival is likely to improve in patients with unresectable or borderline resectable pancreatico-biliary malignancies [48, 49]. Biliary decompression to reduce jaundice is important in these patients, prior to neoadjuvant chemotherapy. Plastic stents have been used commonly for this purpose. However, increased complications and frequent need for reintervention are the major concerns with plastic stents for preoperative biliary drainage (PBD). A recent retrospective multicentre study analysed the efficacy of plastic stents (10 Fr or larger) in PBD of patients receiving downstaging chemotherapy for locally advanced or borderline resectable pancreatic adenocarcinoma. A significant proportion of patients (35.6%) required premature stent exchanges [50]. With the availability of SEMS (especially short 4 cm CSEMS), the rate of stent occlusion and cholangitis is low. SEMS also appear to be cost-effective in this setting as the number of reinterventions due to stent occlusion is reduced significantly [46, 51].

Two recent RCTs compared CSEMS with plastic stents for PBD in periampullary and pancreatic neoplasms, respectively. In the first study, (abstract form) PBD was performed for periampullary tumours. The CSEMS group faired better with regard to complication rate, need for reinterventions during preoperative period and overall costs [52]. In the second multicentre study, CSEMS were compared with plastic stents for PBD in pancreatic cancer patients. Stent-related and PBD-related complications were much less in the CSEMS group [53].

Therefore, the current evidence favours the use of CSEMS for preoperative biliary decompression.

However, it must be emphasized that routine preoperative drainage for extrahepatic malignant biliary obstruction is not advisable. An expected delay in surgery, cholangitis and neoadjuvant chemoradiation appear to be valid indications. When indicated, a short fully covered SEMS (4–6 cm length) is preferable to plastic stents.

28.13 Covered vs Uncovered SEMS in Malignant Biliary Obstruction

A number of studies have compared CSEMS and UCSEMS in malignant biliary obstruction (MBO). The first published RCT on this subject by Isayama et al. demonstrated the superiority of CSEMS over UCSEMS [17]. Since then, many randomized controlled trials (RCTs) and few meta-analyses have been published comparing the efficacy of covered and uncovered SEMS in MBO. Five RCTs favour CSEMS, whereas the other six RCTs show either equal or better patency of UCSEMS (Tables 28.3 and 28.4).

From the published studies, it is evident that the prevention of tissue ingrowth in CSEMS did not consistently translate into better stent patency. The probable reasons are stent dysfunction by other mechanisms like tumour overgrowth, sludge formation and migration, all of which are more common with CSEMS.

Moreover, the problem of tissue ingrowth (although to a lesser extent) has been observed even with CSEMS in few studies [15, 54, 55]. In a multicentre randomized study, Kullman and colleagues found tumour ingrowth in nine patients (4.5%) receiving CSEMS for distal MBO [56]. In another large retrospective study, Lee and colleagues found tumour ingrowth as a cause of recurrent obstruction in 9% of patients in covered group [57]. However, it should be emphasized that occassionally it may not be feasible to differentiate the cause of stent obstruction on cholangiographic images (ingrowth, overgrowth, sludge).

It needs to be emphasized here that the published studies differ in their definition of stent patency, study population (exclusion or inclusion of advanced disease), types of covered SEMS (fully or partially covered) and route of stent placement (transhepatic or endoscopic). The heterogeneity in these studies does not allow drawing firm conclusions on the superiority of one stent type over the other.

Table 28.3 Randomized trials showing non-superiority of CSEMS over UCSEMS

Study	PC/UC/FC	Stent type (covering)	Cause of occlusion (%)			Migration (%)	Patency (median)
			TI	TO	Sludge		
Kullman et al. [56]	PC-200 UC-200	Nitinella (C and UC) (polyurethane)	19 45	30 22	6 2	3 0	154 first 199 quartile
Telford et al. [58]	PC-68 UC-61	Wallstent (C and UC) (silicone)	17 30	9 0	11 4	12 2	357 711
Lee et al.[a] [59]	PC-20 UC-20	Niti-S, ComVi, Zilver	0 10	20 5	20 50	10 0	207 mean 413
Ung et al. [60]	FC-34 UC-34	Hanarostent (silicone) Hanarostent	13 Cause not 17 mentioned			NA	153 127
Yang et al. [61]	PC-51 UC-52	Bonastent (silicone) Bonastent	5.9 19.2	7.8 1.9	– –	5.9 0	395 365
Walter D et al. [47]	PC-71 UC-75	Wallstent (premalume) Wallstent	0 8	2.8 1.3	7 4	0 1.3	299 mean 288

C covered, *UC* uncovered, *PC* partially covered, *FC* fully covered, *TI* tumour ingrowth, *TO* tumour overgrowth

[a]Percutaneous

Table 28.4 RCTs showing superiority of CSEMS

Study	PC/UC/FC	Stent type	Cause of occlusion (%)			Migration (%)	Patency—days (median)
			TI	TO	Sludge		
Isayama et al. [17]	PC-57 UC-55	Diamond Diamond	0 76	50 9	25 0	2 0	304 mean 161
Kitano et al. [63]	PC-60 UC-60	WallFlex WallFlex	0% 71	5% 9	18% 27	0 0	583 314
Krokidis et al.[a] [64]	FC-30 UC-30	Viabil Wallstent	0 89	50 11	50 11	0 0	227 mean 166
Krokidis et al.[a] [65]	FC-40 UC-40	Viabil Luminexx	0 92	50 10	0 8	0 0	234 mean 166
Hu B et al. [66]	PC-56 UC-56	Antireflux	6 25	2 9	4 4	10 2	390 300

[a]Percutaneous

Therefore, at this point it would be unfair to advocate any one of these SEMS (covered or uncovered) in extrahepatic MBO. Choice of SEMS should be tailored to the needs of each patient. Various factors that should be taken into account before choosing between covered and uncovered SEMS include location of stricture (hilar vs extrahepatic), diagnostic certainty (malignant, benign or uncertain), purpose of drainage (preoperative or palliative) and cost. UCSEMS are preferred for hilar strictures as they do not impede the flow from branch ducts or contralateral bile ducts. CSEMS may be preferred in cases of diagnostic uncertainty or preoperative biliary drainage. For the palliation of extrahepatic MBO, both stents appear to have equal efficacy.

28.14 Complications of Covered SEMS

28.14.1 Migration

CEMS have the inherent tendency to migrate. Migration rates in recent randomized studies range from 0% to 12% [17, 47, 56, 58, 59, 61, 63–66]. In fact the major focus in the last decade has been to develop adequate antimigration strategies in these stents. Various antimigration strategies have been discussed later in this chapter.

28.14.2 Cholecystitis and Pancreatitis

The risk of cholecystitis and pancreatitis with CSEMS has been variable in different studies (Table 28.5). The risk of cholecystitis with CSEMS in randomized studies varies from 0% to 6.5% [17, 56, 58, 59, 63]. The potential risk factors for cholecystitis in various studies include tumour involvement of the cystic duct orifice (CDO) and high axial force (AF) of the stent. In a recent multicentre retrospective analysis including 300 patients with CSEMS, cholecystitis was observed in 8.0% of patients. However, the incidence of cholecystitis was more in patients with tumour involvement of CDO (16.8%) and in patients with SEMS of high AF (10.8%). The incidence of cholecystitis was especially high (25%) among patients with both the risk factors, i.e. tumour involvement of CDO and SEMS with high AF [67]. Therefore, in patients with tumour involvement of cystic duct, placing an uncovered SEMS with low AF appears to be an attractive strategy to prevent cholecystitis.

The incidence of pancreatitis after CSEMS in various studies ranges from 0% to 9% [17, 56, 58, 59, 63]. The probable mechanisms involved in the development of post-ERCP pancreatitis (PEP) are blockage of pancreatic duct orifice by coating of CSEMS and tensile forces associated with the expansion of SEMS. Pancreatic cancer appears to be a protective factor for PEP [68, 69]. Endoscopic sphincterotomy prior to CSEMS placement does not appear to reduce the risk of PEP in patients

Table 28.5 Comparison of cholecystitis and pancreatitis between covered and uncovered SEMS

Study	No. of patients	Pancreatitis	Cholecystitis
Isayama et al. [17]	C: 57 U: 55	8.8% 1.8% (NS)	3.5% 0% (NS)
Telford et al. [58]	C-68 UC-61	0% 2% (NS)	7% 7% (NS)
Kullman et al. [56]	C-200 UC-200	1.5% 2% (NS)	1.1% 1.1% (NS)
Kitano et al. [63]	C-120 UC-120	1.6% 0% (NS)	1.6% 3.3% (NS)
Lee et al. [59]	C-171 UC-578	5.8% 1% (S)	0 0.6% (NS)

C covered SEMS, *UC* uncovered SEMS, *S* significant, *NS* non-significant

with unresectable pancreatic cancer. In a recent well-designed RCT, the incidence of PEP was similar in patients with or without sphincterotomy before SEMS placement (no sphincterotomy 8.1% vs 9.3% in sphincterotomy group) [70].

There is a paucity of studies, which specifically compare the difference in incidences of cholecystitis or pancreatitis in covered and uncovered group. Nevertheless from the available data, the risk of these complications appears equal between the two groups.

28.14.3 Stent-Induced De Novo Strictures and Ulcerations

Ulceration and bleeding have been noticed with the use of CSEMS with anchoring fins [71]. In one study, 17 patients with post-liver transplant biliary leak underwent FCSEMS placement. Clinically significant biliary strictures requiring repeat stent placement were found in 6/17 (35%). Cholangioscopic bile duct ulcerations developed in additional three patients (18%) after stent removal [72]. Outward radial force by the flared end of SEMS has been proposed as one of the mechanisms responsible for these de novo biliary strictures. In an attempt to reduce bile duct injuries, Moon et al. used a modified FCSEMS with the shortest possible length (Bonastent M-Intraductal; Standard SciTech Inc., Seoul, South Korea) in patients with refractory BBS. No incidence of stent-induced stricture occurred in this study [73].

28.15 Future of Covered SEMS

Covered SEMS have been refashioned from time to time to increase the stent patency and reduce migration rates. The alterations have imparted these stents with antimigratory properties, antireflux capability and drug-eluting potential. Some of these modifications have been elucidated in the following section.

28.15.1 Antimigration Systems

A high rate of migration is the "Achilles' heel" of CSEMS. CSEMS have undergone multiple modifications aimed to reduce migration rates. Some of these alterations include anchoring fins, flared ends, bare outer end, partially uncovered stents, etc. (Table 28.6). Park et al. compared the two antimigration modalities, i.e. anchoring flap vs flared-end FCSEMS, in a pilot study. None of the stents in anchoring flap (AF) group migrated, whereas the migration rate was 33% in flared-end group [30]. Similar results were reproduced in another small study in patients with BBS, where only one migration occurred in AF SEMS group [74]. In a multicentre RCT, Kitano et al. compared CSEMS with an uncovered flared end to UCSEMS. No migration was observed in either group, but the patency of CSEMS was much longer than UCSEMS [65].

Isayama et al. used a modified stent with flare and bank structure (modified Zeo stent, Zeon Medical Inc.) in distal malignant biliary strictures. This stent had flared ends, with a 1 cm raised bank located 1 cm from each flared end. The migration rate was 12.9% for the primary group and 30% for the reintervention group [76].

Despite development of these antimigration systems, migration still remains a trouble with FCSEMS. None of the antimigratory changes are flawless. Anchoring fins may cause ulceration and bleeding from the bile duct mucosa, during removal of SEMS [32]. Moreover, it may be difficult to remove these SEMS as anchoring fins can get embedded into the bile duct wall. Walter et al.

Table 28.6 Antimigration properties and migration rates of various CSEMS

	WallFlex	Viabil	Hanarostent	ComVi	Niti-S Bumpy
Material	Platinol	Nitinol	Nitinol	Nitinol	Nitinol
Covering	Premalume	ePTFE/FEP	Silicone	ePTFE	PTFE
Antimigratory mechanism	Flared ends	Anchoring fins	Anchoring flaps	Uncovered outer layer	Flared ends segmental RF
Migration rate	8–13% (PC-FC) [8, 30, 75]	0–5% [10, 32]	0–3.3% [30, 74]	3–10% [10, 59]	31% [33]

ePTFE expanded polytetrafluoroethylene

used a novel CSEMS (Niti-S Bumpy) with flared ends and variable segmental radial forces to minimize migration. However, the results were disappointing in terms of migration (31%) [33].

Among other techniques to prevent stent migration, the use of an anchoring double-pigtail plastic stent appears attractive. Park et al. used a 5 Fr double-pigtail plastic stent as an anchoring stent to prevent migration of FCSEMS in BBS. Stent migration was significantly less in the anchoring group (6.3%) than in the non-anchoring group (41.2%) [77].

The mechanical properties of SEMS also play an important role in migration. A SEMS with low AF and high RF is less likely to migrate. Isayama et al. compared the results between different covered SEMS and correlated them with their mechanical properties. CSEMS with the maximum AF had the highest migration rates [10].

Therefore, while choosing a CSEMS, not only that the antimigration properties like fins or flaps have to be taken into account, mechanical properties like AF or RF of the SEMS should be considered as well.

28.15.2 Antireflux Metallic Stents (ARMS)

Cholangitis due to stent blockage is one of the major hurdles with biliary stents. Duodenobiliary reflux and occlusion of the stent due to food scraps may contribute to stent dysfunction and subsequent cholangitis. In a recent study, Misra et al. found that the reflux of duodenal contents is universally present after SEMS placement [78]. Disruption of the sphincter mechanism by transpapillary metallic stent placement may predispose to reflux of duodenal contents [79]. Some CSEMS are more prone to occlusion by food scraps than others (Wallstent 4%, ComVi stent 16%) [10]. Antireflux stents were developed in an attempt to reduce duodenobiliary reflux. Hu et al. compared partially covered antireflux SEMS with UCSEMS in a randomized study [66]. The author's group had previously demonstrated the feasibility and safety of ARMS in a pilot study [80]. ARMS were prepared by attaching a silicone valve to the duodenal end of a commonly used partially covered SEMS. Stent patency was better and cholangitis was significantly lower in ARMS group [66]. However, the results would have been more confirmatory if both the arms included covered SEMS.

In a pilot study, the occluded SEMS were replaced with ARMS in 13 patients. The patency of ARMS was longer than previous SEMS [81].

ARMS appear promising for preventing stent occlusion and cholangitis due to duodenobiliary reflux. However, the experience is limited to a handful of pilot studies only, and randomized trials are warranted to conclude their utility.

28.15.3 Drug-Eluting Stents (DES)

The concept of DES originated from intervention cardiology where these stents are being used for many years now. Drug-eluting coronary stents have superior patency than bare stents. The chemotherapeutic agents (paclitaxel or gemcitabine) used in

DES have cytotoxic, anti-inflammatory and antiproliferative properties. With respect to biliary use, DES are still in evolution and the experience is limited to few animal and small human studies [82–87]. An ideal DES should have a sustained and adequate local drug delivery and minimum possible systemic drug delivery. At present, the DES are not ready for regular use in human beings; however, the future appears promising. An ongoing RCT (NCT02460432) is comparing the efficacy of DES (Niti-S Mira-Cover III Biliary Stent) with covered biliary stent (ComVi) for the treatment of malignant biliary obstruction.

28.15.4 Biodegradable Stents

Biodegradable or bioabsorbable stents are made up of absorbent materials like polydioxanone or polylactide. Impregnation with barium sulphate imparts radiopaque character to them. The proposed advantages of these stents include elimination of the need for stent removal, reduced proliferation and future possibilities of impregnation with antitumour agents. Since their initial use in animal models over a decade ago, no significant progress has been made, and these stents are still not available for human use. These stents have weak radial expansion force, and therefore adequate expansion and subsequent stricture resolution may be hampered [88–90].

28.16 Summary

Covered metal stents play an important role in the current armamentarium for biliary drainage. The covering of CSEMS has largely overcome the problem of tissue ingrowth. The integration of antimigratory features in these stents has reduced migration rates. However, there are a lot of scopes for improvement, and an ideal CSEMS is yet to make its appearance. An ideal CSEMS should have a biodurable covering material, low AF, effective and atraumatic antimigratory design and ease of removability. If confirmed in larger trials, adding drug-eluting and antireflux capacity will improve the efficacy of CSEMS.

References

1. Kaassis M, Boyer J, Dumas R, et al. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc. 2003;57(2):178–82.
2. Prat F, Chapat O, Ducot B, et al. A randomized trial of endoscopic drainage methods for inoperable malignant strictures of the common bile duct. Gastrointest Endosc. 1998;47(1):1–7.
3. Sawas T, Al Halabi S, Parsi MA, et al. Self-expandable metal stents versus plastic stents for malignant biliary obstruction: a meta-analysis. Gastrointest Endosc. 2015;82(2):256–67.
4. Carrasco CH, Wallace S, Charnsangavej C, Richli W, Wright KC, Fanning T, Gianturco C. Expandable biliary endoprosthesis: an experimental study. AJR Am J Roentgenol. 1985;145(6):1279–81.

5. Silvis SE, Sievert CE Jr, Vennes JA, et al. Comparison of covered versus uncovered wire mesh stents in the canine biliary tract. Gastrointest Endosc. 1994;40(1):17–21.
6. Alvarado R, Palmaz JC, Garcia OJ, et al. Evaluation of polymer-coated balloon-expandable stents in bile ducts. Radiology. 1989;170(3 Pt 2):975–8.
7. Soderlund C, Linder S, Bergenzaun PE, et al. Nitinol versus steel partially covered self-expandable metal stent for malignant distal biliary obstruction: a randomized trial. Endoscopy. 2014;46(11):941–8.
8. Isayama H, Mukai T, Itoi T, et al. Comparison of partially covered nitinol stents with partially covered stainless stents as a historical control in a multicenter study of distal malignant biliary obstruction: the WATCH study. Gastrointest Endosc. 2012;76(1):84–92.
9. Isayama H, Nakai Y, Toyokawa Y, et al. Measurement of radial and axial forces of biliary self-expandable metallic stents. Gastrointest Endosc. 2009;70(1):37–44.
10. Isayama H, Nakai Y, Kawakubo K, et al. Covered metallic stenting for malignant distal biliary obstruction: clinical results according to stent type. J Hepatobil Pancreat Sci. 2011;18(5):673–7.
11. Yasumori K, Mahmoudi N, Wright KC, et al. Placement of covered self-expanding metallic stents in the common bile duct: a feasibility study. J Vasc Interv Radiol. 1993;4(6):773–8.
12. Pavlova M, Doraganova M. Hydrolytic stability of polyurethane medical adhesive dressing. Biomaterials. 1994;15:59–62.
13. Bang BW, Jeong S, Lee DH, et al. The biodurability of covering materials for metallic stents in a bile flow phantom. Dig Dis Sci. 2012;57(4):1056–63.
14. Kim DH, Kang SG, Choi JR, et al. Evaluation of the biodurability of polyurethane-covered stent using a flow phantom. Korean J Radiol. 2001;2(2):75–9.
15. Rossi P, Bezzi M, Salvatori FM, et al. Clinical experience with covered wallstents for biliary malignancies: 23-month follow-Up. Cardiovasc Intervent Radiol. 1997;20:441–7.
16. Severini A, Mantero S, Tanzi MC, et al. In vivo study of polyurethane-coated Gianturco-Rosch biliary Z-stents. Cardiovasc Intervent Radiol. 1999;22(6):510–4.
17. Isayama H, Komatsu Y, Tsujino T, et al. A prospective randomised study of "covered" versus "uncovered" diamond stents for the management of distal malignant biliary obstruction. Gut. 2004;53(5):729–34.
18. Poley JW, et al. A prospective group sequential study evaluating a new type of fully covered self-expandable metal stent for the treatment of benign biliary strictures. Gastrointest Endosc. 2012;75(4):783–9.
19. Catalano M, Linder J, George S, et al. Treatment of symptomatic distal common bile duct stenosis secondary to chronic pancreatitis: comparison of single vs. multiple simultaneous stents. Gastrointest Endosc. 2004;60:945–52.
20. Costamagna G, Pandolfi M, Mutignani M, et al. Long-term results of endoscopic management of postoperative bile duct strictures with increasing numbers of stents. Gastrointest Endosc. 2001;54:162–8.
21. Draganov P, Hoffman B, Marsh W, et al. Long-term outcome in patients with benign biliary strictures treated endoscopically with multiple stents. Gastrointest Endosc. 2002;55(6):680.
22. Cote GA, Xu H, Slivka A, et al. Fully covered metallic stents achieve comparable efficacy in a shorter time to plastic stents for the first-line endoscopic treatment of benign biliary strictures: interim results of a multicenter, randomized, controlled trial. Gastrointest Endosc. 2015;81(5S):AB194.
23. Devière J, Nageshwar Reddy D, Püspök A, et al. Successful management of benign biliary strictures with fully covered self-expanding metal stents. Gastroenterology. 2014;147(2):385–95.
24. Kahaleh M, Brijbassie A, Sethi A, et al. Multicenter trial evaluating the use of covered self expanding metal stents in benign biliary strictures: time to revisit our therapeutic options? J Clin Gastroenterol. 2013;47(8):695–9.
25. Haapamäki C, Kylänpää L, Udd M, et al. Randomized multicenter study of multiple plastic stents vs. covered self-expandable metallic stent in the treatment of biliary stricture in chronic pancreatitis. Endoscopy. 2015;47(7):605–10.

26. Kaffes A, Griffin S, Vaughan R, et al. A randomized trial of a fully covered self expandable metallic stent versus plastic stents in anastomotic biliary strictures after liver transplantation. Therap Adv Gastroenterol. 2014;7(2):64–71.
27. Kao D, Zepeda-Gomez S, Tandon P, et al. Managing the post liver transplantation anastomotic biliary stricture: multiple plastic versus metal stents: a systematic review. Gastrointest Endosc. 2013;77(5):679–91.
28. Siiki A, Helminen M, Sand J, et al. Covered self-expanding metal stents may be preferable to plastic stents in the treatment of chronic pancreatitis-related biliary strictures: a systematic review comparing 2 methods of stent therapy in benign biliary strictures. J Clin Gastroenterol. 2014;48(7):635–43.
29. Tarantino I, Mangiavillano B, Di Mitri R, et al. Fully covered self-expandable metallic stents in benign biliary strictures: a multicenter study on efficacy and safety. Endoscopy. 2012;44(10):923–7.
30. Park D, Lee S, Lee T, et al. Anchoring flap versus flared end, fully covered self-expandable metal stents to prevent migration in patients with benign biliary strictures: a multicenter, prospective, comparative pilot study. Gastrointest Endosc. 2011;73:64–70.
31. Kahaleh M, Behm B, Clarke BW, et al. Temporary placement of covered self-expandable metal stents in benign biliary strictures: a new paradigm? Gastrointest Endosc. 2008;67(3):446–54.
32. Mahajan A, Ho H, Sauer B, et al. Temporary placement of fully covered self-expandable metal stents in benign biliary strictures: midterm evaluation. Gastrointest Endosc. 2009;70(2):303–9.
33. Walter D, Laleman W, Jansen JM, et al. A fully covered self-expandable metal stent with antimigration features for benign biliary strictures: a prospective, multicenter cohort study. Gastrointest Endosc. 2015;81(5):1197–203.
34. Irani S, Baron TH, Akbar A, et al. Endoscopic treatment of benign biliary strictures using covered self-expandable metal stents (CSEMS). Dig Dis Sci. 2014;59(1):152–60.
35. Tarantino I, Barresi L, Curcio G, et al. Definitive outcomes of self-expandable metal stents in patients with refractory post-transplant biliary anastomotic stenosis. Dig Liver Dis. 2015;pii:S1590-8658(15)00226-1.
36. Cerecedo-Rodriguez J, Phillips M, Figueroa-Barojas P, et al. Self expandable metal stents for anastomotic stricture following liver transplant. Dig Dis Sci. 2013;58(9):2661–6.
37. Saxena P, Diehl DL, Kumbhari V, et al. A US multicenter study of safety and efficacy of fully covered self-expandable metallic stents in benign extrahepatic biliary strictures. Dig Dis Sci. 2015;60:3442–8.
38. Itoi T, Yasuda I, Doi S, et al. Endoscopic hemostasis using covered metallic stent placement for uncontrolled post-endoscopic sphincterotomy bleeding. Endoscopy. 2011;43(4):369–72.
39. Shah JN, Marson F, Binmoeller KF. Temporary self-expandable metal stent placement for treatment of post-sphincterotomy bleeding. Gastrointest Endosc. 2010;72(6):1274–8.
40. Valats J, Funakoshi N, Bauret P, et al. Covered self-expandable biliary stents for the treatment of bleeding after ERCP. Gastrointest Endosc. 2013;78(1):183–7.
41. Irani S, Baron TH, Law R, et al. Endoscopic treatment of nonstricture-related benign biliary diseases using covered self-expandable metal stents. Endoscopy. 2015;47(4):315–21.
42. Canena J, Liberato M, Meireles L, et al. A non-randomized study in consecutive patients with postcholecystectomy refractory biliary leaks who were managed endoscopically with the use of multiple plastic stents or fully covered self-expandable metal stents. Gastrointest Endosc. 2015;82(1):70–8.
43. Cerefice M, Sauer B, Javaid M, et al. Complex biliary stones: treatment with removable self expandable metal stents: a new approach (with videos). Gastrointest Endosc. 2011;74(3):520–6.
44. Jun CH, Park CH, Jin-Jeon M, et al. Feasibility of self-expandable metal stent for preservation of sphincter of Oddi function in patients with common bile duct stones: a pilot study. Gastrointest Endosc. 2015;pii:S0016-5107(15)00051-6.
45. Siddiqui AA, Mehendiratta V, Loren D, et al. Fully covered self-expandable metal stents are effective and safe to treat distal malignant biliary strictures, irrespective of surgical resectability status. J Clin Gastroenterol. 2011;45(9):824–7.

46. Kahaleh M, Brock A, Conaway MR, et al. Covered self-expandable metal stents in pancreatic malignancy regardless of resectability: a new concept validated by a decision analysis. Endoscopy. 2007;39(4):319–24.
47. Walter D, van Boeckel PG, Groenen MJ, et al. Cost efficacy of metal stents for palliation of extrahepatic bile duct obstruction in a randomized controlled trial. Gastroenterology. 2015;149(1):130–8.
48. Artinyan A, Anaya DA, McKenzie S, et al. Neoadjuvant therapy is associated with improved survival in resectable pancreatic adenocarcinoma. Cancer. 2011;117(10):2044–9):15.
49. Petrelli F, Coinu A, Borgonovo K, et al. FOLFIRINOX-based neoadjuvant therapy in borderline resectable or unresectable pancreatic cancer: a meta-analytical review of published studies. Pancreas. 2015;44(4):515–21.
50. Ge PS, Hamerski CM, Watson RR, et al. Plastic biliary stent patency in patients with locally advanced pancreatic adenocarcinoma receiving downstaging chemotherapy. Gastrointest Endosc. 2015;81:360–6.
51. Siddiqui AA, Mehendiratta V, Loren D, et al. Self-expanding metal stents (SEMS) for preoperative biliary decompression in patients with resectable and borderline-resectable pancreatic cancer: outcomes in 241 patients. Dig Dis Sci. 2013;58(6):1744–50.
52. González-Huix F, Figa M, Alburquerque M, et al. Metallic vs. plastic stent in the preoperative treatment for biliary obstruction of resectable periampullary tumors: a randomized controlled trial [abstract]. Gastrointest Endosc. 2014;79:AB401.
53. Tol JA, van Hooft JE, Timmer R, et al. Metal or plastic stents for preoperative biliary drainage in resectable pancreatic cancer. Gut. 2015;pii:gutjnl-2014-308762.
54. Born P, Neuhaus H, Rosch T, et al. Initial experience with a new, partially covered Wallstent for malignant biliary obstruction. Endoscopy. 1996;28:699–702.
55. Hausegger KA, Thurnher S, Bordendofer G, et al. Treatment of malignant biliary obstruction with polyurethane-covered Wallstents. AJR Am J Roentgenol. 1998;170:403–8.
56. Kullman E, Frozanpor F, Söderlund C, et al. Covered versus uncovered self-expandable nitinol stents in the palliative treatment of malignant distal biliary obstruction: results from a randomized, multicenter study. Gastrointest Endosc. 2010;72:915–23.
57. Lee JH, Krishna SG, Singh A, et al. Comparison of the utility of covered metal stents versus uncovered metal stents in the management of malignant biliary strictures in 749 patients. Gastrointest Endosc. 2013;78(2):312–24.
58. Telford JJ, Carr-Locke DL, Baron TH, et al. A randomized trial comparing uncovered and partially covered self-expandable metal stents in the palliation of distal malignant biliary obstruction. Gastrointest Endosc. 2010;72:907–14.
59. Lee SJ, Kim MD, Lee MS, et al. Comparison of the efficacy of covered versus uncovered metallic stents in treating inoperable malignant common bile duct obstruction: a randomized trial. J Vasc Interv Radiol. 2014;25(12):1912–20.
60. Ung KA, Stotzer PO, Nilsson A, et al. Covered and uncovered self-expandable metallic Hanarostents are equally efficacious in the drainage of extrahepatic malignant strictures. Results of a double-blind randomized study. Scand J Gastroenterol. 2013;48:459–65.
61. Yang MJ, Kim JH, Yoo BM, et al. Partially covered versus uncovered self-expandable nitinol stents with anti-migration properties for the palliation of malignant distal biliary obstruction: a randomized controlled trial. Scand J Gastroenterol. 2015;50(12):1490–9.
62. Gwon DI, Ko GY, Kim JH, et al. A comparative analysis of PTFE covered and uncovered stents for palliative treatment of malignant extrahepatic biliary obstruction. AJR Am J Roentgenol. 2010;195(6):W463–9.
63. Krokidis M, Fanelli F, Orgera G, et al. Percutaneous palliation of pancreatic head cancer: Randomized comparison of ePTFE/FEP-covered versus uncovered nitinol biliary stents. Cardiovasc Intervent Radiol. 2011;34:352–61.
64. Krokidis M, Fanelli F, Orgera G, et al. Percutaneous treatment of malignant jaundice due to extrahepatic cholangiocarcinoma: covered viabil stent versus uncovered wallstents. Cardiovasc Intervent Radiol. 2010;33:97–106.

65. Kitano M, Yamashita Y, Tanaka K, et al. Drastic improvement of patency of covered self-expandable metal stents for distal biliary obstruction caused by pancreatic carcinomas: a randomized multicenter study comparing covered and uncovered stents. Gastrointest Endosc. 2013;108(11):1713–22.
66. Hu B, Wang TT, Wu J, et al. Antireflux stents to reduce the risk of cholangitis in patients with malignant biliary strictures: a randomized trial. Endoscopy. 2014;46(2):120–6.
67. Nakai Y, Isayama H, Kawakubo K, et al. Metallic stent with high axial force as a risk factor for cholecystitis in distal malignant biliary obstruction. J Gastroenterol Hepatol. 2014;29(7):1557–62.
68. Shimizu S, Naitoh I, Nakazawa T, et al. Predictive factors for pancreatitis and cholecystitis in endoscopic covered metal stenting for distal malignant biliary obstruction. J Gastroenterol Hepatol. 2013;28(1):68–72.
69. Kawakubo K, Isayama H, Nakai Y, et al. Risk factors for pancreatitis following transpapillary self-expandable metal stent placement. Surg Endosc. 2012;26(3):771–6.
70. Hayashi T, Kawakami H, Osanai M, et al. No benefit of endoscopic sphincterotomy before biliary placement of self-expandable metal stents for unresectable pancreatic cancer. Clin Gastroenterol Hepatol. 2015;13:1151–8.
71. Wang AY, Ellen K, Berg CL, et al. Fully covered self-expandable metallic stents in the management of complex biliary leaks: preliminary data—a case series. Endoscopy. 2009;781–786(9):41.
72. Phillips MS, Bonatti H, Sauer BG, et al. Elevated stricture rate following the use of fully covered self-expandable metal biliary stents for biliary leaks following liver transplantation. Endoscopy. 2011;43:512–7.
73. Moon JH, Choi HJ, Koo HC, et al. Feasibility of placing a modified fully covered self-expandable metal stent above the papilla to minimize stent induced bile duct injury in patients with refractory benign biliary strictures. Gastrointest Endosc. 2012;75(5):1080–5.
74. Mangiavillano B, Manes G, Baron TH, et al. The use of double lasso, fully covered self-expandable metal stents with new "anchoring flap" system in the treatment of benign biliary diseases. Dig Dis Sci. 2014;59:2308–13.
75. Ryozawa S, Isayama H, Maetani I, et al. A prospective multicenter study of a fully-covered metal stent in patients with distal malignant biliary obstruction: WATCH-2 study. Gastrointest Endosc. 2013;77:AB309.
76. Isayama H, Kawakubo K, Nakai Y, et al. A novel fully covered laser-cut nitinol stent with antimigration properties for non-resectable distal malignant biliary obstruction: a multicenter feasibility study. Gut Liver. 2013;7:725–30.
77. Park JK, Moon JH, Choi HJ, et al. Anchoring of a fully covered self-expandable metal stent with a 5F double pigtail plastic stent to prevent migration in the management of benign biliary strictures. Am J Gastroenterol. 2011;106(10):1761–5.
78. Misra SP, Dwivedi M. Reflux of duodenal contents and cholangitis in patients undergoing self-expanding metal stent placement. Gastrointest Endosc. 2009;70(2):317–21.
79. Okamoto T, Fujioka S, Yanagisawa S, et al. Placement of a metallic stent across the main duodenal papilla may predispose to cholangitis. Gastrointest Endosc. 2006;63(6):792–6.
80. Hu B, Wang TT, Shi ZM, et al. A novel antireflux metal stent for the palliation of biliary malignancies: a pilot feasibility study (with video). Gastrointest Endosc. 2011;73:143–8.
81. Hamada T, Isayama H, Nakai Y, et al. Novel antireflux covered metal stent for recurrent occlusion of biliary metal stents: a pilot study. Dig Endosc. 2014;26(2):264–9.
82. Lee DK, Kim HS, Kim KS, Lee WJ, Kim HK, Won YH, et al. The effect on porcine bile duct of a metallic stent covered with a paclitaxel-incorporated membrane. Gastrointest Endosc. 2005;61:296–301.
83. Lee SS, Shin JH, Han JM, Cho CH, Kim MH, Lee SK, et al. Histologic influence of paclitaxel-eluting covered metallic stents in a canine biliary model. Gastrointest Endosc. 2009;69:1140–7.

84. Suk KT, Kim JW, Kim HS, Baik SK, Oh SJ, Lee SJ, et al. Human application of a metallic stent covered with a paclitaxel-incorporated membrane for malignant biliary obstruction: multicenter pilot study. Gastrointest Endosc. 2007;66:798–803.
85. Song TJ, Lee SS, Yun SC, Park do H, Seo DW, Lee SK, et al. Paclitaxel-eluting covered metal stents versus covered metal stents for distal malignant biliary obstruction: a prospective comparative pilot study. Gastrointest Endosc. 2011;73:727–33.
86. Jang SI, Kim JH, Kim M, Yang S, Jo EA, Lee JW, et al. Porcine feasibility and safety study of a new paclitaxel-eluting biliary stent with a Pluronic-containing membrane. Endoscopy. 2012;44:825–31.
87. Chung MJ, Kim H, Kim KS, Park S, Chung JB, Park SW. Safety evaluation of self-expanding metallic biliary stents eluting gemcitabine in a porcine model. J Gastroenterol Hepatol. 2012;27:261–7.
88. Ginsberg G, Cope C, Shah J, et al. In vivo evaluation of a new bioabsorbable self-expanding biliary stent. Gastrointest Endosc. 2003;58:777–84.
89. Itoi T, Kasuya K, Abe Y, Isayama H. Endoscopic placement of a new short-term biodegradable pancreatic and biliary stent in an animal model: a preliminary feasibility study (with videos). J Hepatobiliary Pancreat Sci. 2011;18:463–7.
90. Yamamoto K, Yoshioka T, Furuichi K, et al. Experimental study of poly-L-lactic acid biodegradable stents in normal canine bile ducts. Cardiovasc Intervent Radiol. 2011;34:601–8.

Chapter 29
Stent in Stenting

Osamu Hasebe, Yasuhide Ochi, and Takayuki Watanabe

Abstract Stent occlusion remains a major problem in biliary stenting, and emergency treatment is required. Various second stents, such as plastic stent (PS), uncovered self-expanding metallic stent (SEMS), and covered SEMS, are selected considering primary inserted stent, causes of stent occlusion, and prognosis of the patients. If large amounts of debris or food residue exist in the occluded stent or bile duct, we should remove them before second stent insertion for longer patency. Rate of reocclusion, stent patency, and survival time are not significantly different among PS, uncovered SEMS, and covered SEMS in meta-analysis. Re-intervention of bilateral placement of uncovered SEMS in malignant hilar biliary obstruction (MHBO) is relatively difficult, especially in patients with partial stent in stent placement. Loop technique of guidewire, use of bendable catheter, balloon dilation of stent mesh, and the use of thin delivery system should be attempted for successful re-intervention.

Keywords Stent in stenting • Re-intervention • Self-expanding metallic stent (SEMS) • Malignant hilar biliary obstruction (MHBO)

29.1 Occlusion of Primary Stent and Its Management

Occlusion of the biliary stent occurs suddenly combined with acute cholangitis; we have to treat them immediately. Delayed treatment may result in death because majority of them are elderly patients, suffering from malignancy or undergoing chemotherapy. In emergency ERCP, it is necessary to minimalize cholangiography to avoid worsening of cholangitis and progression to sepsis. If large amounts of debris or food residue exist in the occluded stent or bile duct, we have to remove them before second stent insertion for longer patency [1] (Fig. 29.1). In patients combined with severe cholangitis or high risk of adequate cholangiography, endoscopic nasobiliary drainage (ENBD) for several days following second stent placement is recommended (Fig. 29.2).

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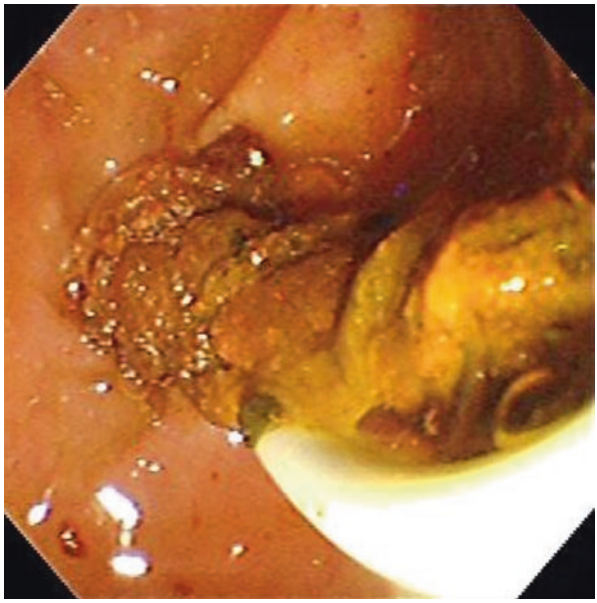

Fig. 29.1 Removal of debris using balloon catheter before second stent placement

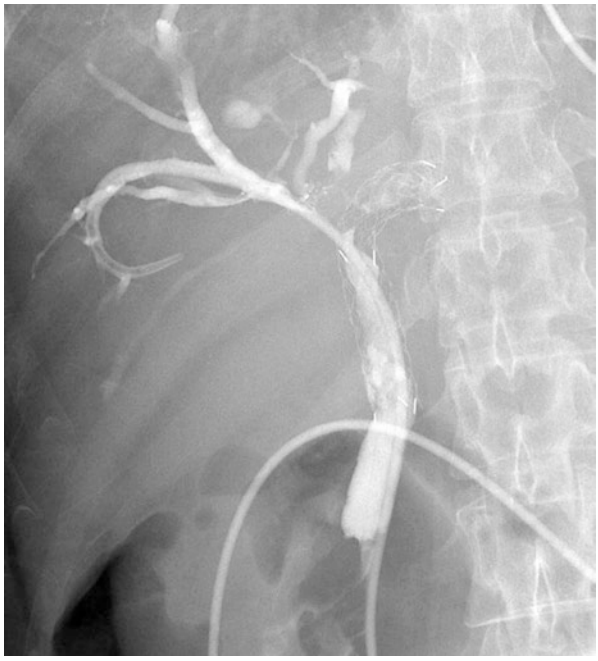

Fig. 29.2 ENBD before second stent placement

Insertion of covered SEMS is reported to be effective in patients with an occluded uncovered SEMS [2], and patency of covered SEMS is similar between primary and secondary placement [3, 4]. However, rate of reocclusion, stent patency, and survival time are not significantly different among PS, uncovered SEMS, and covered

SEMS in meta-analysis [5]. Considering cost-benefit, PS is suitable and enough for patients with poor prognosis shorter than three months.

29.1.1 Plastic Stent (PS)

Occlusion of PS is due to debris. Reinsertion of new PS is performed after removal of occluded stent. Although PS smaller than 8.5 Fr is able to extract through forceps lumen of the scope, the other PS should be extracted with the scope grasping occluded stents. Screw drill (Soehendra stent retriever, Cook Med.) is useful in difficult cases to perform re-cannulate to the bile duct.

29.1.2 Covered Self-Expanding Metallic Stent (Covered SEMS)

Occlusion of covered SEMS is due to debris, food residue, tumor overgrowth, and rarely tumor ingrowth. As covered SEMS is able to remove in most cases, new covered SEMS could be inserted after removal of occluded stent. Long-covered SEMS is available and may expect longer patency in patients with stent occlusion due to food residue (Fig. 29.3). Tumor ingrowth rarely occurs in covered SEMS placed for long periods; we must pay close attention to bleeding and injury of the bile duct for extraction. In these cases removal of covered SEMS is not necessary, and second stent should be placed stent in stenting method.

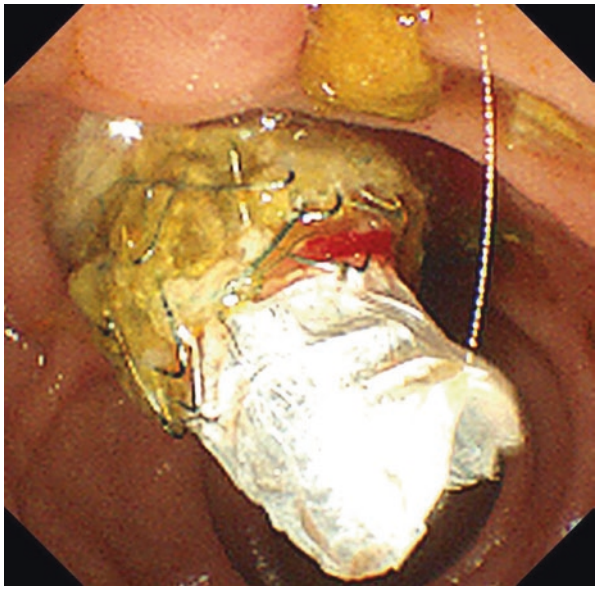

Fig. 29.3 Long-covered SEMS placement in patient with stent occlusion due to food residue

29.1.3 Uncovered Self-Expanding Metallic Stent (Uncovered SEMS)

Occlusion of uncovered SEMS is due to tumor ingrowth, tumor overgrowth, and debris. As uncovered SEMS is not able to extract because filaments of metallic stent are buried in the bile duct, another stents should be inserted in occluded uncovered SEMS. Covered SEMS is favorable as second stent [2] in case without hilar bile duct involvement (Fig. 29.4). On the other hand, uncovered SEMS or PS is selected in case with hilar bile duct involvement. Although uncovered SEMS tends to be selected for patients having better prognosis, PS has similar stent patency in meta-analysis [5] and is suitable for patients having poor prognosis shorter than three months considering cost-benefit (Fig. 29.5). In performing re-intervention of uncovered SEMS, guidewire sometimes passes through stent mesh (Fig. 29.6). In this condition, loop technique of guidewire (Fig. 29.7), use of bendable catheter (Swing-tip catheter, Olympus Med. Systems) (Fig. 29.8), and centering

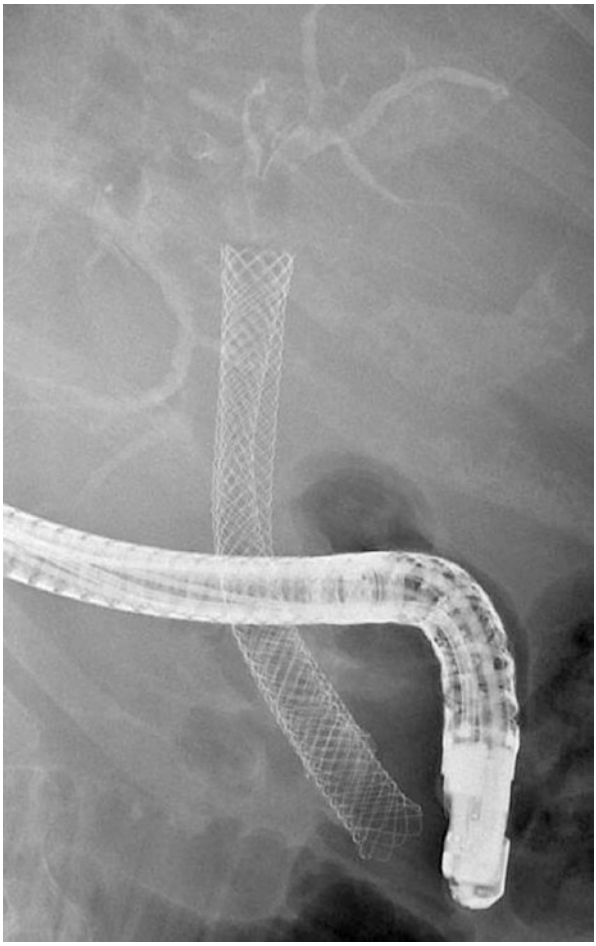

Fig. 29.4 Covered SEMS in uncovered SEMS in patient without hilar bile duct involvement

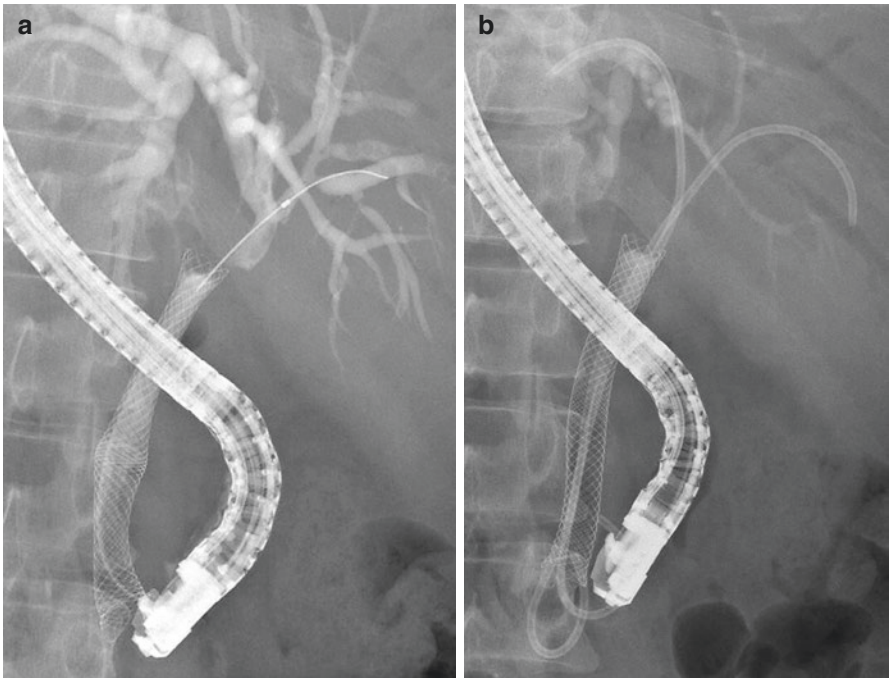

Fig. 29.5 Re-intervention using PS in patient with poor prognosis. (**a**) Tumor overgrowth to hilar bile duct. (**b**) Multiple PS placement in uncovered SEMS

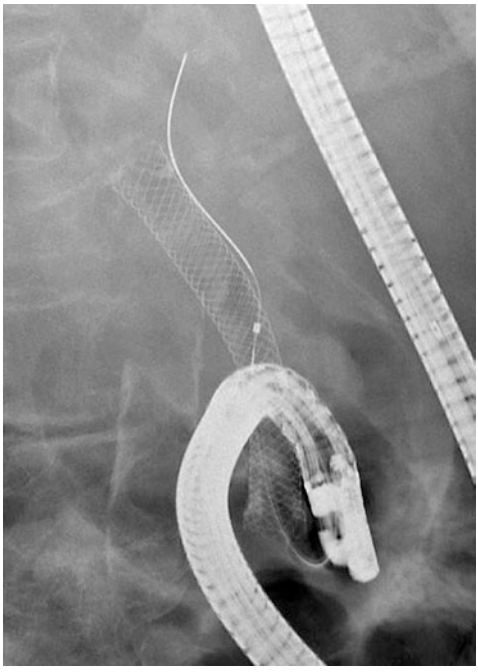

Fig. 29.6 Re-intervention of uncovered SEMS (guidewire passing through stent mesh)

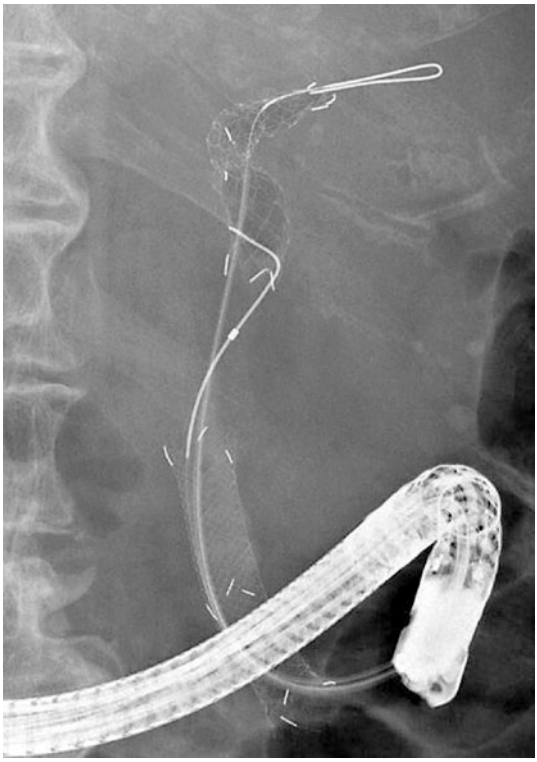

Fig. 29.7 Re-intervention of uncovered SEMS (loop technique of guidewire)

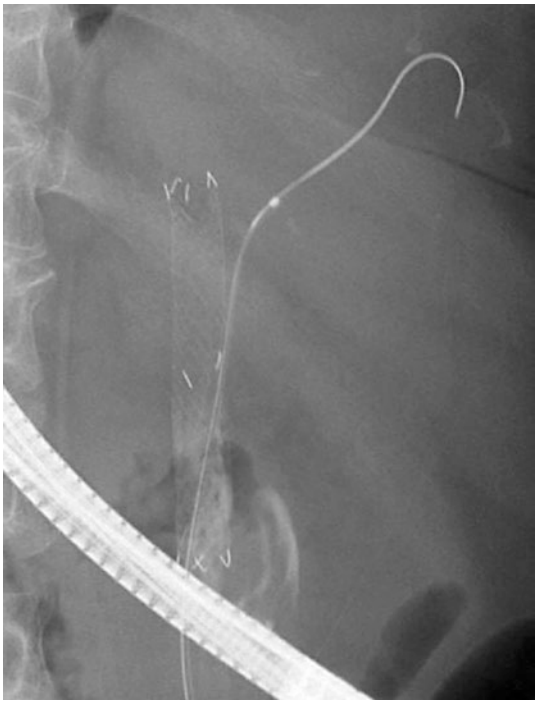

Fig. 29.8 Re-intervention of uncovered SEMS (use of bendable catheter)

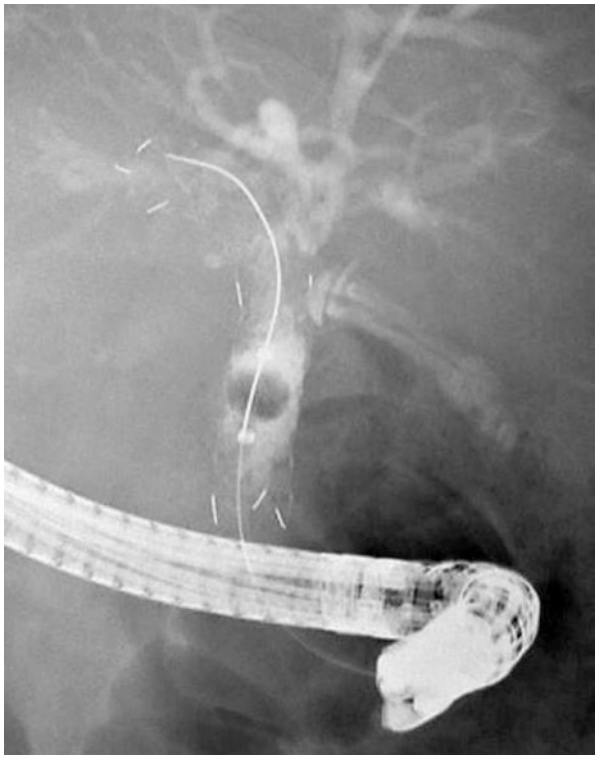

Fig. 29.9 Re-intervention of uncovered SEMS (centering of guidewire using balloon catheter)

of guidewire with balloon catheter (Fig. 29.9) are useful to access true lumen or intended bile duct.

29.2 Stent in Stenting in Malignant Hilar Biliary Obstruction (MHBO)

As patency of SEMS is reported to be longer than PS in MHBO, uncovered SEMS is widely used for primary stent. It is controversial which drainage is better, unilateral or bilateral stenting, partial stent in stent, or side by side placement [6]. Bilateral stenting is successfully performed in progress of endoscopic devices, such as uncovered SEMS with a large open-celled wire mesh (Niti-S Large cell D-type, Century Med. Corp.) and 6Fr thin delivery system (Zilver 635, Cook Med. Bile Rush, Piolax Med.). However, re-intervention of bilateral stenting is more difficult than unilateral stenting. In MHBO stent patency and survival time of second stents showed no statistical difference between PS and SEMS [7]. We usually use uncovered SEMS as second stent for patients with better prognosis longer than three months, but PS is selected for the other cases.

29.2.1 Unilateral Placement of Uncovered SEMS

If occlusion of the stent is observed in primary inserted uncovered SEMS, second stent should be placed in the same portion in stent in stenting method. On the other hand, inadequate drainage or cholangitis due to undrained bile duct is observed; additional stenting should be considered in undrained bile duct.

29.2.2 Bilateral Partial Stent in Stent Placement of Uncovered SEMS

Although success rate of re-intervention is reported to be high in bilateral partial stent in stent placement [8], we have some difficulty in passing guidewire or inserting delivery system through complicated stent mesh. Balloon dilation of stent mesh and uncovered SEMS with thin delivery system is useful in these cases (Fig. 29.10). Multiple PS (Fig. 29.11) or inside placement of PS (Fig. 29.12) is favorable considering re-re-intervention and prevention of cholangitis. Even though bilateral additional stenting could not be achieved, one additional stenting is enough in some degree.

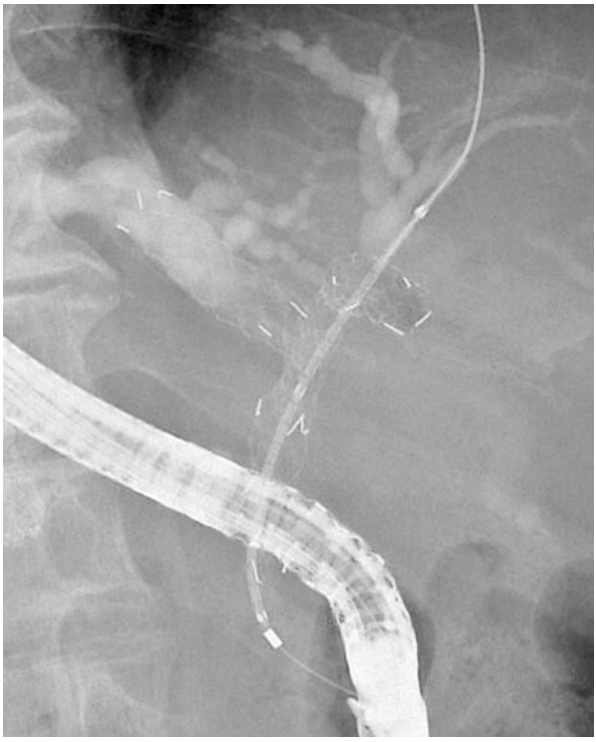

Fig. 29.10 Use of thin delivery system in additional stenting through stent mesh

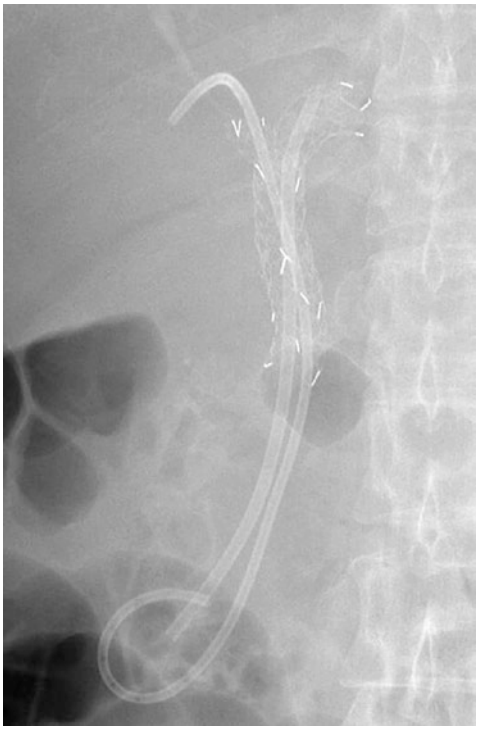

Fig. 29.11 Multiple PS placement after bilateral partial stent in stent placement

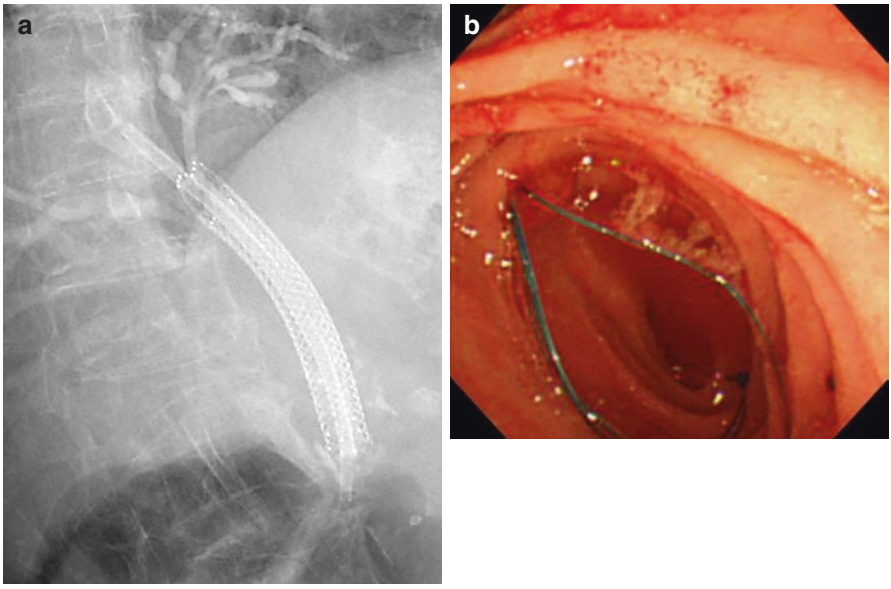

Fig. 29.12 Inside PS placement after uncovered SEMS in patient with hilar bile duct involvement. (**a**) The distal end of PS was placed above the papilla. (**b**) Two threads tied with distal end of PS were seen in duodenum

29.2.3 Bilateral Side by Side Placement of Uncovered SEMS

Re-intervention of bilateral side by side placement is easier than partial stent in stent placement in MHBO. Most important point is to adjust lower end of two uncovered SEMS in common bile duct in primary stenting. That would make possible to insert guidewire in two parallel stents easily (Fig. 29.13).

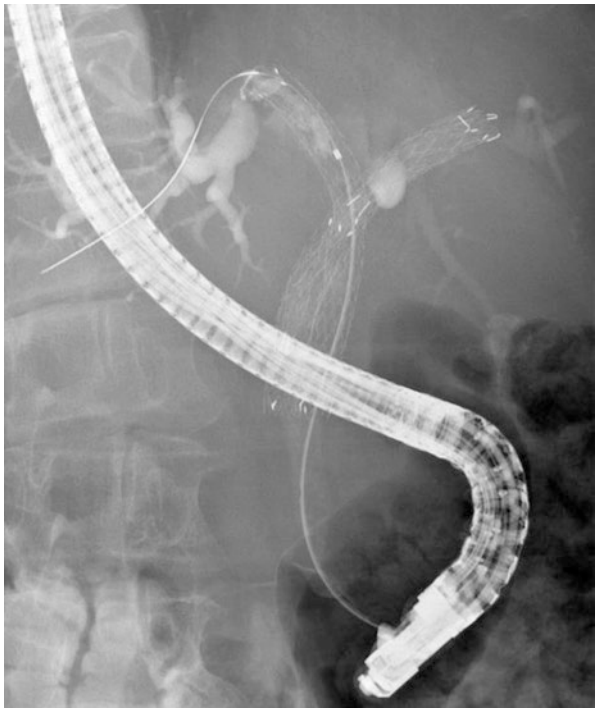

Fig. 29.13 Additional bilateral uncovered SEMS placement after bilateral side by side placement

References

1. Okabe Y, Ishida Y, Ushijima T, et al. Technique of reintervention for stent dysfunction in patients with malignant hilar biliary stricture. Dig Endosc. 2013;25(Suppl.2):90–3.
2. Togawa O, Kawabe T, Isayama H, et al. Management of occluded metallic stents in patients with malignant distal biliary obstructions using covered metallic stents. J Clin Gastroenterol. 2008;42:546–9.
3. Ornellas LC, Stefanidis G, Chuttani R, et al. Covered Wallstents for palliation of malignant biliary obstruction : primary stent placement versus reintervention. Gastrointest Endosc. 2009;70:676–83.
4. Kida M, Miyazawa S, Iwai T, et al. Endoscopic management of malignant biliary obstruction by means of covered metallic stents: primary stent placement vs. Re-intervention. Endoscopy. 2011;43:1039–44.
5. Shah T, Desai S, Haque M, et al. Management of occluded metal stents in malignant biliary obstruction: similar outcomes with second metal stents compared to plastic stents. Dig Dis Sci. 2012;57:2765–73.
6. Kawakami H, Itoi T, Kuwatani M, et al. Technical tips and troubleshooting of endoscopic biliary drainage for unresectable malignant hilara biliary obstruction. J Hepatobiliary Pancreat Sci. 2015;22:E12–21.
7. Ridtitid W, Perknimitr R, Janchai A, et al. Outcome of second interventions for occluded metallic stents in patients with malignant biliary obstruction. Surg Endosc. 2010;24:2216–20.
8. Kato H, Tsutsumi K, Kawamoto H, et al. Current status of endoscopic biliary drainage for unresectable malignant hilar biliary strictures. World J Gastroinntest Endosc. 2015;7:1032–8.

Part VIII
POCPS

Chapter 30
Peroral Cholangioscopy for the Diagnosis of Biliary Tract Diseases

Toshio Tsuyuguchi, Harutoshi Sugiyama, Yuji Sakai, and Naoya Kato

Abstract Peroral cholangioscopy permits direct visualization and tissue sampling of indeterminate biliary lesions and treats difficult bile duct stones. Accurate differential diagnosis is essential in the planning of therapy, can avoid unnecessary surgery in cases of benign disease, and aids in assessing the potential resectability of tumors. The main indication of cholangioscopy is diagnosis of indeterminate biliary strictures, because brushing cytology and biopsies are limited by relative low sensitivity. Standard peroral cholangioscopy is a mother-baby system. The newly developed video peroral cholangioscope (CHF-B260: Olympus, Japan) can provide not only high-resolution digital images but also narrowband imaging which may identify neoplasm. Mother-baby scope system has not gained widespread acceptance, because of its fragility and the need for two skillful endoscopists. To overcome this disadvantage, single-operator system (SpyGlass: Boston Scientific, USA) was developed and used frequently. Recently, direct peroral cholangioscopy (DC) by using an ultraslim video scope has been reported. Compared to standard mother-baby system, DC has relatively large working channel and durability but technical difficulty in the insertion into the bile duct. In addition, intrahepatic bile duct exploration is arduous task for DC. A meta-analysis of SpyGlass cholangioscopy showed that targeted biopsies under cholangioscope cannot improve diagnostic power compared to conventional brush cytology and biopsies. Therefore better visualization is essential for improving sensitivity of malignant biliary strictures. In this chapter, we reviewed peroral cholangioscopy, focusing on diagnosis of the biliary tract diseases.

Keywords Peroral cholangioscopy • Bile duct stricture • Bile duct carcinoma

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Abbreviations

CT Computed tomography
ERC Endoscopic retrograde cholangiography
ERCP Endoscopic retrograde cholangiopancreatography

30.1 Introduction

Direct intraductal visualization of biliary pathology has long been recognized as the best way to evaluate indeterminate biliary lesions. Although both of the percutaneous and peroral cholangioscopy can be used, the peroral approach is preferable for a less invasive method. Peroral cholangioscopy (mother-baby scope system) was initially described in the mid-1970s [1] as fiber-optic cholangioscopes which were difficult to use and easily fractured during passage over the elevator of the duodenoscope [2, 3]. Images through the use of video adapters may be insufficiently less than optimal. Recently, video cholangioscopy has been developed, which facilitates higher-quality images of the bile duct than previous fiber-optic scopes [4]. However, peroral cholangioscopy has not gained widespread acceptance, because of the need for two skillful endoscopists [5]. To overcome this disadvantage, the SpyGlass single-operator direct visualization system was developed and first clinically tested in 2007 by Chen et al. [6]. Since then, various groups have reported their experience for diagnosis and treatment of biliary diseases [7–13]; however, image quality is suboptimal with the fiber-optic scope. Recently, direct peroral video cholangioscopy, using ultraslim video endoscope with high-resolution video imaging and a relatively large working channel of 2 mm for accessories, has been reported [14, 15], however, not can be accepted as a standard cholangioscopy due to its technical difficulty. In this chapter, current status of peroral cholangioscopy was reviewed, focusing on the diagnosis of biliary tract diseases.

30.2 Methods

30.2.1 Mother-Baby Scope System

Mother-baby scope system was the standard peroral cholangioscopy platform. Initially used scopes were fiber-optic, and its image quality was suboptimal. A video cholangioscope (CHF-B260, Olympus, Japan) has been developed, which facilitates high-resolution digital images than those of previous fiber-optic scope (Fig. 30.1). The video cholangioscope can provide not only white light observation but also narrowband imaging (NBI) [16]. NBI has been introduced to emphasize mucosal surface abnormalities by filtering light in the green and blue spectrums, resulting in

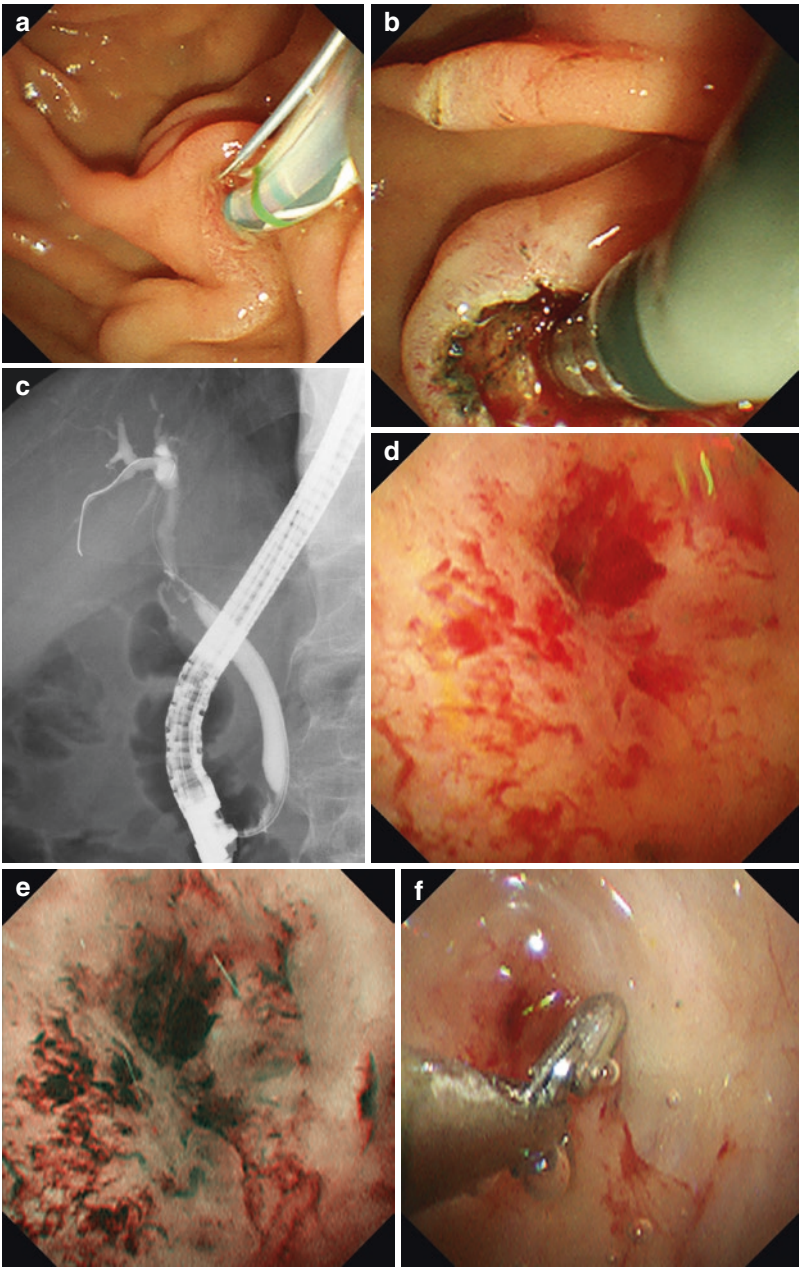

Fig. 30.1 Method of mother-baby system. Endoscopic images showing (**a**) endoscopic sphincterotomy and (**b**) insertion of baby scope into the bile duct. X-ray showing (**c**) extrahepatic bile duct stricture. Peroral video cholangioscopic views of (**d**) white light imaging and (**e**) narrowband imaging showing extrahepatic bile duct carcinoma with tortuous dilated vessels. Video cholangioscopic view showing (**f**) targeted biopsy. X-ray showing (**g**) cholangioscopy and biopsy forceps

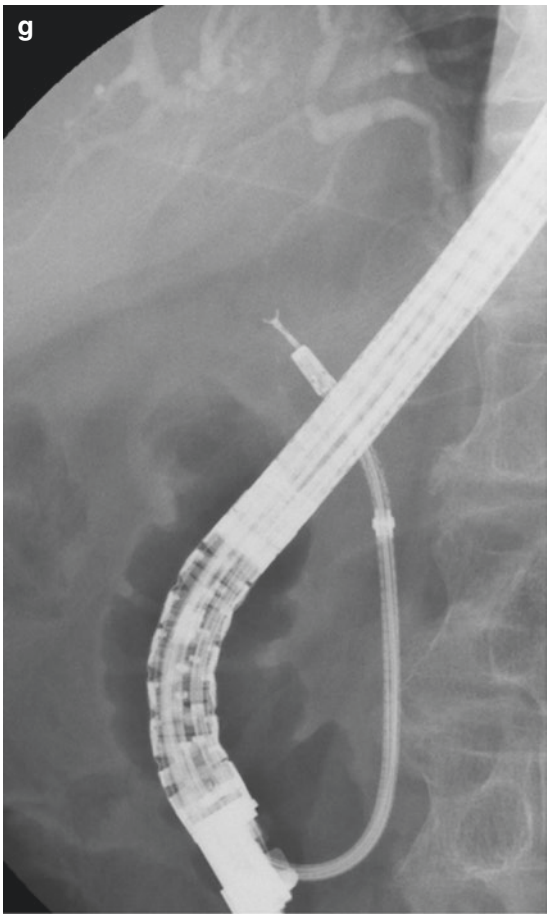

Fig. 30.1 (continued)

better diagnosis of gastrointestinal lesions [17]. Mother-baby scope system required two experienced endoscopists, and the tip part of cholangioscope can be easily broken by the elevator of mother duodenoscope (TJF-260V, Olympus, Japan). Therefore endoscopists who operate mother scope should avoid putting a load on the tip part of the baby scope during the procedure. To insert cholangioscope into the bile duct, endoscopic sphincterotomy was performed first (Fig. 30.1a). Then the baby scope was carefully inserted into the bile duct with or without a guidewire assistant (Fig. 30.1b). Saline irrigation or carbon dioxide insufflation is necessary to obtain fine cholangioscopic view. Compared with saline irrigation, carbon dioxide insufflation can clear the visual field more quickly [18]. Saline irrigation, however, can achieve better quality of images in patients with severe stenosis or protruding papillary lesions. Saline irrigation becomes necessary when using NBI (Fig. 30.1e), because both of bile and blood appear red under NBI observation.

30.2.2 Single-Operator Systems

Conventional peroral cholangioscopy system, with limited maneuverability and inadequate irrigation, required two experienced endoscopists. SpyGlass (Boston Scientific, Natick, Massachusetts, USA) was developed for single-operator systems, equipped with four-way tip deflection and separate irrigation channels that offered a good luminal view (Fig. 30.2). However, the fiber-optic scope was inferior in image quality compared with video scope (Fig. 30.3), resulting in limited use in diagnosing indeterminate biliary lesions [19]. In 2015, new SpyGlass system has equipped a single-use video scope to improve its image quality. Clinical utility of the new system is now awaiting further investigation.

30.2.3 Direct Peroral Video Cholangioscopy

Recently, direct peroral video cholangioscopy (DC) by using an ultraslim upper GI endoscope has been reported [14]. Compared to criterion standard mother-baby system, ultraslim endoscope was equipped with high-resolution video imaging and relatively large working channel [20–23]. DC requires an adequate endoscopic sphincterotomy to facilitate insertion of the endoscope. Insertion rates have improved with intraductal anchoring balloons. Before the insertion of the ultraslim endoscope into the bile duct, balloon catheter with guidewire was lodged in a branch of the intrahepatic duct. The endoscope was then advanced over the balloon catheter

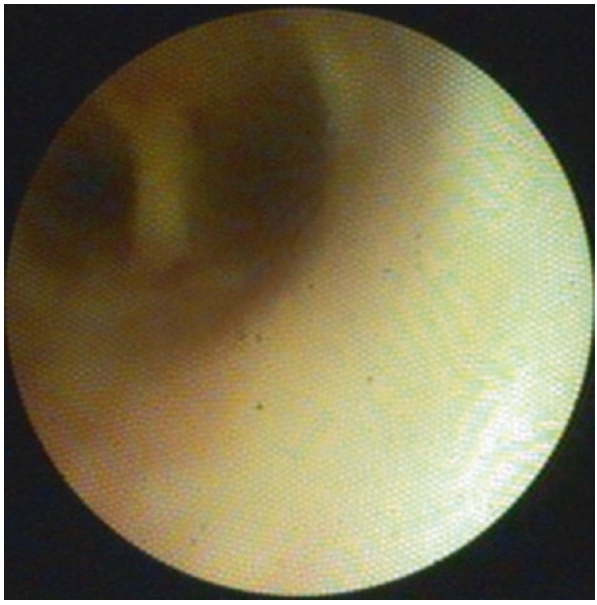

Fig. 30.2 SpyGlass image showing bifurcation of bile duct

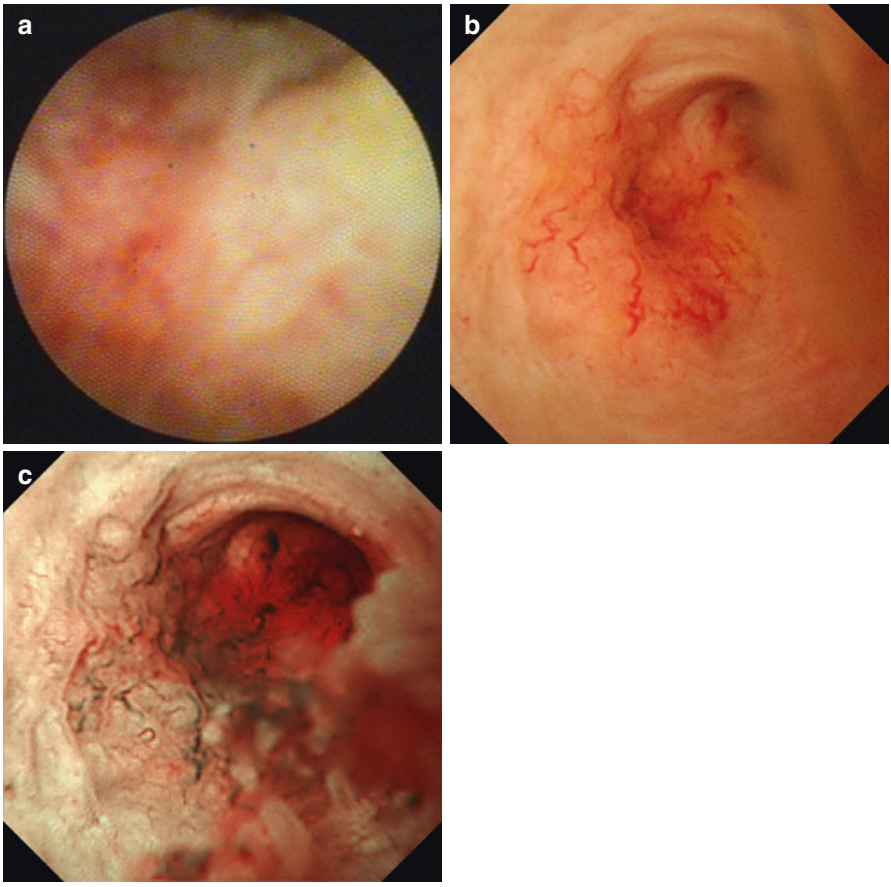

Fig. 30.3 Endoscopic images of bile duct carcinoma with the same patient showing (**a**) SpyGlass, (**b**) video cholangioscope image, and (**c**) video cholangioscope image with narrowband images

into the common bile duct. A retrospective multicenter study reported that successful intubation of papilla is 88.5% (115/130) and complications were 7.7% without no mortality [24]. Intraductal anchoring balloon and carbon dioxide insufflation were used in 97.7% and 66.9% of cases. Air embolism occurred in one patient who underwent DC with air insufflation, and this patient suffered cardiac arrest. Fortunately, the patient recovered completely after immediate cardiopulmonary resuscitation. Few episodes of cardiac and cerebral air embolisms have been reported with the anchoring balloon system and were thought to be due to biliovenous fistula [25, 26]. Carbon dioxide insufflation during DC may prevent air embolism; however, further studies are needed.

Although there were no comparative studies of peroral cholangioscopy systems, Pohl et al. conducted randomized clinical trials comparing newly developed mother-baby cholangioscopy and DC [27]. A novel short-access mother-baby (SAMBA,

Karl Storz, Tuttlingen, Germany) system was equipped with shortened-length baby scope, which provides better flexibility in the pancreaticobiliary system and may reduce fragility. Requiring two endoscopists was the same as in other conventional mother-baby system. There were no significant differences in the overall success rates between SAMBA (90%) and DC (86.7%). SAMBA allowed intrahepatic bile duct exploration in all cases, compared with 10.5% of cases in DC ($P < 0.01$). Mother-baby system is better than direct cholangioscopy with regard to intraductal stability and accessibility of intrahepatic bile ducts.

30.2.4 Probe-Based Confocal Laser Endomicroscopy

Probe-based confocal laser endomicroscopy (pCLE) provides real-time in vivo microscopic tissue information that may increase sensitivity for malignancy [28, 29]. The pCLE probe can be introduced through the working channel of a duodenoscope. A standardized visual classification of pCLE findings for biliary strictures has been proposed as Miami classification. A prospective, international, multicenter trial evaluating the diagnostic value of pCLE was performed by using Miami classification [30]. One hundred and twenty-eight patients with indeterminate biliary strictures were enrolled, 112 of whom with eligible inclusion criteria were evaluated. The accuracy of the clinical impression of ERCP, pCLE, and tissue sampling trended higher than the accuracy of ERCP and tissue sampling without pCLE but did not reach statistical significance (88% vs. 79%, $P = 0.06$). As authors stated, limitations to this study are the visual criteria themselves. The present visual criteria cannot differentiate inflammatory patterns from benign patterns; further improvement in criteria is needed.

30.3 Indication

Possible indications for cholangioscopy of the bile duct include direct visual assessment, tissue sampling, and therapeutic interventions [31]. Intraductal tumors may mimic large stones, and immobile stones may imitate polypoid tumors. Benign-appearing biliary strictures may be malignant, and strictures thought to be malignant may be benign [32]. The most clinical concerns are indeterminate biliary strictures because brush cytology and biopsies with ERCP are limited by relatively low sensitivity. A meta-analysis with nine eligible clinical studies showed that pooled sensitivity and specificity are 45% and 99% in brushing cytology and 48.1% and 99.2% in biopsies, respectively [33]. A combination of brushing cytology and biopsies only modestly increased the sensitivity (59.4%) with a specificity of 100%. One of the explanations for low sensitivity has been attributed to tumor-associated fibrosis, well-differentiated cancers, or submucosal spread. Endoscopic ultrasonography fine needle aspiration biopsy is an alternative for tissue acquisition, especially

for pancreatic cancer, however, not common for bile duct cancer [34]. The main indication of cholangioscopy is the workup of indeterminate biliary strictures.

30.3.1 Indeterminate Biliary Strictures

The clinical diagnosis of the bile duct cancer was assessed using multimodality imaging approach with transabdominal ultrasound sonography, CT, magnetic resonance imaging (MRI), endoscopic ultrasound sonography, and ERCP [34]. Imaging features without histologic confirmation cannot be definitive enough to make treatment decisions, such as chemotherapy or surgery. Intraductal papillary bile duct tumor is usually depicted as enhanced tumor by dynamic CT; many of them are not difficult to diagnose. Indeterminate stricture, in which a diagnosis has not been made after conventional ERCP with brushing cytology or biopsies, is a good indication of peroral cholangioscopy. Mother-baby scope system is the preferred method for examination of bile duct strictures compared to direct peroral cholangioscopy due to the better stability of the cholangioscope [27]. Although an established visual classification has not been present, visual appearances of malignant stricture were irregularly torturous vessels (Fig. 30.3b, c), easy oozing (Fig. 30.4), or irregular surface [32]. On the basis of those visual classification, peroral cholangioscopy significantly improved sensitivity (100% vs. 57.9%, $P < 0.05$) and accuracy (93.4% vs. 78.1%, $P < 0.05$) in the diagnosis of indeterminate bile duct strictures compared to ERC with brushing cytology of

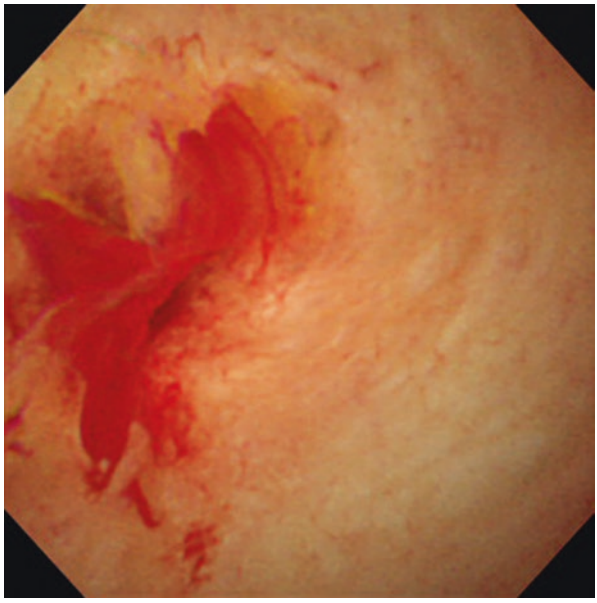

Fig. 30.4 Video cholangioscopic image showing easy oozing of bile duct carcinoma

biopsies without peroral cholangioscopy. In their study, three types of mother-baby cholangioscope (fiber-optic, video, and catheter-based type) were used. Video cholangioscope (CHF-B260, Olympus, Japan) with narrowband images (NBI) can provide excellent quality digital images (Fig. 30.3c), which offers better diagnostic power than other types of cholangioscope. A prospective multicenter study was conducted to evaluate indeterminate bile duct lesions by using video peroral cholangioscope [35]. Malignant appearance is defined as follows: irregular, dilated and tortuous vessels, friability, irregular papillogranular surface, or a nodular elevated surface-like submucosal tumor. Although indeterminate biliary lesions included biliary strictures as well as papillary tumor, visual impression of peroral video cholangioscopy provided excellent sensitivity of 96.1% and accuracy of 92.1% in diagnosis. As authors stated, the high rate of accurate diagnosis may be influenced by the following facts: the procedure was performed by specialists, the use of NBI combined with white light, and the high ratio of malignancies, most of them are bile duct cancer. Compared to video peroral cholangioscopy, SpyGlass peroral cholangioscopy had inferior fiber-optic images. A systematic review of SpyGlass peroral cholangioscopy in the diagnosis of indeterminate biliary stricture demonstrated that the pooled sensitivity and specificity of visual impression for detection of malignancy were 84.5% and 82.6%, respectively [19]. Although there are no comparative trials of video peroral cholangioscopy and SpyGlass cholangioscopy, these data suggest that better visualization improves diagnostic power. In 2015, SpyGlass system was updated to overcome visual inferiority; clinical studies using the new system will clarify the utility in the near future.

30.3.2 Targeted Biopsies Under Cholangioscope

Theoretically, targeted biopsies under cholangioscope were an ideal method to take tissues, because sampling errors can be avoided, as compared to transpapillary biopsies under fluoroscopic guidance [36, 37]. A systematic review of targeted biopsies under SpyGlass cholangioscopy showed that the pooled sensitivity and specificity of targeted biopsies in the diagnosis of indeterminate biliary strictures were 66.2% and 97.0%, respectively [19]. The sensitivity of 66.2% was comparable to the sensitivity of 59.4%, which was reported in the meta-analysis of conventional brush cytology and biopsies [33]. Similarly, targeted biopsies under video peroral cholangioscopy had no significant differences compared to fluoroscopic transpapillary biopsies (92.3% vs. 91.4%) [35]. A prospective comparative study between visual impression of video cholangioscopy and targeted biopsies was conducted. The diagnostic accuracy of visual impression was significantly higher than that of the biopsies (97.0% vs. 60.6%, $P = 0.0018$) [38]. These results show that biopsies under cholangioscope cannot improve diagnostic power. One explanation is that smaller size of the biopsy fragments via the cholangioscope may influence pathological findings [39].

30.3.3 Preoperative Assessment of Longitudinal Extension of Cholangiocarcinoma

Surgery is the only curative treatment for patients with cholangiocarcinoma; preoperative assessment of longitudinal extension of cholangiocarcinoma is important to achieve curative resection. Mucosal cancerous extent must be accurately evaluated preoperatively in order to determine the resection margin. There are three prospective studies of preoperative assessment using video peroral cholangioscopy. First report by Kawakami et al. showed that extension of cholangiocarcinoma was correctly diagnosed by ERC alone, ERC with peroral cholangioscopy, and ERC with peroral cholangioscopy plus mapping biopsy in 22%, 77%, and 100% of all cases, respectively [40]. Second report by Osanai et al. showed that the accuracy rates for the diagnosis of tumor extension were as follows: ERC alone, ERC with peroral cholangioscopy, and ERC with peroral cholangioscopy plus mapping biopsy were 73.5%, 83.7%, and 92.9%, respectively [35]. Third report by Nishikawa et al. evaluated both the hepatic side and papillary side tumor extension [41]. Accuracy rates for the diagnosis of tumor extension were improved from 70.0% of ERC to 86.7% of ERC with peroral cholangioscopy in the hepatic side and from 83.7% of ERC to 95.3% of ERC with peroral cholangioscopy in the papillary side, respectively. When cholangioscope can pass the biliary strictures, video peroral cholangioscopy was effective in the preoperative assessment of longitudinal extension of cholangiocarcinoma. Further refinements of video cholangioscopy with stricture-passing capability are needed to estimate throughout intra- and extrahepatic bile ducts over the stricture.

30.3.4 Primary Sclerosing Cholangitis

Patients with primary sclerosing cholangitis (PSC) have a risk of cholangiocarcinoma with a lifetime risk of 10–15% [42, 43]. The occurrence of cholangiocarcinoma in patients with PSC means poor outcome of survival and liver transplantation. A significant proportion of patients with PSC developed dominant bile duct strictures, which suggest possible sign of malignancy. Bile duct brushing cytology is one of the most common methods for early diagnosis of cholangiocarcinoma [44]. However, bile duct brushing for a diagnosis of cholangiocarcinoma in primary sclerosing cholangitis had relatively low sensitivity of 43% and high specificity of 97% in a meta-analysis [45]. Bile duct brushing is not useful for early detection of cholangiocarcinoma in patients with PSC. In 2006, Tischendorf et al. reported usefulness of fiber-optic peroral cholangioscopy in the diagnosis of dominant biliary strictures in patients with PSC. Twelve of fifty-three patients with PSC developed cholangiocarcinoma [46]. Compared to ERC,

peroral cholangioscopy had a better sensitivity (92% vs. 66%, $P = 0.25$) and a significantly different accuracy (93% vs. 55%, $P < 0.001$). However, diagnosis of cholangiocarcinoma with peroral cholangioscopy remains technically challenging. Awadalla et al. followed 40 of 41 patients with PSC who underwent peroral cholangioscopy for a median of 17.0 months [47]. Cholangiocarcinoma was found in the explant of two of the eight patients at the hilum and right anterior lobe at 1 and 12 months post cholangioscopy, respectively. They concluded that detection of cholangiocarcinoma in patients with PSC were still challenging. Early detection of high-grade dysplasia to identify candidates for liver transplantation are needed to improve long-term survival. NBI was useful to detect dysplasia in the esophagus, stomach, and colon, however, not proven in the bile duct. Azeem et al. conducted a prospective observational study using NBI video peroral cholangioscopy (CHF-Y0002, Olympus) to detect biliary dysplasia among the patients with PSC [48]. Thirty patients with PSC were enrolled (median follow-up, 319.5 days), four patients of whom had a final diagnosis of cholangiocarcinoma. Surveillance NBI visualized the hypervascular mucosal change which suggests dysplasia; however, peroral cholangioscopy-directed biopsy did not improve the dysplasia detection rate. Authors speculated that the restricted ability to manipulate the cholangioscope disturbed targeted biopsies exactly at the point of interest. However, available NBI cholangioscopy has no magnifying function as used in the upper and lower gastrointestinal video scope [17]; its vascular imaging may be insufficient to evaluate mucosal dysplasia changes. Therefore magnifying function of cholangioscopy is desired for improving diagnostic power in accurately assessing lesions of biliary tract.

30.3.5 Intraductal Papillary Neoplasms of the Bile Duct

Intraductal papillary neoplasm of the bile duct (IPNB) is a rare variant of bile duct tumors characterized by prominent papillary proliferation with or without mucin secretion [49]. ERC is useful for the detection of mucobilia, however, failed to locate the tumors in the dilated bile duct with fulfilled mucin. Peroral cholangioscopy can approach the bile duct directly, and it can confirm extension of the tumor [50]. When endoscopists observe mucobilia or a mucin-filled papillary orifice, the presence of IPNB must be considered, and peroral cholangioscopy should be performed to confirm the diagnosis. In patients with excessive mucin, targeted biopsies under cholangioscope are intractable because sufficient irrigation for keeping the cholangioscopic view clear was difficult in the presence of thick mucin during the procedure. Transpapillary forceps biopsies on the basis of information obtained from peroral cholangioscopy observation were recommended. On the contrary, IPNB without mucin secretion can be visualized clearly by peroral cholangioscopy (Fig. 30.5); targeted biopsies are preferred to confirm pathological evidence.

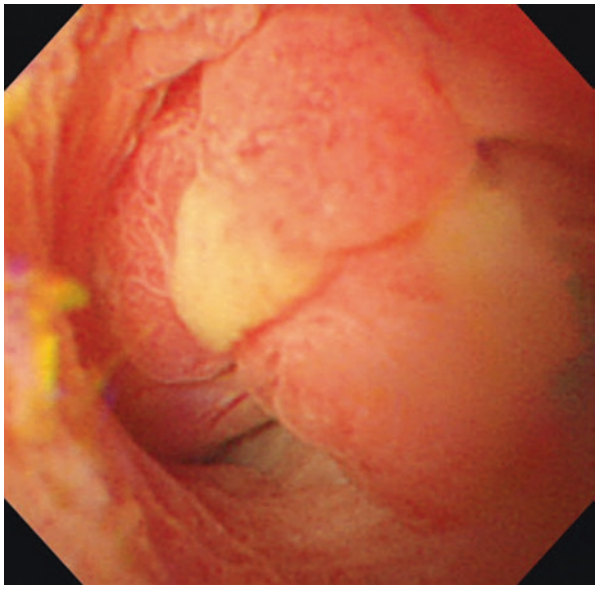

Fig. 30.5 Video cholangioscopic image showing papillary tumor of the bile duct

30.4 Complications

Peroral cholangioscopy is a relatively safe procedure. The most common complication was cholangitis (4.1%, 16/392) [51]. Continuous saline irrigation to take a good view often causes intraductal pressure elevation, resulting in acute cholangitis. Overall complication rate was 7.1% (44/618) in three prospective and four retrospective studies (range, 2.0–13.3%). Air embolism is a rare, however, fatal complication which was associated with DC [26]. Carbon dioxide insufflation was recommended for DC.

30.5 Conclusion

The main purpose of cholangioscopy is indeterminate biliary strictures. Visual impression of cholangioscopy is essential to diagnose indeterminate strictures, because targeted biopsies under cholangioscopic view cannot improve diagnostic power. New imaging techniques such as pCLE or NBI are expected to gain more visual diagnostic power. Further improvements in cholangioscopes and techniques are needed.

References

1. Nakajima M, Akasaka Y, Fukumoto K, et al. Peroral cholangiopancreatoscopy (PCPS) under duodenoscopic guidance. Am J Gastroenterol. 1976;66:241–7.

2. Shah RJ, Langer DA, Antillon MR, et al. Cholangioscopy and cholangioscopic forceps biopsy in patients with indeterminate pancreaticobiliary pathology. Clin Gastroenterol Hepatol. 2006;4:219–25.
3. Tsuyuguchi T, Fukuda Y, Saisho H. Peroral cholangioscopy for the diagnosis and treatment of biliary diseases. J Hepato-Biliary-Pancreat Surg. 2006;13(2):94–9.
4. Itoi T, Osanai M, Igarashi Y, et al. Diagnostic peroral video cholangioscopy is an accurate diagnostic tool for patients with bile duct lesions. Clin Gastroenterol Hepatol. 2010;8:934–8.
5. Ghersi S, Fuccio L, Bassi M, et al. Current status of peroral cholangioscopy in biliary tract diseases. World J Gastrointest Endosc. 2015;7:510–7.
6. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc. 2007;65:832–41.
7. Chathadi KV, Chen YK. New kid on the block: development of a partially disposable system for cholangioscopy. Gastrointest Endosc Clin N Am. 2009;19:545–55.
8. Bhat YM, Kochman ML. Novel management of complex hilar biliary strictures with the Spyglass Direct Visualization System (with video). Gastrointest Endosc. 2009;69:1182–4.
9. Chen YK, Parsi MA, Binmoeller KF, et al. Single-operator cholangioscopy in patients requiring evaluation of bile duct disease or therapy of biliary stones (with videos). Gastrointest Endosc. 2011;74:805–14.
10. Ramchandani M, Reddy DN, Gupta R, et al. Role of single-operator peroral cholangioscopy in the diagnosis of indeterminate biliary lesions: a single-center, prospective study. Gastrointest Endosc. 2011;74:511–9.
11. Manta R, Frazzoni M, Conigliaro R, et al. SpyGlass single-operator peroral cholangioscopy in the evaluation of indeterminate biliary lesions: a single-center, prospective, cohort study. Surg Endosc. 2013;27:1569–72.
12. Alameel T, Bain V, Sandha G. Clinical application of a single-operator direct visualization system improves the diagnostic and therapeutic yield of endoscopic retrograde cholangiopancreatography. Can J Gastroenterol. 2013;27:15–9.
13. Sethi A, Widmer J, Shah NL, et al. Interobserver agreement for evaluation of imaging with single operator choledochoscopy: what are we looking at? Dig Liver Dis. 2014;46:518–22.
14. Larghi A, Waxman I. Endoscopic direct cholangioscopy by using an ultra-slim upper endoscope: a feasibility study. Gastrointest Endosc. 2006;63(6):853–7.
15. Choi HJ, Moon JH, Ko BM, et al. Overtube-balloon-assisted direct peroral cholangioscopy by using an ultra-slim upper endoscope (with videos). Gastrointest Endosc. 2009;69:935–40.
16. Itoi T, Sofuni A, Itokawa F, et al. Peroral cholangioscopic diagnosis of biliary-tract diseases by using narrow-band imaging (with videos). Gastrointest Endosc. 2007;66:730–6.
17. Boeriu A, Boeriu C, Drasovean S, et al. Narrow-band imaging with magnifying endoscopy for the evaluation of gastrointestinal lesions. World J Gastrointest Endosc. 2015;7:110–20.
18. Doi S, Yasuda I, Nakashima M, et al. Carbon dioxide insufflation vs. conventional saline irrigation for peroral video cholangioscopy. Endoscopy. 2011;43:1070–5.
19. Navaneethan U, Hasan MK, Lourdusamy V, et al. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review. Gastrointest Endosc. 2015;82:608–14.
20. Tsou YK, Lin CH, Tang JH, et al. Direct peroral cholangioscopy using an ultraslim endoscope and overtube balloon-assisted technique: a case series. Endoscopy. 2010;42:681–4.
21. Albert JG, Friedrich-Rust M, Elhendawy M, et al. Peroral cholangioscopy for diagnosis and therapy of biliary tract disease using an ultra-slim gastroscope. Endoscopy. 2011;43:1004–9.
22. Meves V, Ell C, Pohl J. Efficacy and safety of direct transnasal cholangioscopy with standard ultraslim endoscopes: results of a large cohort study. Gastrointest Endosc. 2014;79:88–94.
23. Itoi T, Nageshwar Reddy D, Sofuni A, et al. Clinical evaluation of a prototype multi-bending peroral direct cholangioscope. Dig Endosc. 2014;26:100–7.
24. Farnik H, Weigt J, Malfertheiner P, et al. A multicenter study on the role of direct retrograde cholangioscopy in patients with inconclusive endoscopic retrograde cholangiography. Endoscopy. 2014;46:16–21.

25. Gaidhane M, Kahaleh M. Single-operator cholangioscopy in biliary disorders: going beyond visualization. Gastrointest Endosc. 2011;74:815–6.
26. Efthymiou M, Raftopoulos S, Antonio Chirinos J, et al. Air embolism complicated by left hemiparesis after direct cholangioscopy with an intraductal balloon anchoring system. Gastrointest Endosc. 2012;75:221–3.
27. Pohl J, Meves VC, Mayer G, et al. Prospective randomized comparison of short-access mother-baby cholangioscopy versus direct cholangioscopy with ultraslim gastroscopes. Gastrointest Endosc. 2013;78:609–16.
28. Meining A, Shah RJ, Slivka A, et al. Classification of probe-based confocal laser endomicroscopy findings in pancreaticobiliary strictures. Endoscopy. 2012;44:251–7.
29. Heif M, Yen RD, Shah RJ. ERCP with probe-based confocal laser endomicroscopy for the evaluation of dominant biliary stenoses in primary sclerosing cholangitis patients. Dig Dis Sci. 2013;58:2068–74.
30. Slivka A, Gan I, Jamidar P, et al. Validation of the diagnostic accuracy of probe-based confocal laser endomicroscopy for the characterization of indeterminate biliary strictures: results of a prospective multicenter international study. Gastrointest Endosc. 2015;81:282–90.
31. Victor DW, Sherman S, Karakan T, et al. Current endoscopic approach to indeterminate biliary strictures. World J Gastroenterol. 2012;18:6197–205.
32. Fukuda Y, Tsuyuguchi T, Sakai Y, et al. Diagnostic utility of peroral cholangioscopy for various bile-duct lesions. Gastrointest Endosc. 2005;62:374–82.
33. Navaneethan U, Njei B, Lourdusamy V, et al. Comparative effectiveness of biliary brush cytology and intraductal biopsy for detection of malignant biliary strictures: a systematic review and meta-analysis. Gastrointest Endosc. 2015;81:168–76.
34. Miyazaki M, Yoshitomi H, Miyakawa S, et al. Clinical practice guidelines for the management of biliary tract cancers 2015: the 2nd English edition. J Hepatobiliary Pancreat Sci. 2015;22:249–73.
35. Osanai M, Itoi T, Igarashi Y, et al. Peroral video cholangioscopy to evaluate indeterminate bile duct lesions and preoperative mucosal cancerous extension: a prospective multicenter study. Endoscopy. 2013;45:635–42.
36. Iqbal S, Stevens PD. Cholangiopancreatoscopy for targeted biopsies of the bile and pancreatic ducts. Gastrointest Endosc Clin N Am. 2009;19:567–77.
37. Draganov PV, Chauhan S, Wagh MS, et al. Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study. Gastrointest Endosc. 2012;75:347–53.
38. Nishikawa T, Tsuyuguchi T, Sakai Y, et al. Comparison of the diagnostic accuracy of peroral video-cholangioscopic visual findings and cholangioscopy-guided forceps biopsy findings for indeterminate biliary lesions: a prospective study. Gastrointest Endosc. 2013;77:219–26.
39. Hartman DJ, Slivka A, Giusto DA, et al. Tissue yield and diagnostic efficacy of fluoroscopic and cholangioscopic techniques to assess indeterminate biliary strictures. Clin Gastroenterol Hepatol. 2012;10:1042–6.
40. Kawakami H, Kuwatani M, Etoh K, et al. Endoscopic retrograde cholangiography versus peroral cholangioscopy to evaluate intraepithelial tumor spread in biliary cancer. Endoscopy. 2009;41:959–64.
41. Nishikawa T, Tsuyuguchi T, Sakai Y, et al. Preoperative assessment of longitudinal extension of cholangiocarcinoma with peroral video-cholangioscopy: a prospective study. Dig Endosc. 2014;26:450–7.
42. Razumilava N, Gores GJ, Lindor KD. Cancer surveillance in patients with primary sclerosing cholangitis. Hepatology. 2011;54:1842–52.
43. Claessen MMH, Vleggaar FP, Tytgat KJ, et al. High lifetime risk of cancer in primary sclerosing cholangitis. J Hepatol. 2009;50:158–64.
44. Tharian B, George NE, Tham TC. What is the current role of endoscopy in primary sclerosing cholangitis? World J Gastrointest Endosc. 2015;7:920–7.

45. Trikudanathan G, Navaneethan U, Njei B, et al. Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. Gastrointest Endosc. 2014;79:783–9.
46. Tischendorf JJ, Kruger M, Trautwein C, et al. Cholangioscopic characterization of dominant bile duct stenoses in patients with primary sclerosing cholangitis. Endoscopy. 2006;38(7):665–9.
47. Awadallah NS, Chen YK, Piraka C, et al. Is there a role for cholangioscopy in patients with primary sclerosing cholangitis? Am J Gastroenterol. 2006;101(2):284–91.
48. Azeem N, Gostout CJ, Knipschield M, et al. Cholangioscopy with narrow-band imaging in patients with primary sclerosing cholangitis undergoing ERCP. Gastrointest Endosc. 2014;79:773–9.
49. Ohtsuka M, Shimizu H, Kato A, et al. Intraductal papillary neoplasms of the bile duct. Int J Hepatol. 2014;2014:459091.
50. Tsuyuguchi T, Sakai Y, Sugiyama H, et al. Endoscopic diagnosis of intraductal papillary mucinous neoplasm of the bile duct. J Hepato-Biliary-Pancreat Surg. 2010;2010(17):230–5.
51. Ramchandani M, Reddy DN, Lakhtakia S, et al. Per oral cholangiopancreatoscopy in pancreatico biliary diseases-expert consensus statements. World J Gastroenterol. 2015;21:4722–34.

Chapter 31
Peroral Pancreatoscopy (POPS)

Taketo Yamaguchi, Emiri Kita, Rintaro Mikata, and Taro Hara

Abstract Peroral pancreatoscopy (POPS) is useful especially in the diagnosis of complicated cases with pancreatic stenosis or intraductal opacity as well as intraductal papillary mutinous neoplasm of the pancreas (IPMN). Practically, POPS requires more advanced techniques and the need to care much about adverse events after the examination compared to a usual endoscopy. Accordingly, both the careful consideration for the proper POPS indication and the acquisition of basic POPS technique are essential. However, POPS procedure is not more than the ERCP technique. Once acquired the basic technique of POPS, examiner should get used to it by the experience with various cases. We intend to describe in this manuscript concerning indication, basic technique, and limitation of POPS with some literary review.

Keywords Per-oral pancreatoscopy · Intraductal papillary mucinous neoplasia of the pancreas (IPMN) · Indeterminate strictures of the main pancreatic duct · Pathological sampling · Intraductal stone therapy

31.1 Introduction

Peroral pancreatoscopy (POPS) can directly observe pancreatic duct and visualize minute change of the duct wall, leading to a precise diagnosis and treatment for pancreatic diseases. POPS was first developed in 1975, made it clinical use in the late 1980s [1, 2], and has been mechanically improved to overcome various limitations. Many researchers have studied clinical usefulness of POPS on various

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pancreatic diseases [3, 4], and indication of POPS may find in situations where other imaging modalities including EUS are unconvincing (i.e., delineation of main duct intraductal papillary mucinous neoplasia extension, sampling of indeterminate main pancreatic duct strictures). However, POPS has not yet been regarded as a common diagnostic procedure mainly because of its fragility and low maneuverability. Thus, POPS is selectively utilized evaluating intraductal papillary mutinous neoplasm of the pancreas (IPMN) or indeterminate pancreatic duct stricture [4–7]. Nonetheless, newly developed scopes including video pancreatoscope improved optical resolution equipped with narrowband imaging (NBI), and single-operator scope (so-called Spyglass) has potential to enhance practicality of POPS [8, 9]. In addition, there have been many studies of diagnostic usefulness of POPS especially on the IPMNs [3, 7, 10].

This chapter intends to describe methods, indications, general outcomes, and future of POPS.

31.2 Equipment and Technique

There are two main techniques of POPS: "two-operator method" and "single-operator method"; each technique involves mother-baby pancreatoscopy and requires optimal devices (Fig. 31.1). Therapeutic duodenoscope with 4.2-mm working channel (e.g., TJF 260V: Olympus Medical Systems, Tokyo, Japan) is mainly used as "mother scope" and 2.6- to 4-mm diameter pancreatoscopes (e.g., CHF BP260: Olympus Medical Systems, Tokyo, Japan) as "baby scope". Recent development of instrument in video endoscope enables to offer narrowband imaging (NBI) (Olympus Medical Systems, Tokyo, Japan) which provides advanced vascular pattern detection of tumor vessels (e.g., dilated, tortuous blood vessels) [8, 11] (Fig. 31.2).

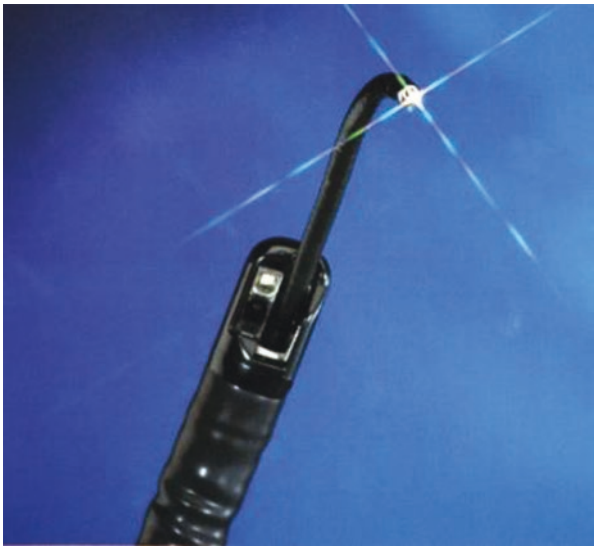

Fig. 31.1 Mother-baby pancreatoscopy

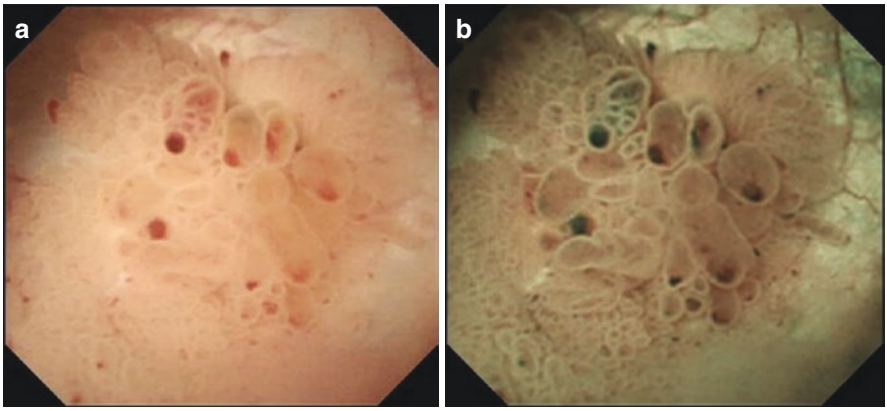

Fig. 31.2 Narrow band imaging (NBI). White light showing papillary projection with scares vascular image of the pancreatic duct wall (**a**). NBI clearly providing advanced vascular pattern detection of tumor vessels (**b**)

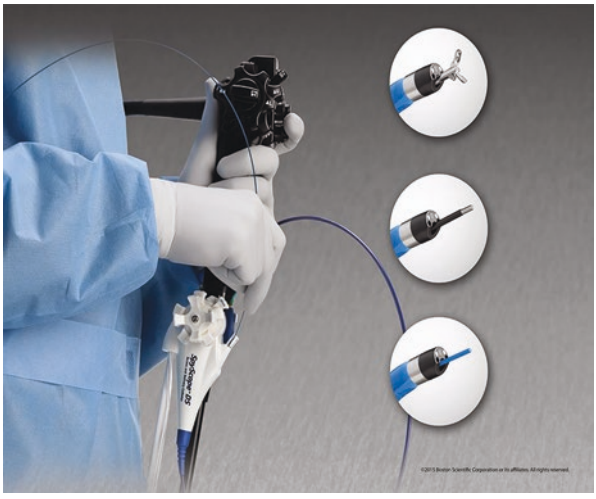

Fig. 31.3 Semi-disposable SpyGlass Direct Visualization System (Boston Scientific, Natick, MA)

The semi-disposable SpyGlass direct visualization system (Boston Scientific, Natick, MA) integrates four-way tip deflection which enhances maneuverability of the scope within the pancreatic duct. The scope has two working channels which enable to irrigate and aspirate into the duct adequately enough to improve the clearance of debris or mucinous substance in the duct, resulting in better inspection [10, 12].

Now, new SpyGlass is launched: SpyGlass DS (Boston Scientific, Natick, MA, Fig. 31.3). It is equipped with digital image sensor which makes up for the disadvantages of low visualization of currently used SpyGlass. Actually, imaging resolution of SpyGlass DS is reported to improve four to five times as compared to that of SpyGlass.

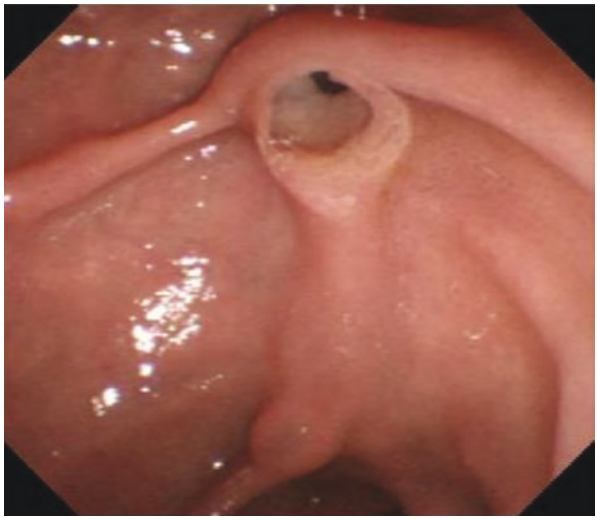

Fig. 31.4 Patulous papillary orifice in IPMN

The method of POPS is not different to that of mother-baby cholangioscopy, and mostly the scope is introduced through the major papilla, and in some cases, it may also be possible through the minor papilla [13]. If the papillary orifice is patulous, as is often the case with IPMN, the scope will pass through with little difficulty (Fig. 31.4), but if not, an endoscopic sphincterotomy (EST) might be mandatory [4]. In most cases, a guide-wire will be necessary in order to introduce the scope to the tail of the main pancreatic duct. After introduction of the scope, pancreatic duct is often examined from tail to head, irrigating with saline to clear the view and under fluoroscopy to locate lesions [14].

POPS has an advantage of obtaining tissue biopsy sample under direct vision through the 1.2- to 2.6-mm working channels. Nonetheless, tissue sampling in POPS is sometimes difficult not only because the biopsy forceps are small for adequate specimen but also because they have low maneuverability in the pancreatic duct. Recently, introduction of efficient forceps in SpyGlass examination has been reported (Fig. 31.5); however, data are limited enough to evaluate sophisticated results of diagnostic accuracy of biopsy for histopathological examination [10, 13].

Assessment of pancreatic duct by MRCP and ERCP before POPS is essential in order to check those points as below:

1. Duodenal papillary orifice (whether orifice is patulous or not)
2. Pancreatic duct diameter
3. Location of the lesion
4. Pancreatic duct state (winding, tortuous)

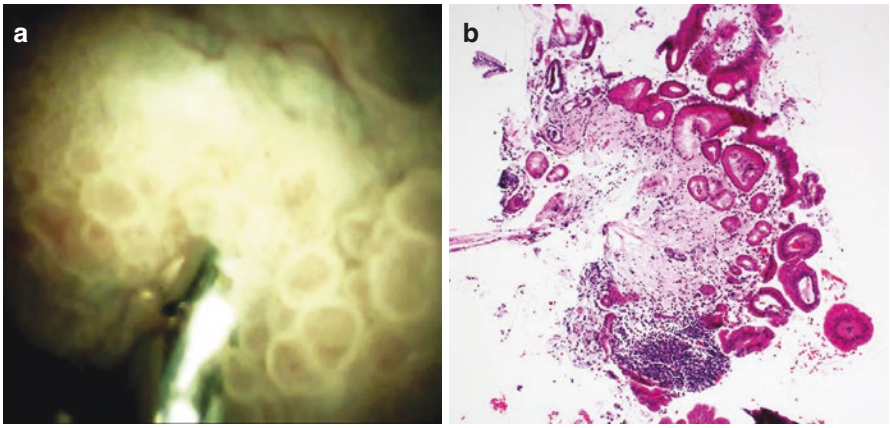

Fig. 31.5 Tissue sample acquisition by POPS. Papillary projection is under biopsied by biopsy forceps (**a**). Adequate amount of sample for pathological interpretation was collected (**b**)

31.3 Diagnostic Applications of POPS

Ideally, indication of POPS may be any pancreatic ductal abnormalities when imaging diagnosis is indeterminate or the case of requiring pathological conformation by biopsy or intractable pancreatic stone [15]. However, as POPS still has some abovementioned limitations, indications of POPS are also limited.

31.3.1 Intraductal Papillary Mucinous Neoplasia of the Pancreas (IPMN)

IPMN is characterized by intraductal progression of neoplastic mucinous cells, which usually form papillary protrusion resulting in cystic dilation of the main pancreatic duct and/or branch ducts, and may present various degrees of malignant potential. IPMN is usually classified into three types: main duct type (MD), branch duct type (BD), and mixed duct type (MT).

IPMN is often difficult to diagnose even after the exclusion of benign and malignant tumors based on findings obtained with different imaging techniques [16]. In addition, skip lesions of IPMN have been reported in about 6–19% [17], and then they have potential risk for recurrence in remnant pancreas. Therefore, assessment of skip lesion before resection is important for better prognosis [18]. Under these conditions, POPS will be useful and the best indication in patients with IPMN to determine the better treatment option and to assess the extent of tumor to assist surgical resection (Fig. 31.6).

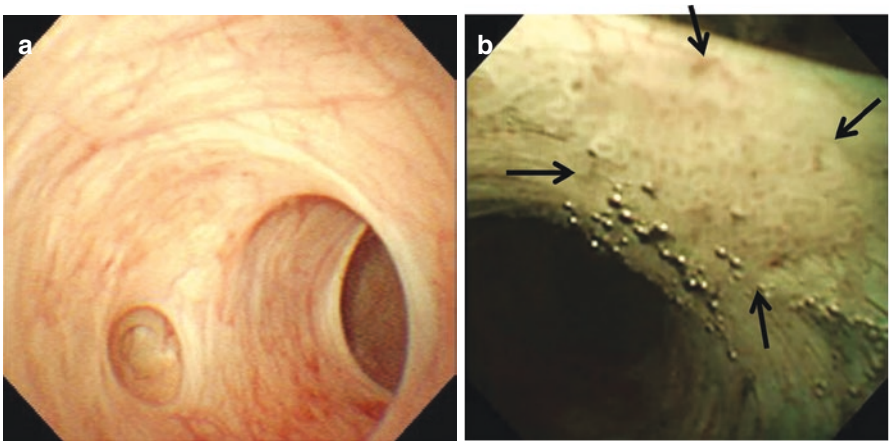

Fig. 31.6 Assessment of skip lesion in IPMN by preoperative POPS examination. Distal pancreatic duct was uneventful (**a**, white light), however skip lesion was detected in the proximal duct (*arrow*), providing useful information for determining surgical margin (**b**, NBI)

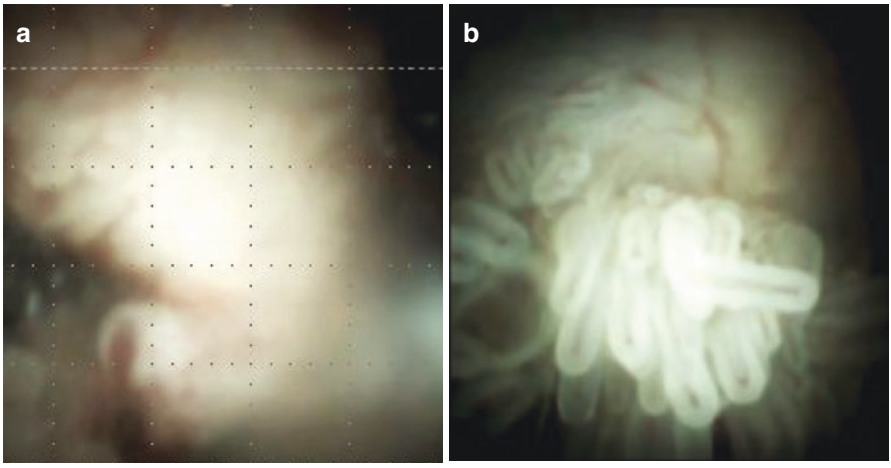

Fig. 31.7 Mucinous substance from the pancreatic duct sometimes prevents clear view of POPS (**a**), requiring cleaning by normal saline (**b**)

Technical success of POPS in IPMN is usually evaluated by the capability of accessing the lesions and observing them directly, which sometimes requires clearing mucinous substance from the pancreatic duct in order to get the clear view (Fig. 31.7). Technical success of POPS in IPMN has been reported in 90–100% [3, 10, 14, 19–21], and in most cases, EST was not required except for SpyGlass that required 38–93% [10, 21]. Various POPS findings related to malignancy have been reported. Protruding lesions were usually classified into five groups according to their findings and correlated well with malignant IPMNs including vegetative, villous, or papillary tumors proliferating blood vessels [3, 4, 14, 21]. On the contrary,

granular mucosa and/or fish-egg-like protrusion without vascular images seem associated with benign IPMNs (Tables 31.1 and 31.2) [3, 4, 14]. NBI allowed better documentation of malignant IPMN features such as proliferating blood vessels into lesion [8, 20].

Diagnostic value of POPS in differentiating benign IPMNs from malignant ones is reported to be ranging from 50 to 68% for sensitivity and from 75 to 100% for specificity [3, 14, 19]. Naturally, diagnostic accuracy of main duct IPMN seems better than for branch duct IPMN, accuracy of 88% for main duct IPMNs and 67% for branch duct ones [3]. A prospective study of 44 patients with IPMN found that

Table 31.1

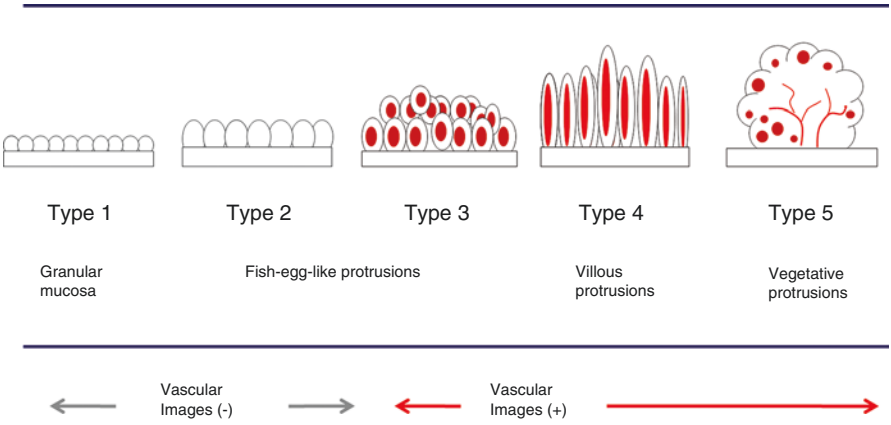

Table 31.2

POPS / Histo-pathological diagnosis.	Type 1	Type 2	Type 3	Type 4	Type 5
Hyperplasia	3	0	0	0	0
Adenoma	0	6	2	1	1
CIS	0	0	7	3	5
Invasive carcinoma	0	0	9	9	5
% malignant lesions	0%	0%	89%	92%	91%

POPS affected clinical decision-making in 76% of cases, improving diagnosis accuracy compared to multidetector CT scan [10].

In Japan, we conducted prospective, multicenter study evaluated diagnostic value and safety of a single-operator Cholangiopancreatoscope, and the accuracy of a pancreatoscopic visual impression of IPMN was 87.5% (14 of 16) [22].

31.3.2 Indeterminate Strictures of the Main Pancreatic Duct

Characteristic POPS findings of malignant duct stricture such as pancreatic duct adenocarcinoma have been documented as a coarse fragile mucosa with/without tumor vessels; conversely, smooth stricture without any significant mucosal changes has been associated with benign lesion including chronic pancreatitis. However, visualization of stricture is often not so easy, and in one prospective study with 115 POPS examination, the area of interest in the main pancreatic duct could be visualized in only 56% of pancreatic cancers [4]. The reason for this low visualization rate was attributed to the difficulty in attaining a forward view of the lesions. Specifically, reasons include tortuous, asymmetric stricture of main pancreatic duct. Conversely, in the same study, visualization of benign strictures and IPMN was reported to be 80% and 95%, respectively. Under these situations and potential limitation relating visualization, indication and benefit of POPS for this kind of situation are thought to be very restricted.

31.4 Pathological Sampling Through POPS

POPS provides an obvious advantage over fluoroscopy-guided ERCP tissue sampling method in diagnosing pancreatic duct lesions [23, 24]. However, sampling through POPS is technically sometimes very difficult, mainly because of low maneuverability of the biopsy forceps in the small and tortuous pancreatic ducts. Recently, a mini forceps (SpyBite) was developed, and successful performance of targeted biopsy under direct visualization of POPS has been reported (Fig. 31.5); nonetheless, only 25% of sensitivity for malignant lesions was documented [10]. Meanwhile, in the case of IPMN, 50% of sensitivity and 100% of specificity for diagnosing malignancy were reported [19].

Cytopathological examination of pancreatic juice collected during POPS will be more useful in patients with IPMN. Our study showed that 102 patients with surgically resected IPMN underwent pancreatic juice collection during POPS and adequate for cytological diagnosis could be obtained in 99% of patients [25]. Sensitivity for the diagnosis of malignant IPMN was significantly higher when collected during POPS though observing the lesion or from a position close to the lesion, compared with collection by usual technique using a catheter (68% vs. 38%, respectively). Sensitivity was much lower for the diagnosis of non-IPMN pancreatic cancer (25%) (Table 31.2). The results may indicate that irrigation cytology during POPS seems to be better than targeted biopsy for the diagnosis of malignant IPMN [25](Table 31.3).

Table 31.3

Diagnostic value	IPMN		PC (n=81)
	By POPS (n=32)	By Catheter (n=71)	
Sensitivity	68.2%*	38.2%	25.4%
Specificity	100%	97.2%	100%
Positive predictive value	100%	92.9%	100%
Negative predictive value	58.8%	62.5%	60.3%

IPMN: Inrtaductal papillary mucinous neoplasm, PC: Pancreatic cancer, * $p<0.05$ vs. PC (χ^2 test)

(Permission from Yamaguchi T et al. 2005 [26])

31.5 Therapeutic Application

31.5.1 Intraductal Lithotripsy in Patients with Pancreatolithiasis

Application of intraductal lithotripsy under direct vision to the treatment of intractable pancreatic stone is one of the good indications of POPS. Specifically, POPS with electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL) produces effective stone fragmentation when extracorporeal shock wave lithotripsy (ESW) or endoscopic removal is not successful [26, 27].

A 10-year experience of intraductal lithotripsy was reported: 46 patients underwent POPS for pancreatic duct stones (n = 31) or using catheter-based system (n = 15), and EHL and/or LL were performed on 39 (85%). Technical success of POPS and catheter-based system was in 27/31 (87%) and in 15/15 (100%), respectively. Complete stone clearance was achieved in 21/31 (68%) and in 11/15 (73%), respectively. POPS-related complications were found in 10%. As a result, overall clinical success of intraductal lithotripsy was 74% [28].

We have treated by LL under POPS 12 patients with difficult main pancreatic duct stones previously treated with ESWL (Fig. 31.8). Those stones were all located at the head of the pancreas, and the mean stone diameter was 12.4 mm (6.0–22.0 mm). The mean diameter of the main pancreatic duct was 7.0 (4.0–10.1 mm), and the duct stricture was noted in 9 (75%). LL was performed 3.4 sessions on average (1–8). Complete stone clearance was achieved in 7 (58.3%) and partial in 5 (41.7%), and then clinical response of decreasing or disappearance of abdominal pain was noted in all of the patients, and the mean main pancreatic duct diameter had significantly decreased to 3.3 mm (1.0–5.3 mm) with no serious adverse events.

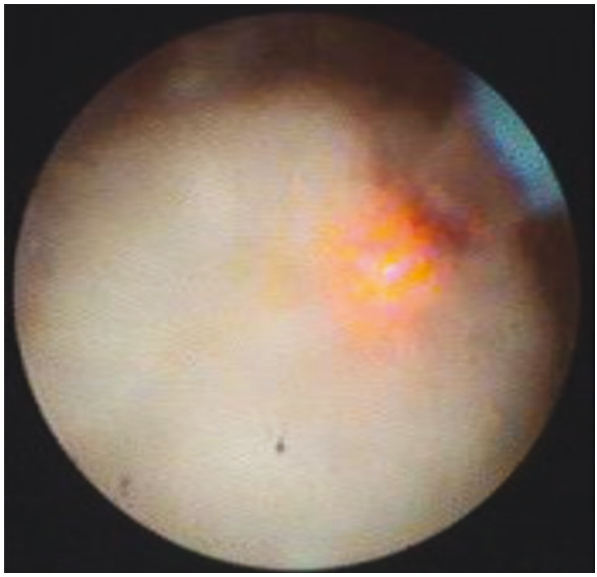

Fig. 31.8 Laser lithotripsy (LL) for pancreatolithiasis. Using SpyGlass system and Holmium YAG laser, pancreatic duct stone depicting white material by POPS was treated under direct vision

31.6 Complications and Limitations

Pancreatitis is the most frequent and problematic complication associated with POPS. Actually, mild to moderate pancreatitis was reported in 10–12% of cases [3, 4, 10, 14]; of them, one death was described because of severe pancreatitis [10]. Increase of intraductal pressure accompanied by saline injection into the pancreatic duct will mostly cause post-POPS pancreatitis. Proper control of saline amount in injecting and sucking is important in order to avoid pancreatitis. Other possible complication may be infection of pancreatic duct (ductitis); however, this complication is very rare, and adequate suction of fluid from pancreatic duct after the examination contributes to prevent it.

The limitation of successful examination by POPS is largely influenced by anatomical factors, specifically in the case of narrowing, winding and tortuous, or structured pancreatic duct, and also obstruction by stones or branch duct-type IPMNs [14]. Actually, the rate of clear visualization by POPS about the area of interest has been reported around 70–80%.

31.7 Conclusion

It is true that the cost of POPS is still high and application of POPS for common clinical use should be limited to designated cases. Under present circumstances, proper selection of POPS indications will be crucial to show its real ability. However, current mechanical advances have made POPS more generally used and increase adaptation in the management of patients with various pancreatic diseases.

References

1. Kawai K, Nakajima M, Akasaka Y, et al. A new endoscopic method: the peroral choledochopancreatoscopy (author's transl) [Article in German]. Leber Magen Darm. 1976;6(2):121–4.
2. Tajiri H, Kobayashi M, Ohtsu A, et al. Peroral pancreatoscopy for the diagnosis of pancreatic diseases. Pancreas. 1998;16(3):408–12.
3. Hara T, Yamaguchi T, Ishihara T, et al. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. Gastroenterology. 2002;122(1):34–43.
4. Yamao K, Ohashi K, Nakamura T, et al. Efficacy of peroral pancreatoscopy in the diagnosis of pancreatic diseases. Gastrointest Endosc. 2003;57(2):205–9.
5. Fujita N, Noda Y, Kobayashi G, et al. Endoscopic approach to early diagnosis of pancreatic cancer. Pancreas. 2004;28(3):279–81.
6. Kodama T, Tatsumi Y, Sato H, et al. Initial experience with a new peroral electronic pancreatoscope with an accessory channel. Gastrointest Endosc. 2004;59(7):895–900.
7. Ringold DA, Shah RJ. Peroral pancreatoscopy in the diagnosis and management of intraductal papillary mucinous neoplasia and indeterminate pancreatic duct pathology. Gastrointest Endosc Clin N Am. 2009;19(4):601–13.
8. Itoi T, Sofuni A, Itokawa F, et al. Initial experience of peroral pancreatoscopy combined with narrow-band imaging in the diagnosis of intraductal papillary mucinous neoplasms of the pancreas (with videos). Gastrointest Endosc. 2007;66(4):793–7.
9. Draganov PV, Lin T, Chauhan S, et al. Prospective evaluation of the clinical utility of ERCP-guided cholangiopancreatoscopy with a new direct visualization system. Gastrointest Endosc. 2011;73(5):971–9.
10. Arnelo U, Siiki A, Swahn F, et al. Single-operator pancreatoscopy is helpful in the evaluation of suspected intraductal papillary mucinous neoplasms (IPMN). Pancreatology. 2014;14(6):510–4.
11. Shah RJ, Chen YK. Video cholangiopancreatoscopy with narrow band imaging: spectrum of mucosal and vascular patterns in patients with pancreaticobiliary pathology [abstract]. Gastrointest Endosc. 2009;68(5):AB117.
12. Chen YK, Pleskow DK. SpyGlass single-operator peroral cholangiopancreatoscopy system for the diagnosis and therapy of bile-duct disorders: a clinical feasibility study (with video). Gastrointest Endosc. 2007;65(6):832–41.
13. Brauer BC, Chen YK, Ringold DA, et al. Peroral pancreatoscopy via the minor papilla for diagnosis and therapy of pancreatic diseases. Gastrointest Endosc. 2013;78:545–9.
14. Yamaguchi T, Hara T, Tsuyuguchi T, et al. Peroral pancreatoscopy in the diagnosis of mucin-producing tumors of the pancreas. Gastrointest Endosc. 2000;52:67–73.
15. Nguyen NQ. Application of per oral cholangiopancreatoscopy in pancreatobiliary diseases. J Gastroenterol Hepatol. 2009;24:962–9.
16. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12:183e97.
17. Sauvanet A, Couvelard A, Belghiti J. Role of frozen section assessment for intraductal papillary and mucinous tumor of the pancreas. World J Gastrointest Surg. 2010;2(10):352–8.
18. Eguchi H, Ishikawa O, Ohigashi H, et al. Role of intraoperative cytology combined with histology in detecting continuous and skip type intraductal cancer existence for intraductal papillary mucinous carcinoma of the pancreas. Cancer. 2006;107:2567–75.
19. Yasuda K, Sakata M, Ueda M, et al. The use of pancreatoscopy in the diagnosis of intraductal papillary mucinous tumor lesions of the pancreas. Clin Gastroeneterol Hepatol. 2005;3:S53–7.
20. Miura T, Igarashi Y, Okano N, et al. Endoscopic diagnosis of intraductal papillary-mucinous neoplasm of the pancreas by means of peroral pancreatoscopy using a small-diameter videoscope and narrowband imaging. Dig Endosc. 2010;22:119–23.
21. Nagayoshi Y, Aso T, Ohtsuka T, et al. Peroral pancreatoscopy using the SpyGlass system for the assessment of intraductal papillary mucinous neoplasm of the pancreas. J Hepatobiliary Pancreat Sci. 2014;21:410–7.

22. Kurihara T, Yasuda I, Isayama H, et al. Diagnostic and therapeutic single-operator cholangiopancreatoscopy in biliopancreatic diseases: prospective multicenter study in Japan. World J Gastroenterol. 2016;22:1891.
23. Iqbal S, Stevens PD. Cholangiopancreatoscopy for targeted biopsies of the bile and pancreatic ducts. Gastrointest Endosc Clin N Am. 2009;19:567–77.
24. Dumonceau J-M. Sampling at ERCP for cyto- and histopathological examination. Gastrointest Endosc Clin N Am. 2012;22:461–77.
25. Yamaguchi T, Shirai Y, Ishihara T, et al. Pancreatic juice cytology in the diagnosis of intraductal papillary mucinous neoplasm of the pancreas: significance of sampling by peroral pancreatoscopy. Cancer. 2005;104:2830–6.
26. Sasahira N, Isayama H, Nagano R, et al. Noncalcified pancreatic stone treated with electrohydraulic lithotripsy using SpyGlass pancreatoscopy. Endoscopy. 2011;43(Suppl 2 UCTN):E272.
27. Seven G, Schreiner MA, Ross AS, et al. Long-term outcomes associated with pancreatic extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc. 2012;75:997–1004.
28. Attwell AR, Brauer BC, Chen YK, Yen RD, Fukami N, Shah RJ. Endoscopic retrograde cholangiopancreatography with per oral pancreatoscopy for calcific chronic pancreatitis using endoscope and catheter-based pancreatoscopes a 10-year single-center experience. Pancreas. 2014;43:268–74.

Chapter 32
Endoscopic Necrosectomy

Tiing Leong Ang and Stefan Seewald

Abstract Walled-off pancreatic necrosis (WON) arises as a complication of severe necrotizing pancreatitis. Direct endoscopic necrosectomy (DEN) is a feasible option when the following criteria are met: (1) presence of a mature wall, (2) endoscopically accessible, (3) significant liquefactive necrosis has occurred, (4) absence of significant coagulopathy, (5) absence of aneurysmal vessels within the WON, and (6) symptomatic. Access to the WON cavity is achieved under EUS guidance, after which the fistula is dilated to permit entry of a gastroscope for DEN. Clinical success rates of 75–91% have been reported. A pilot randomized trial showed that DEN reduced the pro-inflammatory response as well as the composite clinical end point of major complications compared with surgical necrosectomy. Although effective, there is a risk of significant morbidity and mortality. The extent and aggressiveness of DEN need to be individualized and weighed against the risks of complications.

Keywords Pancreatitis • Necrosis • Endoscopy • Necrosectomy

32.1 Background

A walled-off pancreatic necrosis (WON) is a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs more than 3–4 weeks after onset of severe necrotizing pancreatitis. The presence of solid necrotic material within the collection distinguishes it from pseudocysts (PC) [1]. When symptoms from mass effect or infection arise, intervention may be needed. In particular, given the presence of solid debris within WON, simple drainage alone, which is used for PC, may not be adequate, and additional necrosectomy may be required. In these situations,

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treatment options include large-bore percutaneous drainage and irrigation, open or minimally invasive surgical necrosectomy, and direct endoscopic necrosectomy (DEN). DEN is a very attractive option because it avoids the morbidity of surgery and percutaneous drainage [2–4]. This chapter will focus on the indication, technique, and outcome data for DEN. Apart from WON drainage, as part of overall holistic management to prevent recurrence of fluid collections, one must also assess the pancreatic duct to determine if a leak is persistent and, if so, its treatment.

32.2 Indication for Endoscopic Necrosectomy

The key indication is infected WON not responding to conservative treatment with appropriate antibiotics. A prerequisite for DEN is the presence of a well-defined mature wall; otherwise, any endoscopic access will result essentially in free perforation. This usually requires a time frame of 4–6 weeks from onset of the severe necrotizing pancreatitis. The fluid collection must be accessible endoscopically, such as being located within 1 cm of the duodenal or gastric walls; paracolic collections cannot be accessed and would require adjunctive methods such as percutaneous drainage. Coagulopathy, if present, should be corrected. The absence of a mature wall, presence of aneurysmal vessels within the WON cavity, uncorrectable coagulopathy, and a predominantly solid rather than liquid collection are contraindications for DEN. When intervention is needed but the wall remains immature, one option is to perform initial percutaneous drainage and delay DEN till 4–6 weeks, when the wall becomes mature [2, 3]. Although surgical necrosectomy may result in significant morbidity and even mortality, it may still be needed if less invasive interventions are not suitable or unsuccessful. If required, surgery should be delayed till 3–4 weeks, as delayed interventions have been associated with improved outcomes, due to separation of necrotic from non-necrotic tissue planes [4].

32.3 Technique of Endoscopic Necrosectomy

The equipment and accessories used are summarized in Table 32.1. It is important to highlight that a therapeutic linear echoendoscope with a working channel diameter of 3.7–3.8 mm should be used to achieve the initial access to the cavity. The initial drainage is achieved under combined endoscopic ultrasound (EUS), fluoroscopic and endoscopic guidance. After dilatation of the drainage fistula, a gastroscope is inserted for DEN. An irrigation pump will facilitate the process of irrigation of debris. To avoid air embolism, carbon dioxide insufflation should be used [2, 3].

The procedure can be subdivided into two parts: EUS-guided access and drainage and DEN. DEN is performed when the response to drainage remains inadequate. DEN has been performed even at the first endoscopic session [5].

Table 32.1 Equipment for EUS-guided drainage and endoscopic necrosectomy

Endoscope systems 1. Therapeutic echoendoscope with 3.7 or 3.8 mm working channels 2. Gastroscope 3. CO_2 insufflation 4. Irrigation pump
Puncture device and guidewires 1. 19G needle 2. 0.025–0.035″ guidewires
Puncture tract dilators 1. Cautery-based tract dilatation: cystotome catheter or wire-guided needle knife 2. Non-cautery-based tract dilatation: coaxial biliary dilators (6–10Fr) 3. Subsequent balloon dilatation: 10–15 mm biliary balloon dilators (e.g., CRE balloon dilators from Boston Scientific or Hurricane balloon from Cook)
Stents 1. 7–10Fr double pigtail stents (4–5 cm in length) 2. Customized fully covered self-expandable metallic stents
Devices for endoscopic necrosectomy 1. Extraction basket 2. Retrieval net 3. Soft snare

However, the current concept is to adopt a minimally invasive step-up approach for interventions [4, 6].

32.3.1 Initial EUS-Guided Access and Drainage

EUS guidance is the preferred technique to achieve access to the WON. There are no direct comparative data between EUS and non-EUS-guided access for WON. Extrapolating from randomized studies that compared EUS with non-EUS-guided access for PC drainage, the EUS-guided approach would seem superior because it allows drainage of collections without endoluminal bulging [7, 8].

Puncture using a 19G needle: After excluding the presence of blood vessels in the path of the needle by using color Doppler ultrasound, a 19G FNA needle punctures the WON under EUS guidance (Fig. 32.1). A 0.025 or 0.035 in. guidewire is introduced through the needle and is coiled within the pseudocyst under fluoroscopic guidance (Fig. 32.2).

Puncture tract dilatation: The puncture tract is then dilated in order to allow stent placement. This is achieved using cautery or non-cautery-based techniques. Cautery-based techniques involve the use of either the cystostome catheter or of a wire-guided needle knife. Non-cautery-based technique involves the use of coaxial dilators. Cautery techniques are especially useful when thick walls impede non-cautery-based dilatation. When a needle knife is used, it is crucial that only a short length of the needle knife tip is protruded, in order to align the axis of the tip of the knife with the direction of the guidewire. A cystotome catheter has a diathermy ring

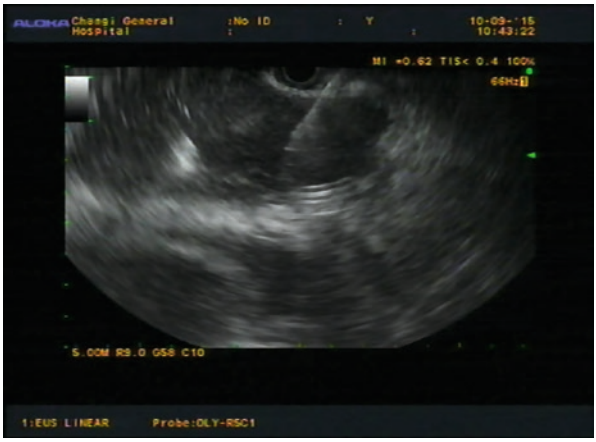

Fig. 32.1 Walled-off necrosis accessed with a 19G fine-needle aspiration needle

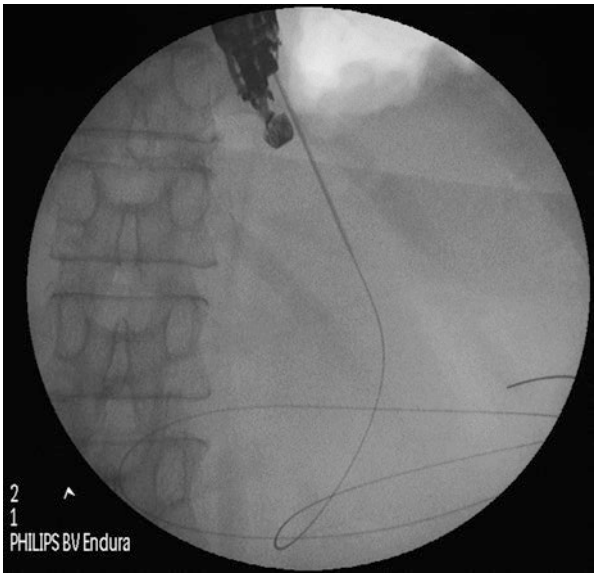

Fig. 32.2 Passage of a guidewire into the walled-off necrosis under fluoroscopy

at the tip, which completely encloses the guidewire, such that the axis can be maintained correctly during the process of electrocautery. The non-cautery technique involves sequential dilatation of the puncture tract by using coaxial dilators, e.g., Soehendra biliary dilators (6–10Fr).

Further balloon dilatation and stent insertion: Conceptually it is possible to just insert a single double pigtail 10Fr stent if a 10Fr coaxial dilator is used. However, it is preferable to dilate the puncture tract to a bigger diameter, so that the infected WON fluid can drain out around and through the stent and multiple plastic stents can be inserted. This is in contrast to PC where a single stent may suffice. Further dilation is performed using an over-the-wire balloon dilator

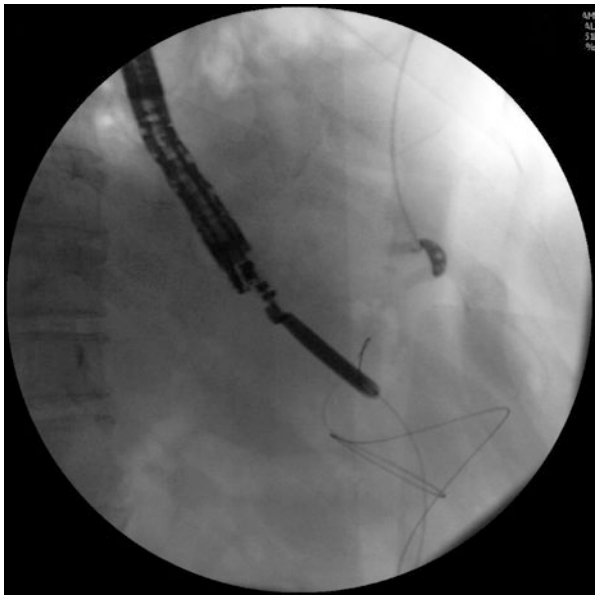

Fig. 32.3 Balloon dilatation of the puncture site

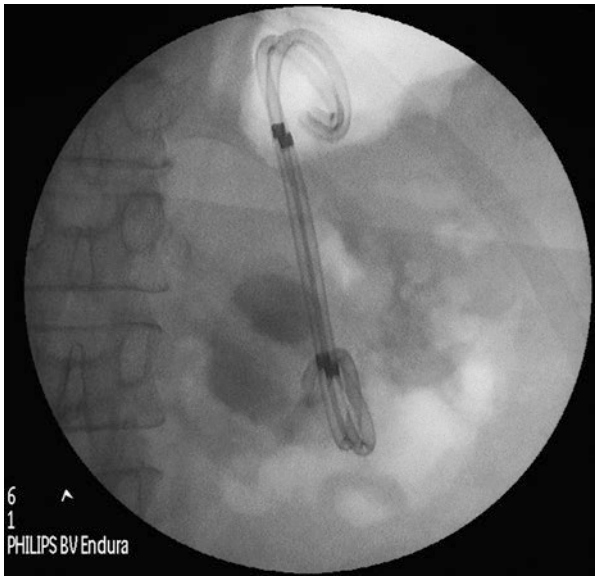

Fig. 32.4 Placement of double pigtail plastic stents

(Fig. 32.3). If only transmural stenting is required, dilatation to 10 mm should suffice. If DEN is intended, dilatation to 15 mm would be required to allow passage of a gastroscope. Two to three double pigtail stents (7–10 Fr) are then inserted under fluoroscopic guidance (Fig. 32.4). When indicated, a 7Fr nasocystic drainage catheter can be inserted for periodic flushing and evacuation of the WON

contents. Multiple stent insertion is usually achieved after recannulating the cavity and reinsertion of guidewire. This may be challenging due to a tangential axis of puncture and poor visibility due to copious fluid draining out. A "double-wire" approach, in which two guidewires are inserted through the same catheter prior to stent placement, has been used to avoid the need for recannulation. In this technique, after wire-guided entry of the cystostome catheter into the WON cavity, a second guidewire is inserted through the cystotome catheter [9]. Variations of this technique include the use of a novel prototype three-layer puncture kit that allows the simultaneous insertion of two guidewires at the initial puncture [10] and the use of a 10Fr Soehendra biliary dilator in place of the cystotome catheter [11]. Sequential transmural stent and drainage catheter placement can then be performed without any risk of loss of access to the WON cavity. It is important to note that the working channel of a therapeutic EUS scope is 3.7–3.8 mm. With two guidewires of 0.025″–0.035″ within the working channel, it is not possible to insert a 10Fr plastic stent due to the reduced space, and a smaller stent of 7–8.5Fr has to be inserted. Once one guidewire has been removed, then the second stent can be up to 10Fr in size. Recent publications have explored the use of customized fully covered self-expandable metallic stents (FCSEMS) for drainage. The lumen-apposing stent (AXIOS, Boston Scientific, USA) is a fully covered, 10 or 15 mm diameter, nitinol, braided stent with bilateral anchor flanges. When fully expanded, the flange diameter is twice that of the "saddle" section and is designed to hold tissue layers in apposition [12]. The "NAGI" stent (Taewoong-Medical Co, Seoul, South Korea) is another specially designed FCSEMS with a 10, 12, or 16 mm diameter in the center and 20 mm ends which can reduce the risk of migration [13]. FCSEMS are delivered constrained in a 10.5Fr catheter that is inserted over the guidewire into the WON and deployed. The potential advantages of FCSEMS are a larger drainage orifice and facilitating repeat entry into the WON for DEN (Figs. 32.5 and 32.6).

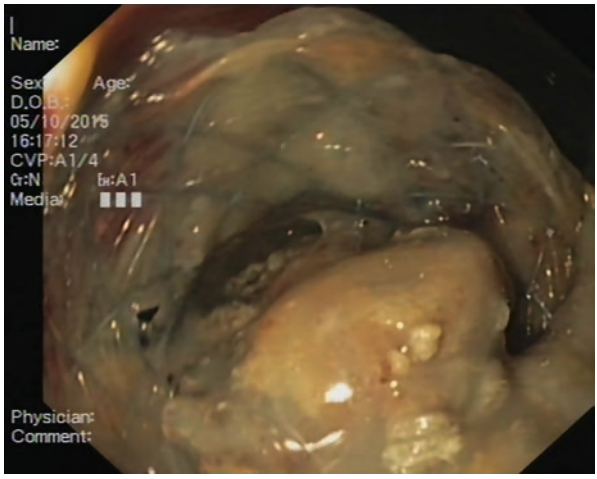

Fig. 32.5 Endoscopic view of fully covered self-expandable metallic stent

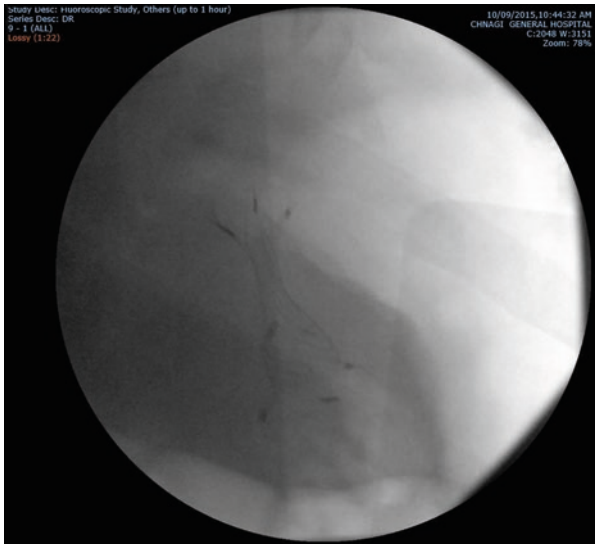

Fig. 32.6 X-ray view of fully covered self-expandable metallic stent

32.3.2 Endoscopic Necrosectomy

When there is a lack of clinical response to transmural drainage alone, DEN is indicated. If plastic double pigtail stents had been inserted for initial drainage, the opening into the WON cavity would have narrowed and large-diameter balloon dilatation to 15 mm must be performed, after which a gastroscope is carefully inserted into the WON cavity. To create space for the endoscope entry, the plastic stents may have to be removed. If a FCSEMS with diameter of 15–16 mm had been inserted, it is possible to insert the endoscope across the SEMS into the WON cavity without the need for further balloon dilatation. Care must be taken not to dislodge the SEMS during the endoscope entry and exit. The first step is to irrigate and aspirate the smaller loose debris. Direct irrigation will help to loosen solid material partially adherent to the wall. Accessories such as dormia basket and retrieval nets are used to gently remove the solid material within the cavity which is deposited within the gastric lumen (Fig. 32.7). It is crucial to perform gentle debridement and not to forcibly pull apart solid material adherent to the wall of the WON, as this may lead to severe bleeding and perforation. Although the ideal is to remove all solid material until a pink granulating wall remains (Fig. 32.8), it is not necessary in all instances. In fact, the use of large-diameter FCSEMS may even reduce the need for DEN. When performed, DEN may need to be staged over a few sessions if the amount of solid material is excessive. By performing repeat sessions, solid debris initially adherent to the wall may actually loosen over time and can then be debrided. If multiple sessions are planned, access is easily maintained by FCSEMS. If plastic stents are used, there is a tendency for the WON opening to narrow and repeat balloon dilatation may be needed. The plastic stents may have to be removed first to create space for entry into the WON

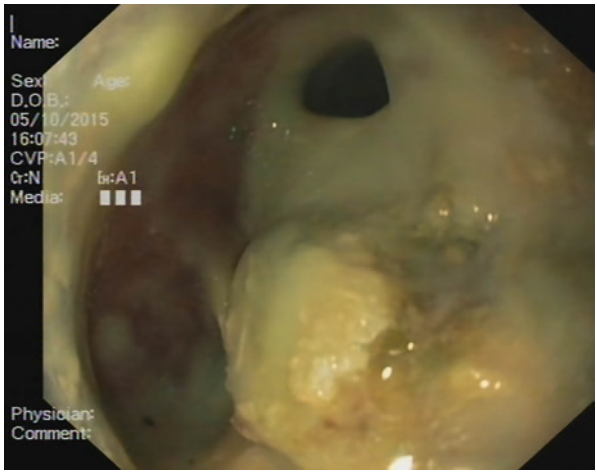

Fig. 32.7 View within the cavity of infected walled-off necrosis

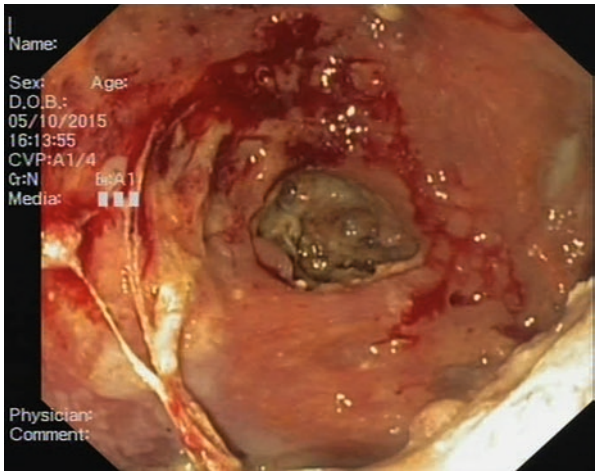

Fig. 32.8 Appearance of the cavity after debridement

cavity and then be reinserted at the end of each DEN session, in order to maintain access and drainage. Once necrosectomy treatment end point has been reached, the stents are left in place for 1–2 months, before being removed. At this point, the pancreatic duct integrity must be assessed, and if disruption is present, pancreatic duct stenting will be needed to prevent reaccumulation of fluid collections; the pancreatic stent is removed after the pancreatic duct disruption has resolved [14]. In the case of disconnected pancreatic duct syndrome, if pancreatic duct stenting is unsuccessful and as an alternative to surgery, plastic transmural stents left in place for a few years can be used to prevent recurrent collections [15]. FCSEMS cannot be left in situ for the long term. After the collapse of the cavity, there is a concern about the inner end of the stent causing tissue injury or erosion. In addition, the membrane of the stent may break down with time, and tissue overgrowth will result in the stent being permanently embedded. Timely removal of a FCSEMS is crucial. A possible time frame

is within 2–3 months, when the collection is expected to fully resolve and before tissue overgrowth or membrane breakdown occurs. It has been reported that removal was not possible after FCSEMS were left for longer than 4 months [16].

32.4 Clinical Outcome After Endoscopic Necrosectomy

The accepted treatment strategy for infected WON is the step-up approach [4]. DEN is a potential minimally invasive treatment option to step up to. Seifert first reported on three patients successfully treated with this technique in 2000 [17]. This was followed by a case series of 13 patients from Hamburg by Seewald et al., where an aggressive endoscopic approach was detailed and which generated significant widespread clinical interest [18]. Treatment was successful in all 13 patients, thus avoiding emergency surgery as an initial treatment. In the long term, surgery was completely avoided in nine patients; it was required due to either abscess extension into the paracolic gutter or disconnected pancreatic duct syndrome with recurrent collections. A retrospective study compared DEN ($n = 25$) with endoscopic drainage using plastic stents ($n = 20$). Successful resolution of WON was accomplished in 88% who underwent DEN versus 45% who received standard drainage ($P < 0.01$), without a change in the total number of procedures. Complications were limited to mild periprocedural bleeding with equivalent rates between groups [19]. Since then, several other single and multicenter case series have been published [20–24]. The key results from large case series are summarized in Table 32.2 [20–24]. The results from these large series demonstrated clinical success rates of 75–91%.

Table 32.2 Clinical outcomes after endoscopic necrosectomy

Authors	*N*	Success rate	Procedure-related complications
Seifert et al. [20]	93	80%	Bleeding: 13 (successful nonsurgical treatment, 10; surgery, 2) Perforation: 5 (conservative treatment, 2; surgery, 2) Air embolism: 2 Fistula: 2 Death: 3 (bleeding, 1; air embolism, 1; perforation, 1)
Yasuda et al. [21]	57	75%	Bleeding: 8 (transfusion alone, 1; angioembolization, 2; endoscopic hemostasis, 5) Perforation: 3 (conservative treatment) Air embolism: 1 Death: 1 (from air embolism)
Seewald et al. [22]	80	83.8%	Bleeding: 12 (conservative treatment) Perforation: 4 (conservative treatment, 3; surgery, 4) Air embolism: 1
Gardner et al. [23]	104	91%	Bleeding: 23 (successful endoscopic hemostasis, 19; angioembolization, 1; surgery, 1; unsuccessful hemostasis, 2) Perforation: 2 (conservative treatment) Pneumoperitoneum: 4 (conservative treatment) Death: 2 (from bleeding)

A pilot randomized controlled trial showed that in patients with infected necrotizing pancreatitis, DEN reduced the pro-inflammatory response as well as the composite clinical end point of major complications compared with surgical necrosectomy [25]. A retrospective study compared outcome and healthcare utilization of DEN versus step-up approach with initial percutaneous catheter drainage (PCD) [26]. Twelve consecutive DEN patients were matched with 12 step-up approach patients. Clinical resolution occurred in 11/12 patients after DEN versus 3/12 step-up approach patients after PCD ($P < 0.01$). Nine step-up approach patients required surgery; seven of these experienced complications. DEN resulted in significantly less new antibiotic use, pulmonary failure, endocrine insufficiency, shorter length of stay ($P < 0.05$), and lower healthcare utilization. DEN ($n = 20$) was compared with minimally invasive surgical necrosectomy ($n = 20$) for clinically sterile WON in another retrospective study [27]. There was no mortality in either group and no difference in complication rates (20%). The failure rate was similar (15% vs. 10%, $P = 0.66$). Although surgery was associated with a lower re-intervention rate (0 vs. 1, $P = 0.008$), DEN was associated with shorter total length of stay (7 vs. 3 days, $P = 0.032$). The cost of the index procedure was significantly higher for the surgery group ($P = 0.014$); however, when considering all readmissions and re-interventions until resolution of the WON, the total cost was similar for both groups.

Comparative studies of DEN against other interventions had used plastic stents for the initial drainage prior to DEN. A retrospective study compared the use of FCSEMS with plastic stents in the treatment of patients with WON. There were no statistically significant differences in rates of technical success, clinical success, and adverse events between both groups. However, the mean procedure times for the first EUS-guided drainage and for re-intervention such as DEN were significantly shorter in the FCSEMS group. There was no statistically significant difference in the total cost between both groups [28].

32.5 Complications

Complications may arise during the initial EUS-guided access and drainage or during the actual DEN procedure. DEN-related complications reported from large series are summarized in Table 32.2 [20–23]. The main potential complications of concern are severe bleeding and perforation. Air embolism may also arise and it is crucial to use CO_2 insufflation. To minimize risk, only fluid collections with a mature wall and within 1 cm of gastrointestinal lumen should undergo DEN. Any coagulopathy, if present, should be corrected. Patients not already on antibiotics should receive prophylactic antibiotics in order to prevent secondary infection of a sterile collection, although in the majority of cases, antibiotics would already have been started for treatment of infection. Perforation rates of 5% have been reported in the context of DEN [20]. This risk can be reduced by adhering to key principles like draining only a collection with a mature wall, performing stepwise

balloon dilatation of the fistula, and performing gentle debridement using saline lavage and aspiration, baskets, soft snares, and retrieval nets.

32.6 Conclusion

A step-up approach for the management of WON is required. DEN is one of the minimally invasive therapeutic interventions. Studies have shown that DEN is effective. Although DEN is proven to be effective, there is a risk of significant morbidity and mortality. Hence, the extent and aggressiveness of DEN will need to be individualized and are weighed against the risks of complications. In fact, meticulous DEN may not be required in all instances, and flushing and irrigation may be adequate from some point of time of repeated interventions. Careful patient selection is crucial to optimize clinical success and minimize complications.

References

1. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
2. Seewald S, Ang TL, Teng KY, et al. Endoscopic ultrasound-guided drainage of abdominal abscesses and infected necrosis. Endoscopy. 2009;41:166–74.
3. Seewald S, Ang TL, Kida M, Teng KY, Soehendra N, EUS 2008 Working Group. EUS 2008 Working Group document: evaluation of EUS-guided drainage of pancreatic-fluid collections (with video). Gastrointest Endosc. 2009;69(2 Suppl):S13–21.
4. Freeman ML, Werner J, van Santvoort HC, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. Pancreas. 2012;41:1176–94.
5. Papachristou GI, Takahashi N, Chahal P, Sarr MG, Baron TH. Peroral endoscopic drainage/debridement of walled-off pancreatic necrosis. Ann Surg. 2007;245:943–51.
6. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011;141:1254–63.
7. Varadarajulu S, Christein JD, Tamhane A, Ernesto R, Drelichman ER, Mel Wilcox CM. Prospective randomized trial comparing endoscopic ultrasound and conventional endoscopy for trans-mural drainage of pancreatic pseudocysts. Gastrointest Endosc. 2008;68:1102–11.
8. Park DH, Lee SS, Moon SH, et al. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. Endoscopy. 2009;41:842–8.
9. Jansen JM, Hanrath A, Rauws EA, et al. Intracystic wire exchange facilitating insertion of multiple stents during endoscopic drainage of pancreatic pseudocysts. Gastrointest Endosc. 2007;66:157–61.
10. Seewald S, Thonke F, Ang TL, et al. One-step, simultaneous double-wire technique facilitates pancreatic pseudocyst and abscess drainage (with videos). Gastrointest Endosc. 2006;64:805–8.
11. Ang TL, Teo EK, Fock KM. EUS-guided drainage of infected pancreatic pseudocyst: use of a 10F Soehendra dilator to facilitate a double-wire technique for initial transgastric access (with videos). Gastrointest Endosc. 2008;68:192–4.

12. Itoi T, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, et al. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). Gastrointest Endosc. 2012;75:870–6.
13. Itoi T, Nageshwar Reddy D, Yasuda I. New fully-covered self-expandable metal stent for endoscopic ultrasonography-guided intervention in infectious walled-off pancreatic necrosis (with video). J Hepatobiliary Pancreat Sci. 2013;20:403–6.
14. Telford JJ, Farrell JJ, Saltzman JR, Shields SJ, Banks PA, Lichtenstein DR, Johannes RS, Kelsey PB, Carr-Locke DL. Pancreatic stent placement for duct disruption. Gastrointest Endosc. 2002;56:18–24.
15. Arvanitakis M, Delhaye M, Bali MA, et al. Pancreatic fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. Gastrointest Endosc. 2007;65:609–19.
16. Chandran S, Efthymiou M, Kaffes A, et al. Management of pancreatic collections with a novel endoscopically placed fully covered self-expandable metal stent: a national experience (with videos). Gastrointest Endosc. 2015;81:127–35.
17. Seifert H, Wehrmann T, Schmitt T, Zeuzem S, Caspary WF. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. Lancet. 2000;356:653–5.
18. Seewald S, Groth S, Omar S, et al. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective treatment algorithm (videos). Gastrointest Endosc. 2005;62:92–100.
19. Gardner TB, Chahal P, Papachristou GI, et al. A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. Gastrointest Endosc. 2009;69:1085–94.
20. Seifert H, Biermer M, Schmitt W, et al. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study). Gut. 2009;58:1260–6.
21. Yasuda I, Nakashima M, Iwai T, et al. Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: the JENIPaN study. Endoscopy. 2013;45:627–34.
22. Seewald S, Ang TL, Richter H, et al. Long-term results after endoscopic drainage and necrosectomy of symptomatic pancreatic fluid collections. Dig Endosc. 2012;24:36–41.
23. Gardner TB, Coelho-Prabhu N, Gordon SR, et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. Gastrointest Endosc. 2011;73:718–26.
24. Ang TL, Kwek AB, Tan SS, Ibrahim S, Fock KM, Teo EK. Direct endoscopic necrosectomy: a minimally invasive endoscopic technique for the treatment of infected walled-off pancreatic necrosis and infected pseudocysts with solid debris. Singap Med J. 2013;54:206–11.
25. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307:1053–61.
26. Kumar N, Conwell DL, Thompson CC. Direct endoscopic necrosectomy versus step-up approach for walled-off pancreatic necrosis: comparison of clinical outcome and health care utilization. Pancreas. 2014;43:1334–9.
27. Khreiss M, Zenati M, Clifford A, et al. Cyst gastrostomy and necrosectomy for the management of sterile walled-off pancreatic necrosis: a comparison of minimally invasive surgical and endoscopic outcomes at a high-volume pancreatic center. J Gastrointest Surg. 2015;19(8):1441.
28. Mukai S, Itoi T, Baron TH, et al. Endoscopic ultrasound-guided placement of plastic vs. biflanged metal stents for therapy of walled-off necrosis: a retrospective single-center series. Endoscopy. 2015;47:47–55.

Part IX
Endoscopic Papillectomy

Chapter 33
Endoscopic Papillectomy: Introduction and How to Treat

Natsuyo Yamamoto, Hiroyuki Isayama, and Kazuhiko Koike

Abstract Ampullary tumor is a comparatively rare tumor derived from the duodenal papilla. It is thought to be associated with the progression of adenoma to carcinoma and is recognized as a premalignant lesion. Recently, endoscopic papillectomy, snaring resection of the ampulla, has been accepted as a less invasive alternative to surgical treatment for cases of ampullary adenoma or adenocarcinoma in adenoma in patients for whom curative resection was possible. The rates of curative resection were reported to be 52–92%, with 0–33% of recurrence rates. However the indications, preprocedural diagnosis, and technique of endoscopic papillectomy are still not standardized. Experts agree that endoscopic ultrasonography is useful, for the diagnosis on the presence of invasion to the muscularis propria, intraductal extension of the lesion, and metastasis to regional lymph nodes. Pancreatitis and bleeding are the most common complications. Pancreatitis is considered to occur due to obstruction of pancreatic duct orifice and thermal damage to the pancreatic parenchyma. Pancreatic stent placement is recommended to avoid obstruction of pancreatic duct orifice. The endoscopic surveillance after endoscopic papillectomy is essential for detecting recurrence of ampullary adenoma.

Keywords Endoscopic papillectomy • Ampullary adenoma • Endoscopic retrograde cholangiopancreatography • Endoscopic ultrasonography

33.1 Introduction

Ampullary tumor is a comparatively rare tumor derived from the duodenal papilla. The duodenal papilla is defined as the area surrounded by the sphincter of Oddi (Fig. 33.1). It consists of the ampullo-biliary segment (Ab), the ampullo-pancreatic

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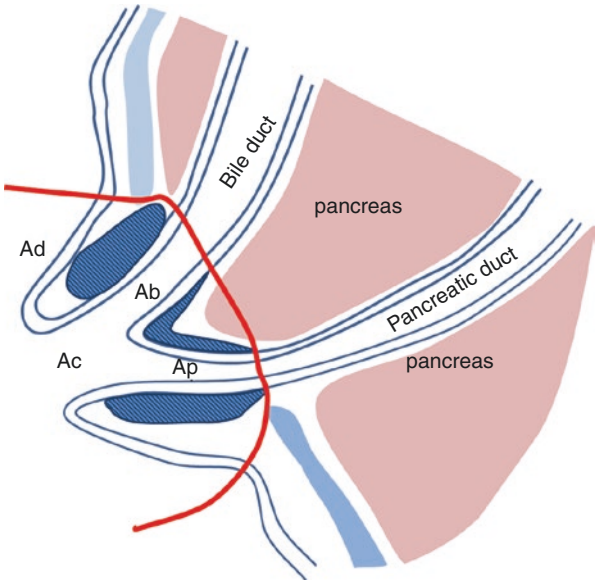

Fig. 33.1 Duodenal papilla. It consists of the ampullo-biliary segment (Ab), the ampullo-pancreatic segment (Ap), the ampullo-pancreatobiliary common duct (Ac), and the ampullo-duodenum (Ad). The area within 2 cm of the ampulla is called the periampullary region

segment (Ap), the ampullo-pancreatobiliary common duct (Ac), and the ampullo-duodenum (Ad). The area within 2 cm of the ampulla is called the periampullary region. Ampullary tumors arise from periampullary lesions. They are commonly detected during the surveillance of familial adenomatous polyposis (FAP), but may also be found incidentally on screening endoscopy without symptoms. In sporadic cases, they may cause obstructive jaundice, recurrent cholangitis, pancreatitis, bleeding, or dilation of the pancreatic and intrahepatic bile ducts. There is no consensus on when ampullary adenomas should be followed up and when they should be resected. Ampullary tumors are thought to develop either from the intestinal epithelium or the epithelium covering the pancreatobiliary ducts. Most ampullary tumors are adenomas or adenocarcinomas [1]. From the results of FAP surveillance, ampullary adenoma is thought to be associated with the progression of adenoma to carcinoma and is recognized as a premalignant lesion, as is colonic adenoma [2–5]. Though the natural history of ampullary adenoma has not been well investigated in sporadic lesions, many endoscopists advocate the resection of ampullary adenoma in this regard.

33.2 The Role of Endoscopic Papillectomy

Classically, surgical resection (local resection or pancreaticoduodenectomy) is the standard treatment for ampullary adenoma. Surgical resection has the advantage of a low recurrence rate, but it is too invasive for cases of localized ampullary

adenoma. Currently, endoscopic papillectomy (EP) has been accepted as a less invasive alternative to surgical treatment for cases of ampullary adenoma in patients for whom curative resection was possible.

EP was first documented by Suzuki and Murakami in 1983 [6]. It involves the resection of the mucosa and submucosa of the duodenal wall, in the area of the anatomical attachments of the ampulla of Vater, including the tissue around the bile duct and the pancreatic duct orifices [7]. Curative resection of EP is reported to be achieved in 52–92% of cases [8–15]. The complication rate is reported as being between 9.7 and 20%, with common complications including post-procedural pancreatitis (0–25%), bleeding (0–25%), perforation (0–8%), and cholangitis (2–3%) [8, 10–19]. At present, EP is considered a less invasive option to surgery, but as a high-risk endoscopic procedure. Therefore the procedure requires specialist expertise. Careful observation after the procedure is important to detect acute complications.

The indications for EP are still not standardized. From previous reports, EP is accepted for patients with ampullary adenomas smaller than 4–5 cm [20] without ductal extension. Intraductal involvement of the lesion is considered to signify non-curative lesions or those with a high risk of recurrence [14]. Adenocarcinoma in adenoma within the mucosal layer is reported to be suitable for EP; there is a rare risk of lymph node metastasis [21], and the misdiagnosis of malignancy on endoscopic forceps biopsy is frequent [13, 22].

33.3 Preprocedural Evaluation for Endoscopic Papillectomy

Recent advancements in endoscopes, endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasonography have contributed to the development of EP. In spite of all this, the accuracy of preprocedural diagnosis is reported only by experts.

The diagnosis of ampullary tumor is performed through endoscopic appearance, biopsy, EUS, and ERCP with intraductal ultrasonography (IDUS). Extracorporeal US, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) are useful for the detection of large lesions, metastasis, and indirect findings (biliary and pancreatic duct dilation). However, they are inappropriate for the evaluation of small lesions.

33.3.1 Endoscopic Appearance and Pathological Diagnosis

The typical endoscopic finding of ampullary adenoma is a villous tumor. The characteristic feature distinguishing between adenoma and adenocarcinoma is the presence of ulceration, which has been observed in patients with malignancy, but never in patients with benign disease. The fold convergence of the duodenum wall

around the ampulla indicates tumor invasion into the duodenal wall. However, ampullary adenomas cannot always be distinguished from ampullary carcinomas according to endoscopic appearance alone. Observation of the ampullary tumor with narrowband imaging (NBI) is reported to be helpful for providing endoscopic images of microvessels and the surface structure of tumors [23] or to enhance tumor margins [24].

Biopsy is very important in differentiating adenoma from carcinoma or other tumors. Pancreatitis may occur following biopsy. The orifice must be carefully confirmed when taking a biopsy from a small lesion. However the accuracy of biopsy is reportedly not high, around 70% [11, 13, 22, 25]. It is thought that severe atypism is observed in the ampullo-pancreatobiliary common duct rather than in the ampulla-duodenum. Therefore, biopsy must be taken from the deep portion of the orifice. When adenocarcinoma is suspected, biopsy followed by endoscopic sphincterotomy [26] or endoscopic ultrasonography-guided fine needle aspiration is considered. However, it is also reported that the sensitivity of biopsy did not change after sphincterotomy [27]. In these results, endoscopic papillectomy is sometimes performed as a major biopsy prior to surgery.

33.3.2 ERCP, IDUS, and EUS (Fig. 33.2)

ERCP is useful for detecting intraductal extension, as well as for treating obstructive jaundice or cholangitis due to ampullary tumor. Endoscopic retrograde cholangiopancreatography (ERCP) can demonstrate intraductal extension of the tumor, but may increase the risk of pancreatitis.

EUS is essential for deciding whether or not endoscopic resection is indicated. The EUS provides information on the presence of invasion to the muscularis propria, intraductal extension of the lesion, and metastasis to regional lymph nodes. EUS is reported as being superior to CT, magnetic resonance imaging, or transabdominal ultrasonography as a diagnostic modality [28, 29]. In meta-analysis, the pooled sensitivity and specificity of EUS in the diagnosis of T1-stage tumors were 77 and 78% [30]. Ridtitid et al. reported that, in a retrospective cohort study of patients with ampullary tumors, the overall accuracy of EUS for the assessment of tumor extent was comparable to ERCP. The authors concluded that ERCP and attempts at endoscopic resection of the ampullary tumor should be avoided in selected cases of local tumor invasion or intraductal extension detected with EUS [31].

ASGE guidelines recommend that ERCP with both biliary and pancreatic duct evaluation should be performed at the time of endoscopic resection to assess for evidence of extension into either ductal system, especially in cases where EUS is not performed [32]. IDUS is inserted through the working channel of the jejunoscope and into the bile and pancreatic ducts after cholangiopancreatography. IDUS may be useful for imaging the detailed anatomy of the ampulla of Vater than EUS. Ito et al. reported that the combination of EUS and IDUS made better accu-

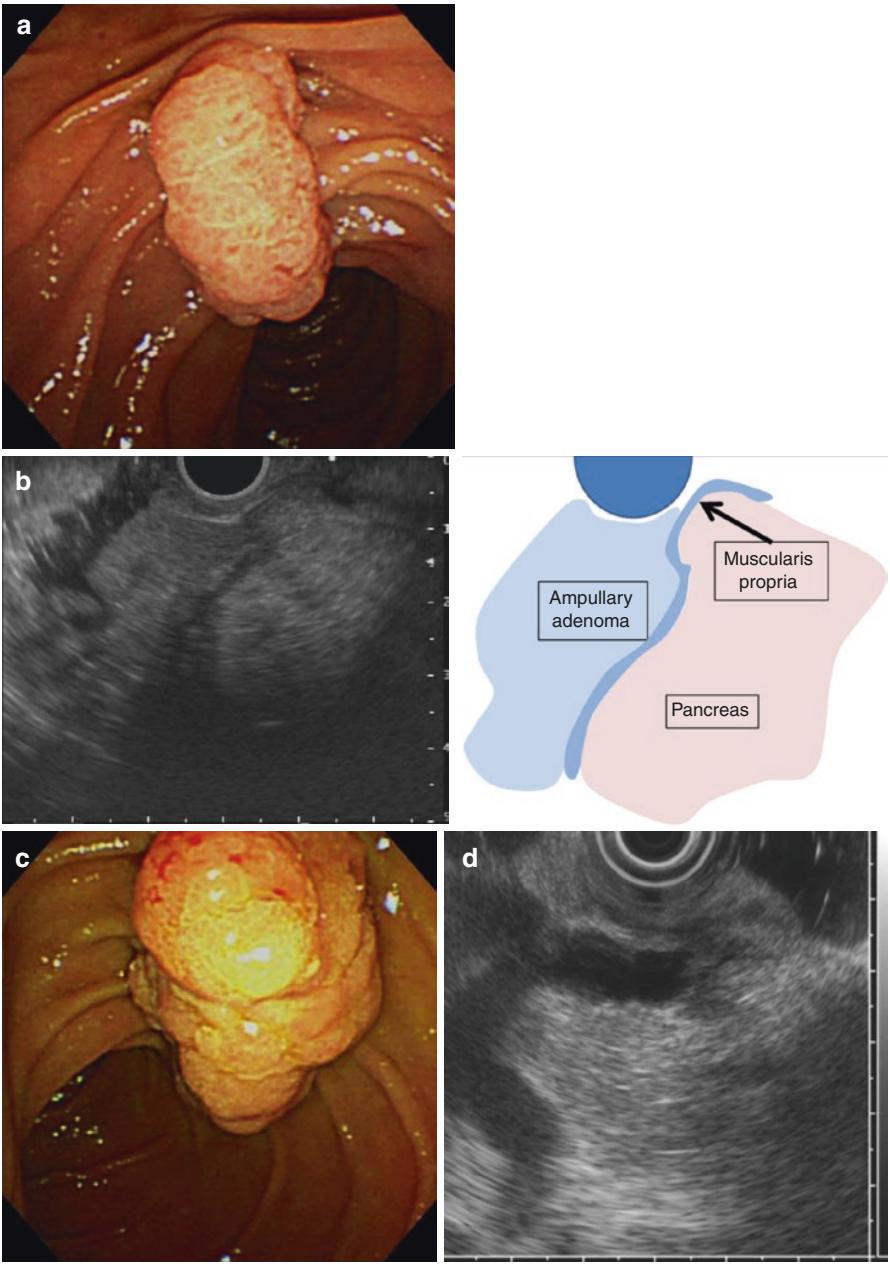

Fig. 33.2 EUS image of ampullary adenoma. (**a**) Endoscopic image of ampullary adenoma. (**b**) EUS image of ampullary adenoma presenting as a hyperechoic mass without ingrowth of the duodenal muscularis propria. (**c**) Endoscopic image of ampullary adenoma with carcinoma component. (**d**) EUS image of bile duct invasion of ampullary adenocarcinoma

racy of preprocedural diagnosis [28]. There are some opinions, however, that all the lesions do not require evaluation with EUS and IDUS before endoscopic therapy, because small lesions (<1–3 cm) without suspicious malignancy have low risk of muscular invasion or ductal extension.

33.4 Techniques of EP (Fig. 33.3)

Generally EP is performed with a duodenoscope in the same manner as polypectomy, using a snare, followed by pancreatic duct stenting for prophylaxis of post-procedural pancreatitis. However, the techniques of EP are not standardized. There is no consensus regarding submucosal injection, the output power or mode of the electrosurgical unit, resection of remnant tumor, sphincterotomy, or prophylactic stent placement.

Achieving en bloc resection without complication is fundamental in performing EP. Complete pathological evaluation is important for the evaluation of the resected margins or malignant foci with invasiveness, as previous pathological diagnosis is often incomplete. In a few case reports, balloon-catheter-assisted papillectomy was documented to facilitate en bloc resection [33, 34]. Piecemeal resection is performed for large lesions, which aims to decrease complications and recurrence. However, histopathological evaluation of the resected margin is then difficult. There are no data comparing safety or recurrence rates between en bloc and piecemeal resections.

33.4.1 Submucosal Lifting

Submucosal saline injection with or without indigo carmine prior to EP has been performed in some reports [15, 17]. Submucosal lifting may reliably indicate malignancy, may prevent the effect of electrosurgical current, and therefore may prevent post-procedural pancreatitis. It may be useful for cases with predominant lateral periampullary extension [35]. However, the mucosal tissue at ampullary lesions does not lift because of tethering by the biliary and pancreatic ducts. Additionally, the elevation of mucosal tissue around the papilla makes snaring difficult. Therefore mucosal injection is not routinely recommended. Recently, “underwater ampullectomy” without submucosal lifting for lateral spreading tumor has been introduced, but its effectiveness is still under investigation [36].

33.4.2 Snaring and Transection

Electrosurgical snare resection is the most common technique. There is no specific type or size of snare for endoscopic ampullectomy. We usually use oval, braided polypectomy snares of 2–3 cm. However, in giant lesions (<3 cm), a large

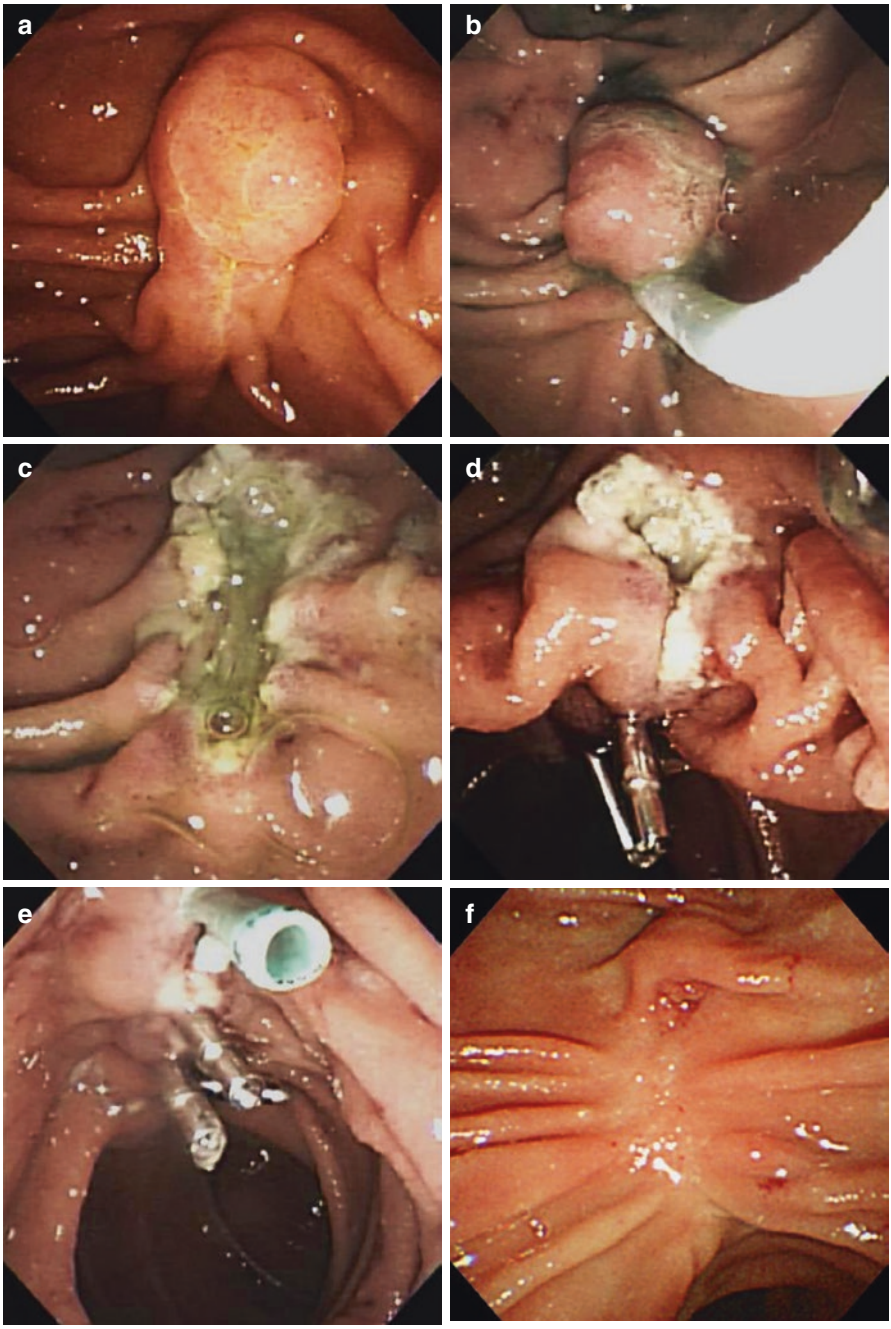

Fig. 33.3 Technique of en bloc ampullectomy by snaring. (**a**) Endoscopic view of ampullary adenoma, diagnosed by previous biopsy and EUS. (**b**) The adenoma is grasped by a snare. (**c**) The adenoma is resected. (**d**) The anal side of the ulcer was closed by using clipping to prevent bleeding. (**e**) A 5Fr pancreatic stent is placed for the prevention of obstructive pancreatitis. (**f**) Endoscopic view at 1 year after the resection

snare is difficult to handle under jejunoscopic view. The snare is placed with the tip on the oral side of the lesion. The snare is closed at the base, and the lesion is resected. In some reports, an incision is made with an electrosurgical needle knife circumferentially around the lesion to facilitate snare capture [11]. When the lesion is held, the snare is stretched, and opposing tension has to be applied for snaring. Though there are no general recommendations regarding the optimal current and power output, there are reports of both pure cutting and blended cutting. Many endoscopists prefer the "blended" or "ERBE Endocut" mode, which aims to decrease bleeding by coagulation. We always use the "Endocut" mode with 100 W output power.

33.4.3 Retrieval of the Resected Tumor

Retrieval of the specimen is very important for the accurate evaluation and tumor staging. Immediately after the transection, the specimen is grasped by a snare and removed from the body in order to avoid intestinal migration. If the specimen is large, a basket catheter or a net forceps is useful. It is important that the tissue is not collected by aspiration through the endoscope, as this will cause the specimen to fragment, making it impossible to evaluate the cut end histopathologically.

33.4.4 Sphincterotomy

Sphincterotomy is often performed after EP for facilitating pancreatic and biliary drainage. However, there is no consensus regarding sphincterotomy.

33.4.5 Treatment of Remnant Tissue

There is no standard technique for treating remnant tumor. Snares, biopsy forceps, and thermal ablation such as argon plasma coagulation are used for the treatment. Argon plasma coagulation is the most common and is useful for ablating remnant tumor as well as for hemostasis or prophylaxis of post-procedural bleeding. However it must be carefully applied to the tissue around the pancreatic and bile duct orifice because it may induce bile duct obstruction or pancreatitis by the thermal effect.

33.5 Complications of EP and Techniques for Their Prevention

33.5.1 Pancreatitis

Pancreatitis is the most common complication. Pancreatitis is considered to occur due to obstruction of pancreatic duct orifice and thermal damage to the pancreatic parenchyma. We sometimes encounter cases of pancreatitis in which bleeding induces obstruction of the pancreatic duct orifice or a pancreatic stent.

Pancreatic stent placement is recommended to prevent post-procedural pancreatitis. The aim of pancreatic stenting is to maintain the pancreatic duct orifice and to prevent pancreatic duct obstruction. One small randomized controlled trial concluded that pancreatic stenting prevented post-procedural pancreatitis [37]. However, pancreatic damage by thermal ablation cannot be prevented. A recent retrospective study suggested that routine pancreatic stent placement may not be necessary. The diameters and lengths of pancreatic stents are not standardized. Generally, a pancreatic stent of 5Fr or 3Fr diameter is used after the resection of the tumor. It is sometimes difficult to find the pancreatic duct orifice. Some endoscopists reported that stent placement before the resection may reduce post-procedural pancreatitis [15]. However once in situ the stent makes resection difficult and may interfere with en bloc resection. The technique of pancreatic duct wire-guided EP or retrieval of intraductally migrated pancreatic stents after EP has been introduced. A randomized controlled trial comparing wire-guided papillectomy and conventional papillectomy reported that there was no significant difference in the post-procedural pancreatitis or complete resection rates between the two methods [38–41]. The removal time of stents is also not standardized. In our experience, we place a 5Fr pancreatic stent with a flap and remove it 7 days after the resection. In cases with pancreas divisum or dominant Santorini's duct, discovered on evaluation by MRCP or EUS, a pancreatic stent is not placed.

33.5.2 Cholangitis

Apart from the risk of post-procedural pancreatitis, obstructive cholangitis does not frequently occur except when caused by obstruction by a clot due to major bleeding. Therefore prophylactic biliary stent placement is generally unnecessary. Sphincterotomy is often performed, but this is not standardized. We do not add sphincterotomy, but a prophylactic biliary stent is placed to minimize the risk of cholangitis for cases in whom hemostasis was performed near bile duct orifice.

33.5.3 Bleeding

Post-procedural bleeding is one of the serious complications. The duodenal papilla is a hypervascular area. Antiplatelet agents and anticoagulated agents should be temporarily stopped as allowed by the condition of concomitant cardiovascular disease. Bleeding is often observed on the anal side of the resected margin [42]. Some endoscopists perform argon plasma coagulation or semi-closure of scar for prevention of bleeding. However there is no data regarding additional procedures for the prevention of bleeding. Post-procedural bleeding can be treated by adrenaline injection, argon plasma coagulation, and clipping. Clipping is sometimes difficult with a duodenoscope because the existence of an elevator interferes with the opening of clips. When bleeding cannot be treated through hemostatic procedures, coiling by arteriography is helpful. Hemostatic procedures may induce perforation or pancreatitis. Therefore excessive hemostasis should be avoided.

33.5.4 Perforation

Perforation usually occurs in the retroperitoneal area. The patients may not have peritoneal irritation signs. However, pancreatitis or bleeding is often observed concurrently with perforation. When perforation is suspected, evaluation by CT scan is informative. If perforation occurs, surgery may be considered, but selected patients can be treated conservatively with antibiotics and NPO [11, 13, 15].

33.5.5 Long-Term Results and Surveillance

The recurrence rate of ampullary adenoma after EP is reported to be 0–33% with a median follow-up period from 19 to 65 months [9–13, 16]. There is no consensus on the duration and modality of surveillance after EP. Recommendation of interval period varies; endoscopy with ERCP at 1, 3, 6, and 12 months after resection and then at yearly intervals for 5 years [10] and endoscopy at 3 or 12 months depending on the results of resection, 6, 12, 18, 24, and 36 months after resection [13], have all been suggested. In our institution, follow-up jejunoscopy and abdominal US is performed at 6-month intervals for 5 years for adenoma cases, and a yearly CT scan is added for patients with adenocarcinoma.

33.6 Conclusions

EP has been established as a first-line treatment for ampullary adenoma without ductal extension. There is still no consensus on preprocedural assessment, technique of EP, management of complications, or surveillance. Biopsy, EUS evaluation

for large lesions, ERCP for further information, pancreatic stent placement for the prevention of pancreatitis, and endoscopic surveillance are recommended.

References

1. Ito K, Fujita N, Noda Y, Kobayashi G, Horaguchi J. Diagnosis of ampullary cancer. Dig Surg. 2010;27:115–8.
2. Bjork J, Akerbrant H, Iselius L, et al. Periampullary adenomas and adenocarcinomas in familial adenomatous polyposis: cumulative risks and APC gene mutations. Gastroenterology. 2001;121:1127–35.
3. Burke CA, Beck GJ, Church JM, van Stolk RU. The natural history of untreated duodenal and ampullary adenomas in patients with familial adenomatous polyposis followed in an endoscopic surveillance program. Gastrointest Endosc. 1999;49:358–64.
4. Bulow S, Bjork J, Christensen IJ, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut. 2004;53:381–6.
5. Seifert E, Schulte F, Stolte M. Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. Am J Gastroenterol. 1992;87:37–42.
6. Suzuki K, Kantou U, Murakami Y. Two cases with ampullary cancer who underwent endoscopic excision. Prog Dig Endosc. 1983;23:236–9.
7. De Palma GD. Endoscopic papillectomy: indications, techniques, and results. World J Gastroenterol. 2014;20:1537–43.
8. Binmoeller KF, Boaventura S, Ramsperger K, Soehendra N. Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc. 1993;39:127–31.
9. Bohnacker S, Seitz U, Nguyen D, et al. Endoscopic resection of benign tumors of the duodenal papilla without and with intraductal growth. Gastrointest Endosc. 2005;62:551–60.
10. Catalano MF, Linder JD, Chak A, et al. Endoscopic management of adenoma of the major duodenal papilla. Gastrointest Endosc. 2004;59:225–32.
11. Cheng CL, Sherman S, Fogel EL, et al. Endoscopic snare papillectomy for tumors of the duodenal papillae. Gastrointest Endosc. 2004;60:757–64.
12. Irani S, Arai A, Ayub K, et al. Papillectomy for ampullary neoplasm: results of a single referral center over a 10-year period. Gastrointest Endosc. 2009;70:923–32.
13. Napoleon B, Gincul R, Ponchon T, et al. Endoscopic papillectomy for early ampullary tumors: long-term results from a large multicenter prospective study. Endoscopy. 2014;46:127–34.
14. Zadorova Z, Dvofak M, Hajer J. Endoscopic therapy of benign tumors of the papilla of Vater. Endoscopy. 2001;33:345–7.
15. Desilets DJ, Dy RM, Ku PM, et al. Endoscopic management of tumors of the major duodenal papilla: refined techniques to improve outcome and avoid complications. Gastrointest Endosc. 2001;54:202–8.
16. Ridtitid W, Tan D, Schmidt SE, et al. Endoscopic papillectomy: risk factors for incomplete resection and recurrence during long-term follow-up. Gastrointest Endosc. 2014;79:289–96.
17. Kahaleh M, Shami VM, Brock A, et al. Factors predictive of malignancy and endoscopic resectability in ampullary neoplasia. Am J Gastroenterol. 2004;99:2335–9.
18. Norton ID, Gostout CJ, Baron TH, Geller A, Petersen BT, Wiersema MJ. Safety and outcome of endoscopic snare excision of the major duodenal papilla. Gastrointest Endosc. 2002;56:239–43.
19. Han J, Kim MH. Endoscopic papillectomy for adenomas of the major duodenal papilla (with video). Gastrointest Endosc. 2006;63:292–301.
20. Hirota WK, Zuckerman MJ, Adler DG, et al. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc. 2006;63:570–80.
21. Yoon SM, Kim MH, Kim MJ, et al. Focal early stage cancer in ampullary adenoma: surgery or endoscopic papillectomy? Gastrointest Endosc. 2007;66:701–7.

22. Yamaguchi K, Enjoji M, Kitamura K. Endoscopic biopsy has limited accuracy in diagnosis of ampullary tumors. Gastrointest Endosc. 1990;36:588–92.
23. Uchiyama Y, Imazu H, Kakutani H, et al. New approach to diagnosing ampullary tumors by magnifying endoscopy combined with a narrow-band imaging system. J Gastroenterol. 2006;41:483–90.
24. Itoi T, Tsuji S, Sofuni A, et al. A novel approach emphasizing preoperative margin enhancement of tumor of the major duodenal papilla with narrow-band imaging in comparison to indigo carmine chromoendoscopy (with videos). Gastrointest Endosc. 2009;69:136–41.
25. Bellizzi AM, Kahaleh M, Stelow EB. The assessment of specimens procured by endoscopic ampullectomy. Am J Clin Pathol. 2009;132:506–13.
26. Bourgeois N, Dunham F, Verhest A, Cremer M. Endoscopic biopsies of the papilla of Vater at the time of endoscopic sphincterotomy: difficulties in interpretation. Gastrointest Endosc. 1984;30:163–6.
27. Menzel J, Poremba C, Dietl KH, Bocker W, Domschke W. Tumors of the papilla of Vater—inadequate diagnostic impact of endoscopic forceps biopsies taken prior to and following sphincterotomy. Ann Oncol. 1999;10:1227–31.
28. Ito K, Fujita N, Noda Y, et al. Preoperative evaluation of ampullary neoplasm with EUS and transpapillary intraductal US: a prospective and histopathologically controlled study. Gastrointest Endosc. 2007;66:740–7.
29. Artifon EL, Couto D Jr, Sakai P, da Silveira EB. Prospective evaluation of EUS versus CT scan for staging of ampullary cancer. Gastrointest Endosc. 2009;70:290–6.
30. Trikudanathan G, Njei B, Attam R, Arain M, Shaukat A. Staging accuracy of ampullary tumors by endoscopic ultrasound: meta-analysis and systematic review. Dig Endosc. 2014;26:617–26.
31. Ridtitid W, Schmidt SE, Al-Haddad MA, et al. Performance characteristics of EUS for locoregional evaluation of ampullary lesions. Gastrointest Endosc. 2015;81:380–8.
32. Chathadi KV, Khashab MA, Acosta RD, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc. 2015;82:773–81.
33. Aiura K, Imaeda H, Kitajima M, Kumai K. Balloon-catheter-assisted endoscopic snare papillectomy for benign tumors of the major duodenal papilla. Gastrointest Endosc. 2003;57:743–7.
34. Kim JH, Moon JH, Choi HJ, et al. Endoscopic snare papillectomy by using a balloon catheter for an unexposed ampullary adenoma with intraductal extension (with videos). Gastrointest Endosc. 2009;69:1404–6.
35. Hopper AD, Bourke MJ, Williams SJ, Swan MP. Giant laterally spreading tumors of the papilla: endoscopic features, resection technique, and outcome (with videos). Gastrointest Endosc. 2010;71:967–75.
36. Flynn MM, Cox DG, Strand DS, et al. Wide-field endoscopic resection of a large laterally spreading adenoma that encompassed the major papilla by combined ampullectomy, EMR, and underwater EMR. Gastrointest Endosc. 2015;81:1270–1.
37. Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. Gastrointest Endosc. 2005;62:367–70.
38. Moon JH, Cha SW, Cho YD, et al. Wire-guided endoscopic snare papillectomy for tumors of the major duodenal papilla. Gastrointest Endosc. 2005;61:461–6.
39. Kim SH, Moon JH, Choi HJ, et al. Usefulness of pancreatic duct wire-guided endoscopic papillectomy for ampullary adenoma for preventing post-procedure pancreatitis. Endoscopy. 2013;45:838–41.
40. Yoon LY, Moon JH, Choi HJ, et al. Wire-guided endoscopic snare retrieval of proximally migrated pancreatic stents after endoscopic papillectomy for ampullary adenoma. Gut Liver. 2011;5:532–5.
41. Lee TY, Cheon YK, Shim CS, et al. Endoscopic wire-guided papillectomy vs. conventional papillectomy for ampullary tumors: a prospective comparative pilot study. J Gastroenterol Hepatol. 2016;31:897–902.
42. Moon JH, Choi HJ, Lee YN. Current status of endoscopic papillectomy for ampullary tumors. Gut Liver. 2014;8:598–604.