Linda S. Lee
Editor

ERCP and EUS

A Case-Based Approach

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Preface

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a diagnostic to a mainly therapeutic procedure over the past 40 years. Endoscopic ultrasound (EUS) with magnetic resonance cholangiopancreatography (MRCP) have largely replaced the diagnostic capabilities of ERCP with their decreased morbidity and comparable accuracy for a variety of pancreaticobiliary disorders. This is reflected by the overall decrease in utilization of ERCP over the recent decades. EUS has begun a similar foray into therapeutics although it remains a mainstay for diagnosis and staging of luminal as well as extraluminal cancers and other lesions. With the inexorable trend towards minimally invasive procedures, EUS offers a complementary approach to ERCP especially with surgically altered anatomy and inaccessible ampullae or biliary and pancreatic ducts.

This practical case-based textbook guides the reader through scenarios involving the use of ERCP and EUS. Both parts of the book begin with chapters providing an overview of the key aspects of training and technique in ERCP and EUS. Historically endoscopic training has resembled an apprenticeship. Recently, attention has been focused on the assessment of competency. This is critical not only during training, but also amongst practicing gastroenterologists, especially with the development of new techniques. The ongoing evolution of endoscopic techniques requires novel ways to train and evaluate endoscopists, which remain in their infancy.

In the ERCP section, special attention is paid to understanding the indications and complications of the procedure and importantly, the steps to minimize complications. While true for all endoscopic procedures, ensuring appropriate indication for an ERCP is the most critical step to preventing complications and thereby protecting the patient as well as the physician. The signature indications for ERCP including biliary stones, biliary strictures, and cholangitis have not changed although innovations including EUS evaluation of the biliary system, balloon sphincteroplasty, single-operator choledochoscopy, and fully covered metal stents have modified our approach to these situations. For pancreatic diseases, development of endoscopic cystgastrostomy and necrosectomy have transformed the paradigm for managing pseudocysts and walled-off pancreatic necrosis and demand intimate knowledge of both ERCP and EUS techniques. The changing landscape of diseases with the appreciation of autoimmune pancreatitis, autoimmune cholangiopathy, intraductal papillary mucinous neoplasm, and postsurgical patients require

not only understanding of these entities, but also insight into the appropriate equipment necessary to fully evaluate and manage these patients.

In the EUS section, the wide variety of accessories and equipment as well as basic cytopathology for the endosonographer is reviewed. The endosonographer must be comfortable with the radial and linear echoendoscopes as well as the high-frequency ultrasound probes and available needles in order to select the appropriate tools for a given procedure. The cornerstone of EUS still involves staging of luminal cancers and evaluating subepithelial lesions. However, EUS has evolved beyond this to play a critical role in the evaluation of benign and malignant pancreaticobiliary diseases as well as lung cancer. The therapeutic role of EUS remains in its adolescence, and currently focuses on celiac plexus neurolysis and endoscopic cystgastrostomy and necrosectomy with recent enthusiasm for EUS-guided biliary and pancreatic access. Improved accessories and devices are required to advance the realm of therapeutic EUS.

Through the use of cases and videos, this textbook provides physicians and trainees who practice or refer patients for ERCP and EUS a clear and practical resource about these procedures. The leading authorities around the world who have contributed to this endeavor provide not only an overview of the standard of care but also their expert opinions, tips, and tricks.

I am deeply grateful to all those who contributed to this book in the midst of their incredibly busy careers and lives. I believe this work will help improve the quality of care provided to patients potentially needing ERCP and EUS, and sincerely hope it serves as a guide to those involved in the care of these patients.

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Part I
Overview of ERCP

Training in Endoscopic Retrograde Cholangiopancreatography

1

Alexander Lee and Linda S. Lee

Introduction

Since its use was first reported in 1968, endoscopic retrograde cholangiopancreatography (ERCP) has served as an effective technique in the evaluation and treatment of pancreatic and biliary diseases. The introduction of endoscopic sphincterotomy in 1974 led to the beginning of therapeutic pancreaticobiliary endoscopy in earnest [1].

Subsequently, increasingly sophisticated radiographic imaging (including ultrasound [US], computed tomography [CT], and magnetic resonance imaging [MRI]) and endoscopic imaging with endoscopic ultrasound [EUS] have been developed, effectively replacing much of diagnostic ERCP. This has led to the evolution of ERCP as a primarily therapeutic procedure [2, 3]. Major clinical indications for ERCP include removal of stones from the bile duct, stent placement for biliary obstruction, treatment of bile and pancreatic duct leaks, and therapeutic maneuvers for the treatment of chronic pancreatitis and complications of acute pancreatitis [1, 5] The role of diagnostic ERCP remains controversial in the workup of certain conditions such as sphincter of Oddi dysfunction (SOD) [5]. With its various diagnostic and therapeutic uses, ERCP affords diverse opportunities for the modern gastrointestinal endoscopist. However, in the current era of cost-conscious healthcare, scrutiny upon operator competence, procedural quality, outcomes, and complications in ERCP continues to intensify [3]. As such, the focus upon training in ERCP and ongoing certification in ERCP continues to increase as well.

Our aim in this chapter is to provide a comprehensive review of current trends and data pertaining to training in ERCP. First, we examine the changing climate of training in ERCP, touching on its original incarnations and focusing closely on the particulars of modern training programs. Second, we highlight current data on how trainees master specific skills in ERCP. Third, we review use of simulators in ERCP training. Fourth, we review current standards and quality indicators for competence in ERCP.

Evolution of Training in ERCP

As poignantly described by one expert, the excitement felt among gastrointestinal endoscopists with the advent of ERCP in the 1960s–1970s was "difficult to overstate," particularly given the limitations in imaging technology at the time [6]. The subsequent development of sphincterotomy

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created a wide open area for therapy and with it, the need for an entirely new kind of endoscopic training [1, 6].

As reported in large scale studies of national health care databases, the 1980s and 1990s saw a rise in utilization of ERCPs. From 1988 to 1996, age-adjusted ERCP rate dramatically increased by nearly threefold from 25.66 per 100,000 to 74.95 per 100,000 [7]. Concomitantly, the academic centers doing the bulk of these procedures were providing instructions in ERCP to growing numbers of trainees during their standard gastroenterology training programs. As ERCP moved fully into the mainstream and practice positions increasingly called for expertise in ERCP, the number of new graduates performing ERCP grew as well [8].

However, there has been widely acknowledged concern that exposure to and training in ERCP are often inadequate in these general gastroenterology training programs, despite a great majority of graduates subsequently performing ERCP in independent practice [9]. The early requirement of 100 ERCPs was put forth by the American Society for Gastrointestinal Endoscopy (ASGE) in 1988; in contrast, with case load being the basic metric for exposure and training, a landmark study by Jowell et al. demonstrated that a minimum of 180 ERCPs were needed to attain competence [10]. More recent data has shown that as many as 400 cases were needed to achieve competence if >80% selective cannulation rate was used as the benchmark [11]. Furthermore, ongoing improvement over the next 300 independently performed ERCPs occurred, leading to > 96 % cannulation success.

General guidelines for training in ERCP have been established in the Gastroenterology Core Curriculum published in 1996, upholding the earlier requirement of 100 ERCPs (including 25 therapeutic cases consisting of 20 sphincterotomies and 5 stent placements) as the threshold for credentialing [12]. These numbers obviously are much lower than real-world thresholds generated in the aforementioned studies, and the ASGE has stated that these numbers are the minimum number of supervised cases that must be completed before competency should be evaluated; a trainee is not considered competent by the ASGE simply by meeting these thresholds alone [13]. In agreement with Jowell et al., the most recent ASGE training guidelines in 1999 state that most trainees require at least 180–200 ERCPs (at least half therapeutic) to achieve competency, while cautioning that absolute threshold numbers can be misleading and that variations in trainee learning patterns create the need for individualized evaluation [14].

It is generally accepted that all trainees in gastroenterology fellowship should have some exposure to ERCP in order to develop a cognitive understanding of the procedure's role [12–14]. However, comprehensive ERCP training to a level of procedural competence appropriate for independent practice requires a unique level of interest, training, and case volume experience. Not all trainees should pursue such advanced training due to both variations in individual skill and regional manpower needs for physicians competent in ERCP. The demands of general gastroenterology fellowship make meeting these requirements for comprehensive ERCP training very difficult in most programs. Thus, though advanced endoscopy training (including specialized ERCP training) is not a prerequisite for independent practice in ERCP, there has been increasing support for making such additional training a formal requirement [15]. The 1990s and 2000s witnessed great growth in the number of advanced fellowships in therapeutic endoscopy to currently over 50 programs in the US that participate in the fellowship match, with ERCP as the original centerpiece [16, 17]. The higher demand was only one of the driving forces for this. As endoscopy has evolved and matured, procedures have become more complex, and ERCP is no exception. With increased complexity and potential morbidity of such procedures, there came increasing concern for specialized training to provide expertise in those procedures in order to optimize outcomes and minimize complications [8].

Currently, advanced endoscopy fellowship programs carry a prespecified emphasis on ERCP, EUS, or both, as well as training in other "higher level" endoscopic procedures such as endoscopic mucosal resection, ablative proce-

dures used for dysplastic Barrett's esophagus, deep enteroscopy, and endoluminal stenting. Programs also offer varying degrees of exposure to NOTES (natural orifice transluminal endoscopic surgery), endoscopic suturing, POEM (peroral endoscopic myotomy), bariatric endoscopy, endoscopic necrosectomy, and EUS-assisted interventional procedures [8]. Advanced endoscopy training programs are not held to standardized curriculum guidelines at this time and are not regulated. Although programs may vary in the design of their training experience, two critical components are necessary for a training program: adequate patient volume and faculty expertise. Not all training programs should offer ERCP training due to limitations of patient volume and available faculty. In the current programs aimed toward ERCP training, the quoted number of completed ERCPs by the trainee is reported between 200 and 700, exceeding the ASGE threshold for competence evaluation in essentially all cases. However, based on the studies cited above on numbers of ERCP and attaining competency, some programs may not be providing adequate numbers of ERCP to their trainees despite meeting the minimum standard set forth by the ASGE (180 ERCPs) in order to assess competency. Duration of programs vary between 1 and 2 years depending on the degree of involvement in teaching, research, general consultation, and general endoscopy, although most programs finish in 1 year [16, 17].

A trainee should investigate all aspects of a training program in ERCP when choosing a program, and understand the program's expectations as well as his or her own career interests to judge whether they align. The single most important factor of the program may be the expertise of the ERCP faculty. Programs should have a minimum of one faculty skilled at ERCP who is acknowledged as an expert by peers and is committed to teaching ERCP. Ideally, there is a panel of experienced faculty who can educate the trainee. In addition, there should be multidisciplinary teams for various disease states in the institution with whom the trainee can interact.

Funding for advanced endoscopy programs is an issue in the US with typically limited, if any, extramural funding available for the trainee. Thus, the trainee may be required to assume additional non-ERCP clinical responsibilities to help support the salary. The program must balance the financial needs with training the fellow. Many ERCP programs occur in academic medical centers where the mission also includes research. Ideally, programs should provide protected research time and mentoring for the trainee to complete a research project. A goal for the trainees should be presenting their endoscopic research at either a national or international meeting. The program should also expose the trainee to the logistics of running an ERCP service in the endoscopy unit, which include scheduling, staffing, equipment maintenance, and management skills.

Cognitive Foundations of Modern Training in ERCP

Expert consensus has proposed that training for procedural competence in ERCP should follow at least 18 months of standard gastroenterology training, during which time the trainee has gained some exposure to the cognitive aspects of ERCP as described previously [13]. Moreover, proficiency with the cognitive and procedural skills associated with basic endoscopic procedures, such as upper endoscopy and colonoscopy, are required to achieve competence in any advanced endoscopic procedure including ERCP. Subsequently, it usually requires about 12 months to achieve the advanced cognitive and technical skills essential to effectively and safely perform ERCP, whether during the standard fellowship or an additional year of advanced fellowship [13–15].

Specific cognitive skills and a comprehensive fund of pertinent knowledge form the foundation of competence in ERCP. Thus, during ERCP training, it is important to gain thorough knowledge of the anatomy and physiology of the pancreatic and biliary systems including anatomic variants and learn to interpret fluoroscopy images. The fellow must also gain a detailed understanding of indications, contraindications, and complications of ERCP in addition to knowing when alternative noninvasive or less invasive

testing should be performed instead of ERCP. The trainee should become well-versed with the issues of informed consent, patient education, procedural sedation, antibiotic prophylaxis, and periprocedural management of anticoagulant/antiplatelet agents. Proper patient selection as well as recognition of which patients and which indications (and the accompanying interventions) carry higher risk of complications and require the accompanying appropriate preprocedural counseling must be emphasized.

The trainee must also be familiar with all the tools and accessories involved with ERCP starting with the scopes, which include the diagnostic and therapeutic duodenoscopes as well as cholangioscopes and pancreatoscopes. While it is highly unlikely that the trainee will be exposed to all the commercially available tools used during ERCP worldwide, s/he should be knowledgeable of representative products from the wide array of accessories, including wires, stents, dilators, cannulas, sphincterotomes, stone extraction balloons, and baskets. With this foundation, the trainee should be capable of easily adapting to the equipment available in his/her independent practice, which may differ from that used during training.

The majority of focus and energy during ERCP training understandably centers around technical procedural skills, but a number of other periprocedural skills should be mastered. Before and during the procedure, the dignity and privacy of the patient must be respected. Principles of conscious sedation, as well as indications for monitored anesthesia care and general anesthesia, must become well understood. Once the procedure begins, the comfort and safety of the patient as well as technical success of the procedure rely on clear and productive communication between the endoscopist and assistant(s); trainees must learn to become especially team-oriented, being aware of multidisciplinary and ancillary staff during the procedure and the importance of multidisciplinary contributions in the patient's care (radiology, surgery, anesthesiology, pathology, oncology, etc.).

During training, the importance of proper post-ERCP management must be emphasized to the trainee. Continuing the theme of team-oriented care, the fellow must be prompt, clear, and concise in reporting findings and recommendations to referring and consulting physicians. Clarity and use of accepted standard terminology in procedural documentation is also important. Then in managing the post-ERCP patient, the trainee must acknowledge the high-risk nature of ERCP and be able to recognize complications. Pancreatitis and cholangitis often do not manifest until hours later, and these and other complications must be expeditiously recognized and treated [13].

Specific Technical Components of Expertise in ERCP

ERCP is recognized as a technically complex procedure, with many elements of cognitive and procedure skill required. In considering each aspect, one important consideration is the wide gradient of difficulty, which demands varying degrees of skill. First introduced by Schutz and Abbott and subsequently adapted by many investigators, a grading system of difficulty has been formally endorsed by the ASGE and American College of Gastroenterology (ACG) (Table 1.1) [18–20]. Grade 2 procedures are likely to require at least 200 procedures, a number which is unlikely to be reached during a 3-year general gastroenterology fellowship, as alluded to previously [8, 13, 20].

Basics and Diagnostics

Passage of the Duodenoscope

Mastery of the standard (forward-viewing) upper endoscope and colonoscope is a prerequisite before the trainee can begin passing the side-viewing duodenoscope. This requires skilled use of the endoscope dials, scope torque, and body movement. Importance of the endoscopic examination prior to reaching the bilioenteric orifice should be emphasized, and this is closely linked with the development of the proprioceptive skills to recognize a structural impediment to scope passage (such as cervical osteophyte or esophageal diverticulum) and subsequently make appropri-

Table 1.1 Grades of difficulty for ERCP. (Adapted from References [18-20].)

Grade of difficulty	Biliary procedures	Pancreatic procedures
Grade 1	Diagnostic cholangiogram	Diagnostic pancreatogram
	Biliary cytology	Pancreatic cytology
	Standard sphincterotomy with removal of stones < 10 mm	
	Stricture dilation, stent or nasobiliary drain for extrahepatic stricture or bile leak	
Grade 2	Diagnostic cholangiogram with Billroth II anatomy	Diagnostic pancreatogram with Billroth II anatomy
	Removal of extrahepatic bile duct stones > 10 mm	Minor papilla cannulation
	Stricture dilation, stent or nasobiliary drain for hilar tumors or benign intrahepatic strictures	
Grade 3	Sphincter of Oddi manometry	Sphincter of Oddi manometry
	Cholangioscopy	Pancreatoscopy
	All therapy with Billroth II anatomy	All pancreatic therapy including pseudocyst drainage
	Removal of intrahepatic stones	
	Removal of any stones with lithotripsy	

ERCP endoscopic retrograde cholangiopancreatography

ate adjustments. Also, the trainee should become comfortable with passage of the duodenoscope in both the nonintubated and intubated patient in the prone, semiprone, or supine positions. Traversing the esophagus, stomach, pylorus, and proximal duodenum requires that the trainee learn a combination of landmarks and proprioceptive cues, while minimizing the introduction of air and endoscope loops. Once the bilioenteric orifice is reached, the trainee must master establishment of the "short" position and proper positioning for cannulation. Navigation of the subgroup of patients with surgically altered anatomy requires a higher level of expertise, particularly for patients with Roux-en-Y anatomy.

There are no published data regarding the number of ERCPs or type of training required to attain competency in duodenoscope passage.

Selective Cannulation

Selective deep cannulation of the desired ductal system is a vital component to both the diagnostic and therapeutic application of ERCP. It requires coordinated manipulation of the scope and the catheter (with/without a guide wire). To obtain mastery of this cornerstone of ERCP, the trainee will need extensive one-on-one training, supplemented by review of literature and/or video media. A thorough understanding of the equipment is important, which includes the endoscope, catheters/sphincterotomes, guide wires, and supplementary tools. The trainee should understand the role of both the assistant and the operator in using this equipment. The trainee must know the periampullary, biliary, and pancreatic anatomy, such that the abnormal or variant anatomy is recognized and the accompanying adjustments can be made. Appropriate need for biopsy and further workup should be recognized as well.

Trainees should be prepared for dealing with difficulty cannulating the desired duct. Low-risk ancillary maneuvers such as contrast or wire assistance and dual-wire technique are options, as are advanced techniques, which require higher level expertise (described later in this chapter). In the event of cannulation failure, the trainee should be aware of when to plan for a repeat attempt and when to make a referral for alternative intervention that could be provided by an interventional radiologist or surgeon.

Given its central role in ERCP, attaining competence in achieving selective cannulation has been perhaps the most investigated aspect of ERCP training. In the 1996 seminal study by Jowell and colleagues, among a pool of 17

trainees, the probability of successfully deeply cannulating the common bile duct was just 0.65 [95% confidence interval (CI) 0.53–0.78] after 180 ERCPs [10]. Another study published that same year by Watkins et al. assessed 21 trainee operators in selective cannulation of pancreatic/bile duct via any papilla, and the cannulation rate increased from 46 to 90% with completion of 10 and then 90 ERCPs [21]. A more rigorous examination of cannulation skill acquisition (though with only one operator) was performed by Verma et al. in 2007; this study demonstrated that the success rate of bile duct cannulation via a native papilla increased from 43% to over 80% with caseload from 0 to 350–400 ERCPs, and then to over 96% with caseload from 400 to 700 ERCPs [11].

Data from the 1990s indicates that successful selective cannulation rates of ≥95% are consistently achieved by experienced endoscopists. Meanwhile, a selective biliary cannulation rate of ≥80% has been widely accepted as a target for trainees [3, 13]. Data continues to emerge regarding the association of ERCP volume with cannulation ability; however, it is important to note that volume is only the most basic benchmark for training. Few data currently exist regarding the methodological or qualitative aspects of training leading to acquisition of this critical skill, an ongoing theme in the ERCP training literature [15, 22].

One area of particular concern in training programs remains the issue of inadvertent repeated non-selective ductal cannulation; that is, repeated cannulation of either the pancreatic duct instead of the desired bile duct, or vice versa, and subsequent possible complications. While numerous studies have described patient-related and procedure-related risk factors contributing to complications associated with ERCP, little is known about the risk attributable to trainee involvement. However, it is known, for example, that high numbers of cannulation attempts and/or pancreatic duct injections are risk factors for post-ERCP pancreatitis [23]. One study showed that trainee involvement was associated with increased risk [24]. A recent study by Kwek et al. demonstrated no difference between trainee-involved ERCPs and ERCPs solely by experienced operators when a protocol was followed in which the supervising endoscopist took over for the trainee if one of the following criteria were met: (1) failed cannulation after 5 attempts, (2) unsuccessful cannulation after 10 min, (3) edematous papilla, (4) pancreatic duct cannulation ≥2 times [25, 26].

Cholangiography/Pancreatography

Similar to EUS, ERCP places the endoscopist in the role as technician and radiologist. Thus, to become skilled in cholangiography and pancreatography, the trainee must become adept at two separate skill sets.

First, the trainee must understand the maneuvers necessary to acquire the best possible fluoroscopic image. This includes the following: positioning of the duodenoscope, patient, and fluoroscopy equipment; volume and dilution of contrast, knowing to avoid overfilling; manipulation of radiation dose and degree of magnification; use of balloon occlusion (in the case of cholangiography).

Second, the trainee must become adept at interpreting the obtained still and dynamic images in real-time. This comes from thorough knowledge of both normal and variant pancreaticobiliary anatomy, as well as the changes associated with biliary disease (such as choledocholithiasis, benign/malignant strictures, primary sclerosing cholangitis, choledochal cysts, bile leaks) and pancreatic disease (pancreatic malignancy, chronic pancreatitis, intraductal papillary mucinous tumors, ductal disruptions leading to pseudocyst). These more cognitive aspects of cholangiopancreatography are developed through one-on-one discussion between trainer and trainee following each ERCP, supplemented by case conferences and didactic sessions.

Third, the trainee must understand proper handling of fluoroscopy in order to minimize radiation exposure to the staff as well as the patient. This involves the use of appropriate protective lead shielding by the staff to the body, thyroid, eyes, and hands (when in the fluoroscopy field). The

trainee must know the well-defined techniques to reduce fluoroscopy exposure including increasing distance from the radiation source, reducing total fluoroscopy time, collimation, placing the image receptor as close to the patient as possible, using magnification only as needed, and changing to a low dose rate setting, if possible [27]. In addition the need to monitor one's own radiation exposure with the use of radiation-exposure dosimeters should be appreciated by the trainee.

There are no published data regarding the number of ERCPs or type of training required to attain competency in cholangiography/pancreatography.

Tissue Sampling

Sampling of the ductal tissue is often performed during ERCP, typically upon recognition of strictures whether benign or malignant. Approaches include brushings for cytology, ductal fluid aspiration for cytology, and/or fluoroscopically guided biopsy. Trainees must know the indications, appropriate technique, and performance characteristics of each.

There are no published data regarding the number of ERCPs or type of training required to attain competency in tissue sampling.

Therapeutics

Sphincterotomy

Biliary sphincterotomy is utilized in ERCP to access the bile duct, remove bile duct stones, and/or facilitate introduction of accessories into the biliary system. Despite being an integral part of ERCP, sphincterotomy is also considered the most dangerous part of ERCP due to risks of bleeding, pancreatitis, and perforation. Thus, proper training in this technique is absolutely essential. This should be taught and performed by the trainee only after proficiency in basic ERCP techniques. Training in sphincterotomy then begins with gaining full understanding of the tools at one's disposal, including sphincterotome devices, guide wires, and electrosurgical current generators (with cutting and/or blended current).

The specific technical aspects of performing biliary sphincterotomy are well-established and described in detail in the literature [28, 29]. Major points of emphasis should be establishing good endoscopic position, well-directed cutting, steady instrument control, and following anatomic landmarks. As the trainee masters sphincterotomy, s/he must also have complete understanding of the associated risks, factors influencing risk, and potential alternative therapies (such as sphincteroplasty or stent placement). An important part of this training is endoscopic management of complications as well, particularly bleeding.

Pancreatic sphincterotomy is a related technique, providing ductal decompression in a manner similar to its biliary counterpart; however, pancreatic sphincterotomy is accompanied by additional risk and can be technically more challenging. A subset of pancreatic sphincterotomy involves minor papillotomy and associated interventions in cases of pancreas divisum. Trainees need thorough understanding of the indications and contraindications to these pancreatic interventions, as well as special accessories to cannulate the minor papilla and proper use of pancreatic duct stenting. Like most pancreatic endotherapy, it should be undertaken only by experienced trainees well-versed in biliary interventions.

Data regarding training and skill acquisition of sphincterotomy is limited. The previously mentioned 1996 version of the ASGE Gastroenterology Core Curriculum put forth 100 ERCPs, including 20 sphincterotomies, as the threshold prior to evaluation of competency; updated guidelines in 1999 stated 180 ERCPs as the threshold including 90 therapeutic cases, with the number of sphincterotomies unspecified [14]. In a review of training in sphincterotomy, Leung and Foster emphasize that so much of endoscopic technique remains difficult to measure—the training experience in ERCP varies from trainee to trainee, and the technical assessment of safe, effective sphincterotomy is

difficult to quantitate and requires a measure of self-awareness. The young endoscopist, whether during training or after completion of it, must be mindful of his/her own skill level and improve upon it continually [28]. However, emerging data has begun to recognize that consistent consensus for quality sphincterotomy is being established, apart from complication rate. In a small prospective survey of biliary endoscopists, there was considerable agreement among the experts in scoring five recorded clinical papillotomies and in differentiating a good cut from a fair cut using a previously reported scoring scale [30]. Interest is growing in the use of ERCP simulator devices to facilitate acquisition of sphincterotomy skills, discussed later in this chapter.

Needle knife sphincterotomy ("pre-cut") is an advanced therapeutic maneuver distinct from standard biliary or pancreatic sphincterotomy, as it is usually used to facilitate deep cannulation in cases when traditional deep cannulation fails. This technique requires a "free-hand" element, which demands the highest level of endoscopic control and proficiency, complete knowledge of ampullary anatomy, and full command of endoscopic maneuvers available to manage complications such as bleeding or perforation. It is known that the trainees' exposure and experience with this technique varies widely, and as such, competency with the needle knife also presumably varies upon completion of training. Given the utility of this technique and its frequently essential role in completing difficult cannulations, appreciation of a need for standardized exposure and training in needle knife sphincterotomy is growing [31].

Dilation

Strictures of the bile duct or pancreatic duct may be treated using dilation, whether via dilating catheters or hydrostatic balloons. Stricture management via dilation is a key skill for the trainee to master, which encompasses an understanding of its indications, technique, and complications. In certain cases, dilation can also be performed at the biliary or pancreatic sphincter using a balloon, usually to facilitate stone extraction, and the trainee should be aware of the associated indications, technique, and complications.

There are no published data regarding the number of ERCPs or type of training required to attain competency in dilation.

Stent Placement

Biliary decompression is a common indication for ERCP. The trainee must become well-versed in the indications for stenting and selection of stent (type, size, and length). S/he must master the endoscopic techniques required for optimal stent placement and positioning. Nasobiliary drainage is currently used less frequently but is still included as a recommended part of ASGE training guidelines for ERCP as well.

The 1988 and 1996 ASGE guidelines put forth 5 stent placements (among the 20 therapeutic cases) as a threshold prior to assessing competency; as mentioned, newer guidelines have increased this number of therapeutic cases [12, 14]. There is no rigorous data regarding the number of ERCPs or type of training required to attain competency in stent placement.

Pancreatic stent placement is a higher-risk endeavor which is usually reserved for experienced operators and advanced trainees. The trainee must learn proper technique and positioning, accompanied by an understanding of which clinical scenarios warrant this maneuver.

Stone Extraction

Removal of bile duct stones is a relatively common maneuver during ERCP that can be accomplished using balloons or baskets; there may also be a need for mechanical lithotripsy. The trainee must master these techniques, and higher level training is necessary for advanced lithotripsy (electrohydraulic and/or laser-assisted). Removal of pancreatic duct stones, also usually reserved for advanced trainees, is a higher-risk endeavor requiring additional expertise.

There are no published data regarding the number of ERCPs or type of training required to attain competency stone extraction.

Advanced Techniques

Advanced Diagnostics

These techniques complement routine ERCP and require a strong foundation in the broad basic skill set outlined thus far, with the addition of advanced training in a specialized referral center with experts. Such techniques include but are not limited to the following.

Sphincter of Oddi Manometry (SOM)

This is a challenging maneuver requiring a commitment to grasping the technical and interpretive aspects of the procedure. Obtaining manometric values must be done in the proper context, given that the relevant patient population is at high risk for post-ERCP pancreatitis and requires a thoughtful and thorough consent process. The trainee must understand the impact of sedation on manometric values and how to interpret the pressure tracing.

Cholangioscopy/Pancreatoscopy

Direct visualization of the ductal systems can be performed using 8F to 10F endoscopes, and the quality and durability of these instruments are continually improving. The trainee must learn the application of these approaches to strictures, neoplasms, and stones.

Intraductal Ultrasound

This advanced technique for evaluating ductal strictures involves use of a 20 MHz transducer passed via the working channel of the ERCP scope and advanced under fluoroscopic guidance over a guide wire. Like any EUS-based procedure, this requires a high level of training in both proper image generation and interpretation, in conjunction with excellent endoscopic control.

Advanced Therapeutics

These techniques are very sophisticated, representing the cutting edge of endoscopic therapy, but they are also challenging and among the highest risk procedures that can be performed by a gastroenterologist. Advanced therapeutic procedures include but are not limited to complex stone extraction requiring electrohydraulic or laser lithotripsy, pancreatic stone/stricture management, pseudocyst drainage, necrosectomy, ampullectomy, photodynamic therapy, brachytherapy, minor papilla therapy, and rendezvous techniques. Generally, trainees will only receive sufficient instruction for competency in these procedures in the context of a dedicated advanced endoscopy fellowship of 12 months or more. Furthermore, training in the most complex of these therapeutic cases can potentially extend beyond fellowship and into full clinical practice, under the tutelage of a more experienced colleague in the endoscopy group.

Use of Simulators in ERCP Training

Endoscopy simulators allow trainees to practice invasive endoscopic procedures in a controlled environment with no risk to patients and opportunities for comprehensive feedback. Colonoscopic simulators have existed since at least the 1970s, and given the relatively higher level of risk for complications in ERCP compared to colonoscopy, simulators for ERCP have been developed over the years as well [32, 33]. The four types include live animals, tissue-based simulators, mechanical simulators, and computer simulators.

Live Animals

Since the early 1990s, anesthetized pigs and dogs have been used for training in ERCP [34, 35]. Major advantages include natural tissue elasticity and sensation, as well as realistic tactile feedback. Disadvantages include cost, ethical and animal welfare concerns, hygiene issues,

need for animal-specific endoscopes, and need for specialized animal facilities with veterinary anesthesia support [3]. Additional issues specific to pigs include the fact that there are two distinct papillae for the pancreatic duct and bile duct, the stomach remains full of food longer, and the distance to the pylorus is lengthened by the long snout [3].

Tissue-Based Simulators

These devices utilize the relevant organs for simulator purposes and are often referred to as "ex vivo" models. Advantages include more realism than mechanical models, lower cost and fewer regulatory issues than animal models. Disadvantages include lengthy and intensive setup and disposal procedures, as well as unfavorable tactile features compared with living tissue [36]. One of the early tissue models for ERCP was the CompactEASIE^{TM} (Erlangen Active Training Simulator Interventional Endoscopy) developed in 1998 as a modified and more lightweight version of the (EASIE). CompactEASIE^{TM} utilized a plastic platform and a specially prepared porcine upper gastrointestinal package (esophagus, stomach, duodenum) with the common bile duct, gallbladder, and liver. This allowed practice of biliary cannulation with discrete cannulation of left/right systems, sphincterotomy, needle knife, basic accessory use, stent placement, and stone extraction [37]. The ASGE has developed a simulator similar to the CompactEASIE^{TM} called the Endo X Trainer, also a plastic table-top platform with porcine organs [36]. Two more recent simulators have involved creation of a neo-papilla utilizing a chicken heart or simulating sphincter muscle using pig stomach and/or rectum (Fig. 1.1) [38, 39].

Mechanical Simulators

Mechanical models suffer from poor mimicry of actual tissue and do not have any inherent variety [36]. The earliest of these were used for general endoscopy rather than ERCP, but newer generations of these devices have addressed some of the shortcomings. The Boškoski-Costamagna ECRP Trainer was developed in 2010 and replicates the duodenum and pancreaticobiliary system using plastic and light metals (Fig. 1.2). This model allows training in cannulation, stone extraction, stenting, balloon dilation, brushing, and biopsy (personal communication). Another relatively novel mechanical simulator, X-Vision ERCP Training System, is a simulated ERCP platform with simulated fluoroscopy.[40]

Computer Simulators

While still theoretically suffering from issues with realism and tactile feedback, computerized models have the advantages of a limitless variety of clinical scenarios, performance/data tracking, standardized training "modules," and

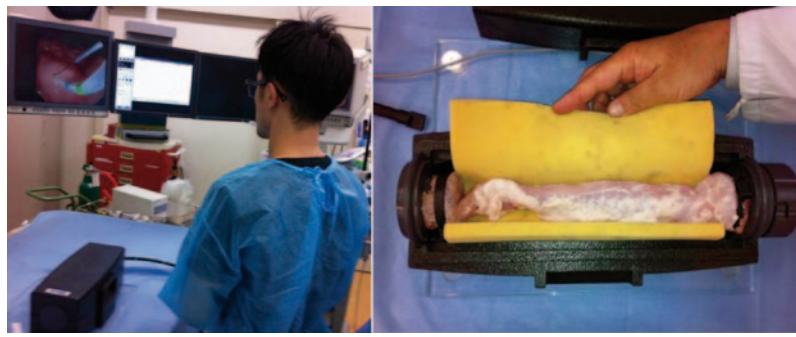

Fig. 1.1 Tissue simulator with simulated papillae created using in vivo and ex vivo porcine stomach and rectum. (Courtesy of Dr. Takao Itoi)

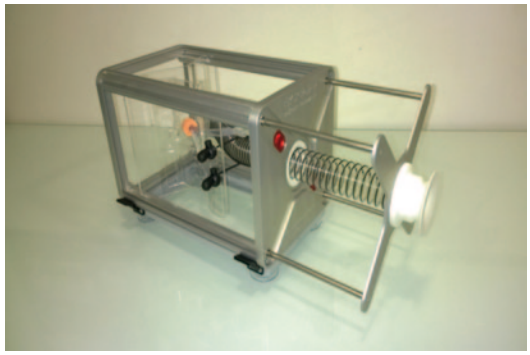

Fig. 1.2 Mechanical simulator made of plastic and light metals that replicates the duodenum and pancreaticobiliary system. (Courtesy of Dr. Ivo Boškoski)

minimal preparatory time or labor [32, 33]. Such simulators were limited by the cost of computer processing and hardware in the 1980s, but the rapid evolution of microprocessors and personal computing have allowed powerful modern simulation devices. A milestone was the Simbionix GI-Mentor^{TM} and its most current version, the GI-Mentor II^{TM} and main rival, the CAE Healthcare AccuTouch^{TM}. These create realistic virtual ERCP environments while leading the trainee through various diagnostic and interventional procedures, didactic modules, and anatomy/pathology atlases [41].

Comparisons Between Simulators

A variety of studies evaluating some of the many aforementioned simulators have shown promising results in ERCP training. However, data comparing the different types of simulators are limited. Sedlack et al. compared a live animal simulator (anesthetized pig), a tissue-based simulator (CompactEASIE^{TM}), and a computerized simulator (GI-Mentor II^{TM}) in terms of tissue pliability, papillary anatomy, visual realism, cannulation realism, and overall ERCP experience using 20 endoscopists and their self-reported experiences after training on the simulators [42]. The tissue-based simulator scored highest for realism, and its usefulness in teaching ERCP skills was noted. Scores for the computerized simulator were statistically significantly lower in nearly all areas compared to the live and tissue-based models. In contrast, one recent study comparing a proprietary mechanical simulator to a proprietary tissue-based simulator (both simulators designed and constructed by the authors) demonstrated that the mechanical simulator was associated with a statistically significant greater increase in understanding and confidence metrics compared to the tissue-based simulator [43]. In a separate study by the same group, this same proprietary mechanical simulator also led to higher confidence scores compared to a commercially available computer simulator, the GI-Mentor II^{TM} [44].

Simulators for ERCP training are widely used in endoscopy workshops all over the world, but their viability for standardized use in gastroenterology fellowship programs remains uncertain. One study did evaluate the impact of mechanical simulator training before starting ERCP training by randomizing fellows to have a 6-h training session tutored by an endoscopist or no training. The simulator-trained fellows had higher rates of successful biliary cannulation with odds ratio 2.89 (95% CI 2.21, 3.80, $p<0.0001$) compared to fellows who did not have exposure to the simulator [45]. Interestingly, more simulator sessions by the fellows on their own did not further improve their ERCP performance. Another multicenter study using a mechanical simulator randomized 16 novice trainees to practice on the simulator versus no simulator use. After 16 weeks, fellows who had practiced on the simulator demonstrated significantly shorter time to cannulation (mean 4.7 vs. 10.3 min) and higher rates of successful cannulation (70 vs. 47%). Of note, the trainees participating in this study had completed less than a mean of 30 ERCPs at the onset of the study. Thus, the authors highlighted these results as an encouraging development for early training in ERCP, particularly given the relatively steep learning curve and complexity associated with ERCP [46]. Such results mirror the simulator-driven improvements in proficiency of esophagogastroduodenoscopy (EGD) or colonoscopy [47]. The Accreditation Council for Graduate Medical Education (ACGME) has formally required the use of simulators during gas-

troenterology fellowship [48]. It must be noted that there is a paucity of data concerning benefit to novice endoscopists learning ERCP on simulators, and cost remains a major issue as well. Even if those issues were overcome, a paradigm shift in the approach to ERCP training will be necessary for simulators to attain widespread acceptance [8].

Posttraining Competence and Quality Indicators in ERCP

As mentioned multiple times throughout this chapter, ERCP is widely recognized as one of the most technically demanding and highest risk procedures performed by a gastroenterologist. As such, scrutiny on the process of ERCP training has been coupled with a growing emphasis on standards for competence and benchmarks of quality in ERCP following the conclusion of training. The ASGE/ACG Taskforce on Quality in Endoscopy outlined a set of quality indicator guidelines in 2015, as shown in Table 1.2 [49].

Intraprocedural quality indicators—cannulation rates, extraction of common bile duct stones, biliary stent placement—have been the subject of particular analysis and research, as these are essentially measures of basic ERCP skills which must be attained during supervised procedural training and cannot be taught in solely didactic or self-driven learning. A comprehensive survey of the literature to substantiate the specified standards is beyond the scope of this chapter. A recent meta-analysis assessed current ERCP performance in the published literature and compared

Table 1.2 Summary of quality indicator for ERCP proposed by ASGE/ACG Taskforce (Adapted from [49])

Quality indicator	Grade of recommendation[a]	Performance Target (%)
Preprocedure		
1. Appropriate indication documented*	1C	>90
2. Documentation of informed consent	1C	>98
3. Prophylactic antibiotics	2B	>98
4. Appropriate credentialing of endoscopist	3	>98
5. Recorded yearly volume of endoscopist	1C	>98
Intraprocedure		
6a. Documentation of cannulation of desired duct	1C	>98
6b. Rate of cannulation of desired duct (native papillae)*	1C	>90
7. Documentation of fluoroscopy time	2C	>98
8. Extraction of common bile duct stones <1cm*	1C	≥90
9. Biliary stent placement for obstruction below bifurcation*	1C	≥90
Postprocedure		
10. Appropriate documentation in procedure report	3	>98
11. Documentation of complications	3	>98
12. Rate of post-ERCP pancreatitis*	1C	N/A
13. Rate of perforation	2C	≤0.2
14. Rate of post-ERCP hemorrhage	1C	≤1
15. Rate of contacting patients ≥ 14 days after ERCP to detect delayed complications	3	>90

ERCP endoscopic retrograde cholangiopancreatography, *ASGE* American Society for Gastrointestinal Endoscopy, *ACG* American College of Gastroenterology

[a] Definitions of grades of recommendation:

1C (clear benefit, based on observational studies, intermediate-strength recommendation, may change when stronger evidence available)

2B (unclear benefit, based on randomized trials with important limitations, weak recommendation, alternative approaches may be better under some circumstances)

2C (unclear benefit, based on observational studies, very weak recommendation, alternative approaches likely to be better under some circumstances)

3 (unclear benefit, based on expert opinion only, weak recommendation, likely to change as data becomes available)

* Priority indicators

it to the targets set by the previous ASGE/ACG Taskforce from 2006, which included cannulation, biliary stone extracton, and nonhilar stent placement rates over 85% and precut use less than 15%. Including 52 articles among the 8005 reviewed articles, the meta-analysis demonstrated overall ERCP quality to meet the established standards with the following success rates: bile duct cannulation 89.3% (95% CI 0.866–0.919), pancreatic duct cannulation 85.0% (95% CI 0.813–0.886), common bile duct stone extraction 88.3% (95% CI 0.825–0.941), and nonhilar biliary stenting 97.5% (95% CI 0.967–0.984) [49]. Precut utilization rate was 10.5% (95% CI 0.087–0.123). While the study group acknowledged the over-representation of academic centers in the meta-analysis pool, another study did examine real-world ERCP performance using a voluntary anonymous Internet-based database through which endoscopists reported details of ERCP cases. Preliminary results encompassing over 18,000 procedures by 63 endoscopists over 3 years demonstrated results comparable to the meta-analysis of the literature, though variability was seen, as one might expect. Mean deep biliary cannulation rate was 97%, with 15 participants at less than 90% [51]. An analysis of complication rates and their associated factors is discussed in Chapter 3.

The debate regarding the procedural volume needed for trainees to reach these quality standards has been highlighted previously in this chapter. Of note, there is a paucity of data regarding how competent trainees are as they complete fellowship and begin practice in ERCP. One very revealing study surveyed third year trainees at 155 general gastroenterology fellowship programs across the US. Among the 69 respondents, it was found that 64% did not achieve competence defined by having 180 ERCPs, and 33% did not feel their training was adequate; yet, 91% planned to perform ERCP independently in practice following completion of fellowship. These fellows performed a median of 140 ERCPs and 35 sphincterotomies during training, with an associated median comfort level for independently performing sphincterotomy of 7.5 on a scale of 1 to 10. The median estimated success rate for independent free cannulation was 75% [9]. This study did not account for dedicated advanced endoscopy trainees. However, it raises concerns regarding competence and quality in ERCP upon completion of training. Tools for assessment of competency in ERCP during training are in the early stages of development and validation, and they may play a larger role as the sophistication and standardization of ERCP training continues to evolve [15, 52].

Credentialing is the process of assessing and validating the qualifications of a physician to provide patient care by evaluating the person's medical license, training, experience, knowledge base competence, and ability to perform the procedure requested independently. The ASGE published guidelines for credentialing and granting hospital privileges to perform gastrointestinal endoscopy [53]. Determining competency and qualifications for credentialing can be challenging. Meeting the intraprocedural quality indicators discussed above in addition to assessing the quality indicators in Table 1.2 may provide some guidance in evaluating the endoscopist's competence. As with credentialing in general gastrointestinal endoscopy, competency is ultimately assessed by the training director or other independent proctor.

Importantly, no standardized criteria exist for credentialing specifically in ERCP, and guidelines for maintaining ERCP privileges vary across institutions. The goal of renewing privileges is to ensure clinical competence while promoting quality improvement and maintaining patient safety. The ASGE has provided useful guidelines for renewing endoscopic privileges [54]. However, each institution must develop and maintain its own guidelines for granting and renewing privileges as well as the minimum number of procedures necessary for renewal. This number must reflect both the cognitive and technical skills required for ERCP. The British Society of Gastroenterology recommends a minimum of 75 ERCPs per year [55]. Of particular concern is a survey study of 1000 ASGE members which revealed that 40% were performing less than 50 ERCPs per year [56]. If the endoscopist does not

perform an ongoing volume of advanced procedures, the quality of patient care may diminish, potentially leading to adverse events [10]. Endoscopists seeking to renew ERCP privileges must document an adequate case load over a set period of time. This should include objective measures such as number of cases, success rates of various techniques, and complications. Given the higher level of risk undertaken in ERCP compared to other gastrointestinal endoscopy procedures, reported quality indicators (including the intraprocedural standards discussed above) may become factors in credentialing and renewing privileges. Endoscopic privileges should be renewed every two years as per the Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) [57]. Contingency plans must be in place when minimal competence has not been demonstrated.

Conclusion

ERCP has evolved from its origins as a diagnostic tool to a powerful primarily therapeutic modality, with an armamentarium of accessories that has grown continually since the first sphincterotomies of the 1970s. Such therapeutic potential is accompanied by a level of procedural challenge that is unique, mandating rigorous and comprehensive training. Indeed, training in ERCP is a multifaceted endeavor requiring a level of endoscopic skill and cognitive understanding beyond that of traditional gastrointestinal endoscopy. Such training encompasses mastering a diverse set of maneuvers that have been highlighted here. The exact number of ERCPs needed for competency may be debated, and the standardization of instruction may evolve, even as the tools to measure a trainee's mastery of ERCP skills mature. However, what is under no debate is the focused, dedicated training that is needed to become an effective ERCPist, and for most, this will require a dedicated year of advanced endoscopy training. Simulators are adjunctive tools that show promise, and further studies will elucidate their role in ERCP training.

Key Points

- ERCP has evolved over the past 40 years into an increasingly complex and primarily therapeutic modality, which requires a high level of expertise.
- The 4th year fellowship (or so-called advanced endoscopy fellowship) has gained favor as the approach to training in ERCP and other advanced endoscopic procedures.
- The process of trainees' acquisition of competency in ERCP is an area of growing research interest, and to date, studies have focused primarily on numbers of completed ERCPs. The most recent ASGE guidelines have identified 180–200 ERCPs as the minimum number to attain competency although absolute numbers alone may be misleading in judging the competence of a particular trainee.
- Appropriate training in ERCP is comprehensive and multifaceted including cognitive, technical, and periprocedural skills essential to good ERCP practice.
- Technical aspects of ERCP training demand an excellent understanding of the duodenoscope and associated tools, skill with varied diagnostic and therapeutic maneuvers, and accurate fluoroscopic image interpretation.
- Advanced techniques in ERCP are associated with greater risk, and use of such maneuvers requires specialized training at referral centers under the tutelage of experienced operators.
- Use of simulators in ERCP training has shown promise in recent reports and require further study.
- Specific quality indicators for ERCP have been established with particular emphasis on success rates for biliary cannulation, stone extraction, and biliary stenting. This coincides with growing interest in standardization of measures of quality and competence in ERCP.

References

1. Adler DG, Baron TH, Davila RE, Egan J, Hirota WK, Leighton JA, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. Gastrointest Endosc. 2005;62(1):1–8.

2. Baron TH, Petersen BT, Mergener K, Chak A, Cohen J, Deal SE, et al. Quality indicators for endoscopic retrograde cholangiopancreatography. Am J Gastroenterol. 2006;101(4):892–7.
3. Hochberger J MD, Maiss J. ERCP training. In: Baron TH KR, Carr-Locke DL, editor. ERCP. Philadelphia: Elsevier; 2008. p. 61–70.
4. Sherman S. What is the role of ERCP in the setting of abdominal pain of pancreatic or biliary origin (suspected sphincter of Oddi dysfunction)? Gastrointest Endosc. 2002;56(6 Suppl):S258–66.
5. Carr-Locke DL. Therapeutic role of ERCP in the management of suspected common bile duct stones. Gastrointest Endosc. 2002;56(6 Suppl):S170–4.
6. Cotton PB. Are low-volume ERCPists a problem in the United States? A plea to examine and improve ERCP practice-NOW. Gastrointest Endosc. 2011;74(1):161–6.
7. Mazen Jamal M, Yoon EJ, Saadi A, Sy TY, Hashemzadeh M. Trends in the utilization of endoscopic retrograde cholangiopancreatography (ERCP) in the United States. Am J Gastroenterol. 2007;102(5):966–75.
8. Heller SJ, Tokar JL. Current status of advanced gastrointestinal endoscopy training fellowships in the United States. Adv Med Educ Pract. 2011;2:25–34.
9. Kowalski T, Kanchana T, Pungpapong S. Perceptions of gastroenterology fellows regarding ERCP competency and training. Gastrointest Endosc. 2003;58(3):345–9.
10. Jowell PS, Baillie J, Branch MS, Affronti J, Browning CL, Bute BP. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. Ann Intern Med. 1996;125(12):983–9.
11. 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(3):394–400.
12. Tavill AS, Bissell DM, Katz S, Richter JE, Freston JW, Walsh JH, Keeffe EB, Roth BE. Training the gastroenterologist of the future: the gastroenterology core curriculum. The Gastroenterology Leadership Council: American Association for the Study of Liver Diseases, American College of Gastroenterology, American Gastroenterological Asssociation, and American Society for Gastrointestinal Endoscopy. Gastroenterology. 1996;110(4):1266–300.
13. Chutkan RK, Ahmad AS, Cohen J, Cruz-Correa MR, Desilets DJ, Dominitz JA, et al. ERCP core curriculum. Gastrointest Endosc. 2006;63(3):361–76.
14. ASGE Training Committee, Adler DG, Bakis G, Coyle WJ, DeGregorio B, Dua KS, Lee LS, McHenry Jr. L, Pais SA, Rajan E, Sedlack RE, Shami VM, Faulx AL. Principles of training in gastrointestinal endoscopy. From the ASGE. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc. 1999;49(6):845–53.
15. Hellier MD, Morris AI. ERCP training–time for change. Gut. 2000;47(4):459–60.
16. Rosenthal LS. Is a fourth year of training necessary to become competent in EUS and ERCP? Notes from the 2008 class of advanced endoscopy fellows. Gastrointest Endosc. 2008;68(6):1150–2.
17. Stevens T. Advanced endoscopy fellowships: weighing the pros and cons. Gastrointest Endosc. 2006;64(5):784–5.
18. Schutz SM, Abbott RM. Grading ERCPs by degree of difficulty: a new concept to produce more meaningful outcome data. Gastrointest Endosc. 2000;51(5):535–9.
19. Schutz SM. Grading the degree of difficulty of ERCP procedures. Gastroenterol Hepatol (N Y). 2011;7(10):674–6.
20. Johanson JF, Cooper G, Eisen GM, Freeman M, Goldstein JL, Jensen DM, et al. Quality assessment of ERCP. Endoscopic retrograde cholangiopacreatography. Gastrointest Endosc. 2002;56(2):165–9.
21. Watkins JL, Etzkorn KP, Wiley TE, DeGuzman L, Harig JM. Assessment of technical competence during ERCP training. Gastrointest Endosc. 1996;44(4):411–5.
22. Lohr JM, Aabaken L, Arnelo U, Gronroos J, Halttunen J, Hauge T, et al. How to cannulate? A survey of the Scandinavian Association for Digestive Endoscopy (SADE) in 141 endoscopists. Scand J Gastroenterol. 2012;47(7):861–9.
23. Dumonceau JM, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH, et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. Endoscopy. 2010;42(6):503–15.
24. Cheng CL, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. Am J Gastroenterol. 2006;101(1):139–47.
25. Kwek BE, Ang TL, Teo EK, Fock KM. Making ERCP training safe: a protocol-based strategy to minimize complications during selective biliary cannulation. J Interv Gastroenterol. 2012;2(2):66–9.
26. Lim BS. Quality matters: a protocol-based strategy in ERCP training. J Interv Gastroenterol. 2012;2(2):76–7.
27. Pedrosa MC, Farraye FA, Shergill AK, Banerjee S, Desilets D, Diehl DL, et al. Minimizing occupational hazards in endoscopy: personal protective equipment, radiation safety, and ergonomics. Gastrointest Endosc. 2010;72(2):227–35.
28. Leung J, Foster E. How do we ensure that trainees learn to perform biliary sphincterotomy safely, appropriately, and effectively? Curr Gastroenterol Rep. 2008;10(2):163–8.
29. Leung J. Fundamentals of ERCP. In Cotton PB LJ, editor. ERCP. Oxford: Blackwell; 2005. p. 17–80.
30. Leung JW, Leung FW. Papillotomy performance scoring scale–a pilot validation study focused on the cut axis. Aliment Pharmacol Ther. 2006;24(2):307–12.

31. Anastassiades CP, Saxena A. Precut needle-knife sphincterotomy in advanced endoscopy fellowship. Gastrointest Endosc. 2013;77(4):637–40.
32. Baillie J. Endoscopic retrograde cholangiopancreatography simulation. Gastrointest Endosc Clin N Am. 2006;16(3):529–42, viii.
33. Cohen J, Thompson CC. The next generation of endoscopic simulation. Am J Gastroenterol. 2013;108(7):1036–9.
34. Gholson CF, Provenza JM, Silver RC, Bacon BR. Endoscopic retrograde cholangiography in the swine: a new model for endoscopic training and hepatobiliary research. Gastrointest Endosc. 1990;36(6):600–3.
35. Noar MD. An established porcine model for animate training in diagnostic and therapeutic ERCP. Endoscopy. 1995;27(1):77–80.
36. Desilets DJ, Banerjee S, Barth BA, Kaul V, Kethu SR, Pedrosa MC, et al. Endoscopic simulators. Gastrointest Endosc. 2011;73(5):861–7.
37. Hochberger J, Maiss J, Magdeburg B, Cohen J, Hahn EG. Training simulators and education in gastrointestinal endoscopy: current status and perspectives in 2001. Endoscopy. 2001;33(6):541–9.
38. Matthes K, Cohen J. The Neo-Papilla: a new modification of porcine ex vivo simulators for ERCP training (with videos). Gastrointest Endosc. 2006;64(4):570–6.
39. Itoi T, Gotoda T, Baron TH, Sofuni A, Itokawa F, Tsuji S, et al. Creation of simulated papillae for endoscopic sphincterotomy and papillectomy training by using in vivo and ex vivo pig model (with videos). Gastrointest Endosc. 2013;77(5):793–800.
40. Frimberger E, von Delius S, Rosch T, Karagianni A, Schmid RM, Prinz C. A novel and practicable ERCP training system with simulated fluoroscopy. Endoscopy. 2008;40(6):517–20.
41. Gerson LB, Van Dam J. Technology review: the use of simulators for training in GI endoscopy. Gastrointest Endosc. 2004;60(6):992–1001.
42. Sedlack R, Petersen B, Binmoeller K, Kolars J. A direct comparison of ERCP teaching models. Gastrointest Endosc. 2003;57(7):886–90.
43. Leung JW, Wang D, Hu B, Lim B, Leung FW. A head-to-head hands-on comparison of ERCP mechanical simulator (EMS) and Ex-vivo Porcine Stomach Model (PSM). J Interv Gastroenterol. 2011;1(3):108–13.
44. Leung J, Lim B, Ngo C, Lao WC, Wing LY, Hung I, et al. Head-to-head comparison of practice with endoscopic retrograde cholangiopancreatography computer and mechanical simulators by experienced endoscopists and trainees. Dig Endosc. 2012;24(3):175–81.
45. Liao WC, Leung JW, Wang HP, Chang WH, Chu CH, Lin JT, et al. Coached practice using ERCP mechanical simulator improves trainees' ERCP performance: a randomized controlled trial. Endoscopy. 2013;45(10):799–805.
46. Lim BS, Leung JW, Lee J, Yen D, Beckett L, Tancredi D, et al. Effect of ERCP mechanical simulator (EMS) practice on trainees' ERCP performance in the early learning period: US multicenter randomized controlled trial. Am J Gastroenterol. 2011;106(2):300–6.
47. Walsh CM, Sherlock ME, Ling SC, Carnahan H. Virtual reality simulation training for health professions trainees in gastrointestinal endoscopy. Cochrane Database Syst Rev. 2012;6:CD008237.
48. (ACGME) ACfGME. (2014). https://www.acgme.org/acgmeweb/Portals/0/PFAssets/2013-PR-FAQ-PIF/144_gastroenterology_int_med_07132013.pdf. Accessed 1 June 2014.
49. Adler DG, Lieb JG, Cohen J, Pike IM, Park WG, Rizk MK, et al. Quality indicators for GI endoscopic procedures. Gastrointest Endosc. 2015;81(1):54–66.
50. DeBenedet AT, Elmunzer BJ, McCarthy ST, Elta GH, Schoenfeld PS. Intraprocedural quality in endoscopic retrograde cholangiopancreatography: a meta-analysis. Am J Gastroenterol. 2013;108(11):1696–704; quiz 1705.
51. Cotton PB, Romagnuolo J, Faigel DO, Aliperti G, Deal SE. The ERCP quality network: a pilot study of benchmarking practice and performance. Am J Med Qual. 2013;28(3):256–60.
52. Waller HM, Connor SJ. Cumulative sum (Cusum) analysis provides an objective measure of competency during training in endoscopic retrograde cholangio-pancreatography (ERCP). HPB (Oxford). 2009;11(7):565–9.
53. Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, et al. Methods of granting hospital privileges to perform gastrointestinal endoscopy. Gastrointest Endosc. [Guideline]. 2002;55(7):780–3.
54. Dominitz JA, Ikenberry SO, Anderson MA, Banerjee S, Baron TH, Cash BD, et al. Renewal of and proctoring for endoscopic privileges. Gastrointest Endosc. 2008;67(1):10–6.
55. Cotton PB. Endoscopic retrograde cholangiopancreatography: maximizing benefits and minimizing risks. Gastrointest Endosc Clin N Am. 2012;22(3):587–99.
56. Cote GA, Keswani RN, Jackson T, Fogel E, Lehman GA, McHenry L, et al. Individual and practice differences among physicians who perform ERCP at varying frequency: a national survey. Gastrointest Endosc. 2011;74(1):65–73.e12.
57. Joint commission on accreditation of healthcare organizations. Comprehensive accreditation manual for hospitals: the official handbook, management of the environment of care chapter. (Revisions appear in italics and become effective Jan. 1, 1998.). Jt Comm Perspect. 1997;17(1):EC7–9.

Indications for ERCP

2

Joseph K. Kim and David L. Carr-Locke

Introduction

ERCP was first introduced as a realistic endoscopic procedure in the early 1970s. Since then, the diagnostic and therapeutic clinical applications have changed significantly in parallel with improvements in noninvasive and invasive visualization of the biliary and pancreatic ductal systems. What was once predominantly a combined diagnostic endoscopic and radiographic modality, ERCP has taken on new roles as a more sophisticated diagnostic and therapeutic set of procedures including direct visualization of the ducts, tissue interrogation and sampling, and treatment of a wide variety of biliary and pancreatic disorders (Fig. 2.1a, b, c, d, e, f, g, h and i). In the USA, over 500,000 ERCPs were performed in 2008. In 2009, there were an estimated 1.1–1.3 million cases worldwide. The number of diagnostic ERCPs decreased 6 % while therapeutic ERCPs increased by 12 % up to 2001 [1]. This interventional shift is attributed to the introduction, improvement, and acceptance of other diagnostic modalities such as endoscopic ultrasound (EUS), computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP). EUS combined with ERCP has become an appropriate alternative to percutaneous radiological access to an obstructed duct when ERCP alone fails or is not possible.

Despite these changes in the role and range of therapeutic possibilities of ERCP, the basic indications have not. These can be divided into three main categories for the evaluation and treatment of:

1. Stone disease (jaundice, biliary pain, cholangitis, biliary pancreatitis, pancreatic duct stones)
2. Ampullary/papillary abnormalities (Sphincter of Oddi dysfunction (SOD), ampullary cancer)
3. Biliary and pancreatic ductal abnormalities (leaks, strictures, malignancies)

As we shall discuss later in this chapter, there are significant complications of ERCP that one must consider before considering this procedure. Therefore, it is of paramount importance to have an appropriate indication for proceeding.

Stone Disease

Choledocholithiasis

This is still the most common reason for undertaking ERCP (Figs. 2.2, 2.3, 2.4, 2.5). Gallstone disease affects approximately 20 million adults in the USA with an estimated annual healthcare cost of $ 5.8 billion [2]. Biliary stone disease is responsible for a spectrum of clinical presentations from asymptomatic (detected by imaging) to biliary obstruction, cholangitis, and acute biliary pancreatitis. Choledocholithiasis is seen in up to 15 % of patients with cholelithiasis, 10–20 % of

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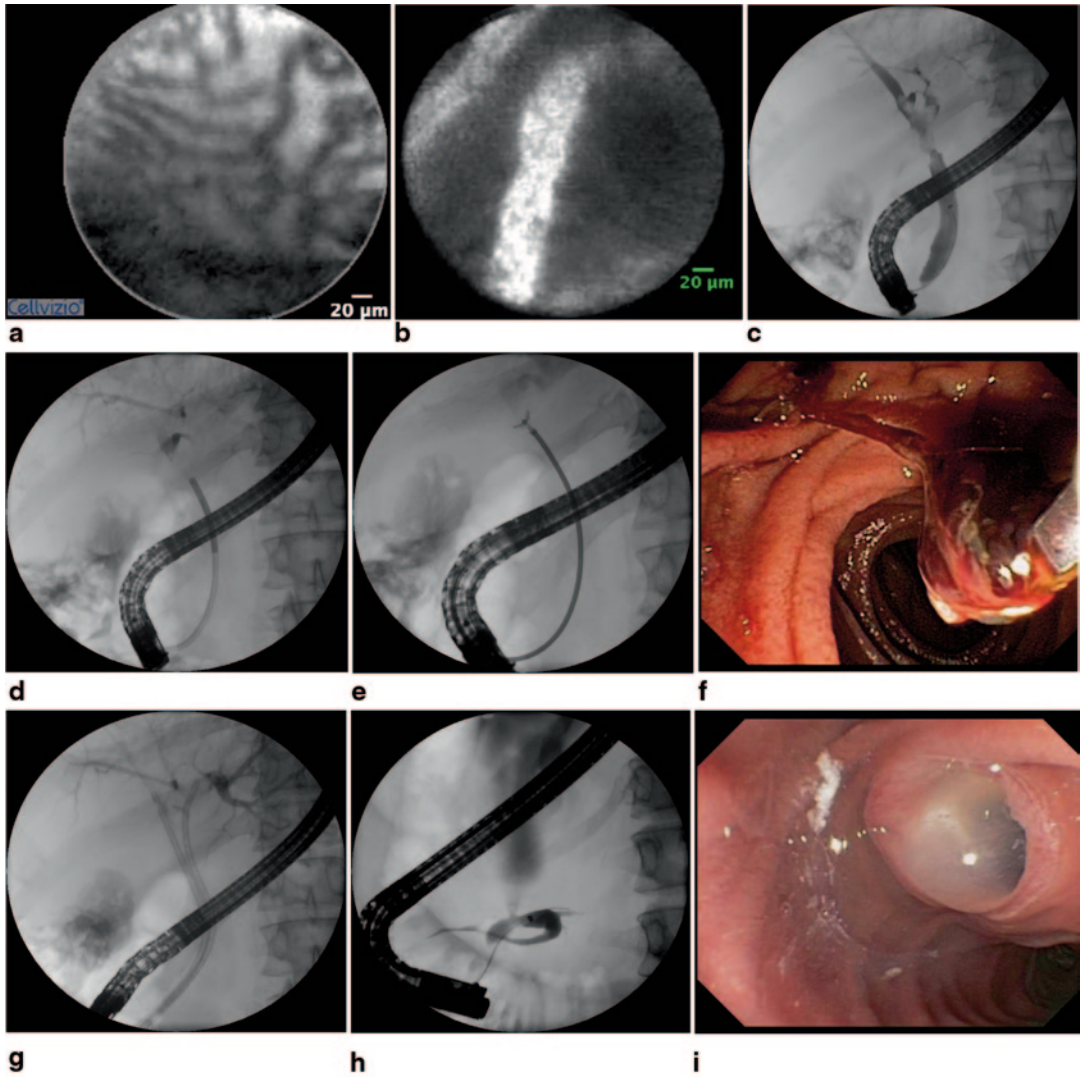

Fig. 2.1 **a** Probe-confocal laser endomicroscopy (*pCLE*) image of normal bile duct with reticular network of *thin dark branching bands* and *light gray* background. **b** pCLE image of bile duct malignancy with *thick dark bands* and *thick white band* (two criteria for malignant stricture). **c** Endoscopic retrograde cholangiography (*ERC*) showing filling defect at the hepatic duct confluence. **d** Fluoroscopy showing cholangioscope advanced to the lesion in **c. e** Biopsy of the lesion in **c. f** Tissue removed with biopsy forceps (*intraluminal cholangiocarcinoma*) from lesion in **c. g** Bilateral plastic stents in the same patient with hilar cholangiocarcinoma. **h** Anomalous union of the bile and pancreatic ducts with type 1 choledochal cyst. **i** Mucus at the papilla in main duct intraductal papillary mucinous neoplasm

those undergoing cholecystectomy, and up to 21% presenting with gallstone pancreatitis [2, 3]. The necessity of expediently diagnosing symptomatic choledocholithiasis is important, as the consequences of failing to do so may result in unfavorable outcomes. Predictors of a high likelihood of choledocholithiasis include jaundice, cholangitis, severe pancreatitis, alkaline phosphatase (AP) more than twice the upper limit of normal (ULN), increased gamma glutamyl transferase (GGT), and increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) [4]. One study categorized the likelihood of having ongoing choledocholithiasis as "moderate," "strong" or

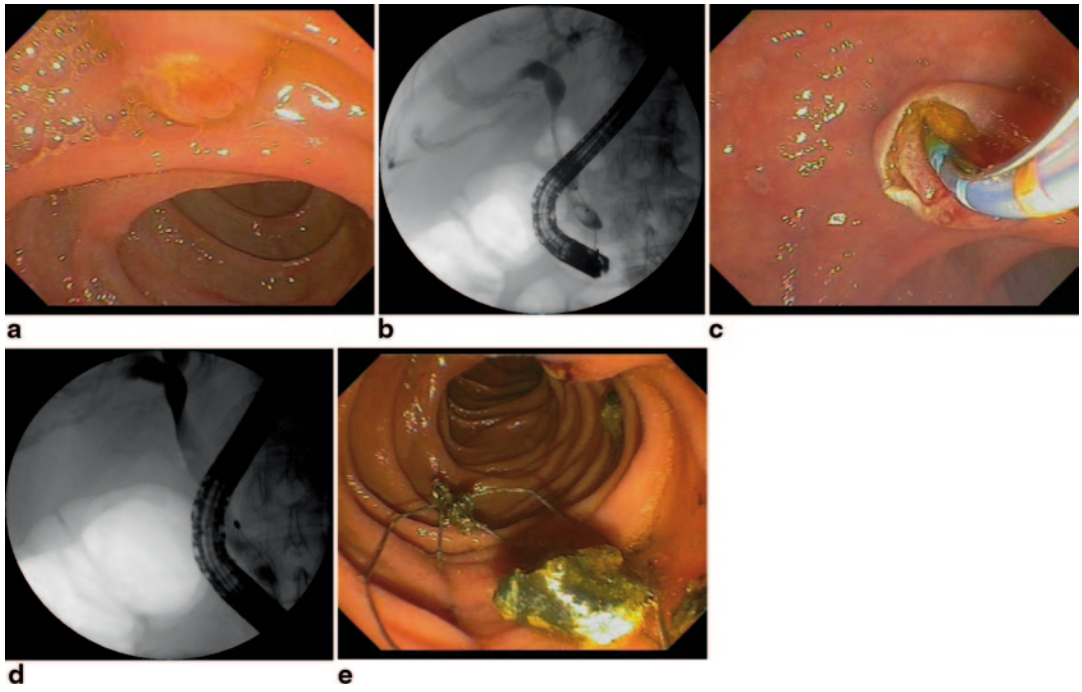

Fig. 2.2 **a** Sequence from normal papilla. **b** ERC with distal CBD stones. **c** Sphincterotomy. **d, e** Basket extraction of stones. *ERC* endoscopic retrograde cholangiography

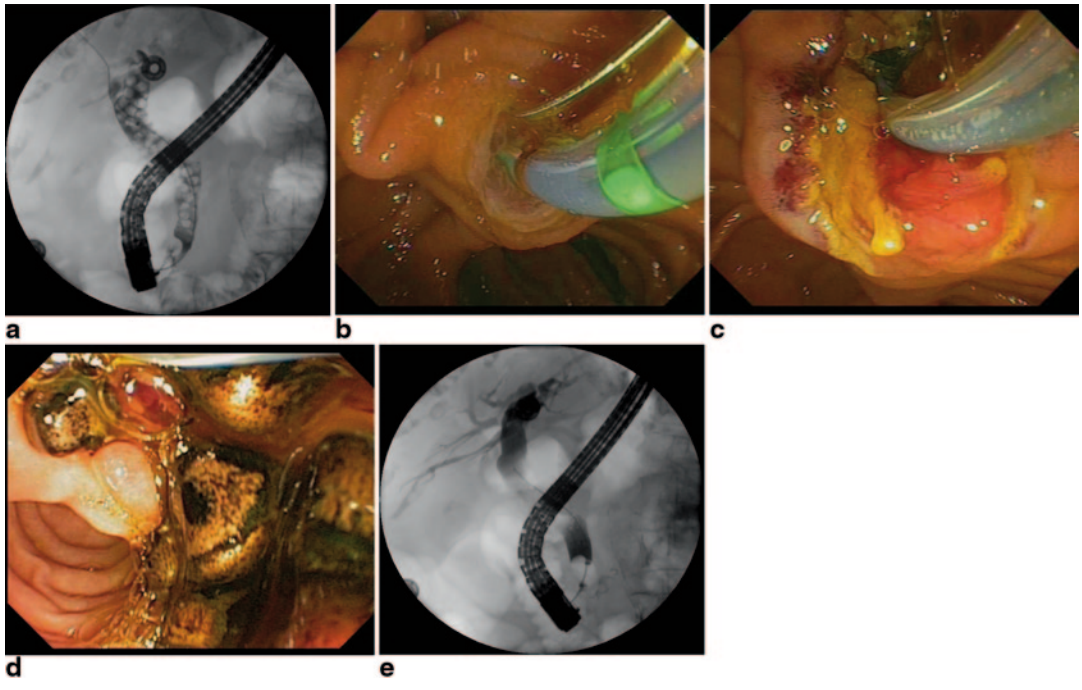

Fig. 2.3 **a** Sequence of ERC showing multiple stones filling extrahepatic bile duct; **b, c** Sphincterotomy in the 11 o'clock direction; **d** balloon extraction; and **e** Occlusion cholangiogram with biliary stone extraction balloon inflated in distal CBD showing no residual stones. *ERC* endoscopic retrograde cholangiography, *CBD* common bile duct

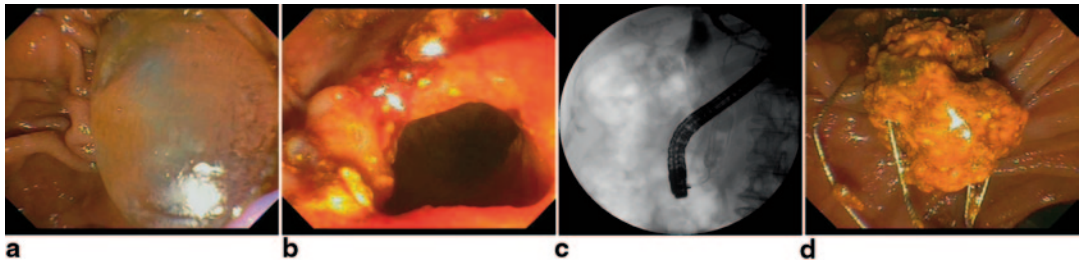

Fig. 2.4 **a, b** Large diameter balloon dilation of the papilla after sphincteromy with **c**, **d** basket extraction of stone material

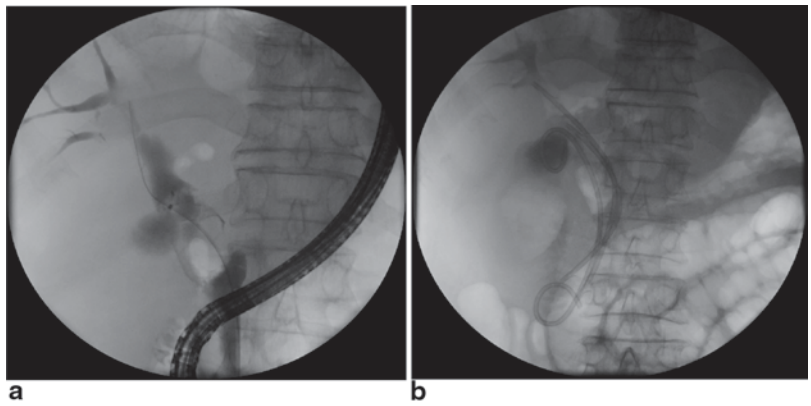

Fig. 2.5 **a** Stone in a cholecystocholedochal fistula, **b** causing biliary obstruction (*Mirizzi syndrome*) treated by CBD and gallbladder stent placement preoperatively. *CBD* common bile duct

"very strong." Those included in the "very strong" category included visualized choledocholithiasis on transabdominal ultrasound, clinical cholangitis, and a total bilirubin >4 mg/dL. "Strong" indicators included a dilated common bile duct (CBD) > 6 mm and total bilirubin between 1.8-4 mg/dL. "Moderate" indicators included abnormal liver tests, age>55, and clinical gallstone pancreatitis [5]. Based on several prospectively supported algorithms, patients can be risk-stratified into "low," "intermediate," or "high" risk for choledocholithiasis [6]. Patients who are "high risk" benefit the most from ERCP as opposed to other noninvasive modalities. In support, the American Society for Gastrointestinal Endoscopy (ASGE) recommends that only patients meeting the criteria for high suspicion undergo an ERCP for choledocholithiasis since it allows for immediate diagnosis and treatment [7]. Sphincterotomy and stone extraction with or without lithotripsy can be performed using the numerous tools now available in order to relieve biliary or pancreatic ductal obstruction caused by stones.

In 1988, Neoptolemos and Carr-Locke et al. were the first to examine the role of early (less than or equal to 72 h) ERCP in gallstone pancreatitis. Prior to this time, ERCP had been considered contraindicated in this setting. The study demonstrated that only patients predicted to have severe disease, by the modified Glasgow criteria, benefited from ERCP. Although mortality was not affected by early ERCP, overall complications were significantly decreased in the ERCP group (24%) compared to those who received conventional supportive treatment (61%) [8]. In 1993, Fan et al from Queen Mary Hospital, Hong Kong, published a study of 195 patients randomized to either early ERCP within 24 h versus conservative treatment. Morbidity in the ERCP group was significantly decreased compared to patients managed by conservative therapy (16 vs. 33%) [9].

The latest American College of Gastroenterology (ACG) guidelines published in 2013 state that patients with acute pancreatitis and concurrent acute cholangitis should undergo ERCP within 24 h of admission. However, the guidelines further state that "ERCP is not needed in most patients with gallstone pancreatitis who lack laboratory or clinical evidence of ongoing biliary obstruction" [10]. Controversy remains in this area concerning the absolute need for concomitant cholangitis and evidence for biliary obstruction, and there is inconsistency in guidelines for and against this inclusion.

Pancreatic Stones

Nearly always in the setting of chronic pancreatitis, pancreatic duct stones are treated in much the same way as bile duct stones and with the same accessories in symptomatic patients. The treatment of asymptomatic nonobstructing pancreatic duct stones is questionable but an argument can be made for removing stones that are causing complete main duct obstruction in order to improve exocrine function although such patients are not truly asymptomatic. There are differences in approach from biliary stones since the pancreatic duct is a more fragile and tortuous structure, may carry strictures as part of the spectrum of chronic pancreatitis, the stone(s) may be located in the duct and may be impacted, all of which renders the successful extraction of pancreatic stones more problematic compared to their biliary counterparts. Extracorporeal shock wave lithotripsy (ESWL) is a useful adjunct and, if not available, may significantly influence the choice of endoscopic, which may need to be sequential, or surgical therapy.

Ampullary/Papillary Abnormalities

Sphincter of Oddi Dysfunction

The modified Milwaukee classification for biliary SOD, used by many for more than two decades, are:

Type I	Biliary-type pain
	Elevated ALT, AST, or AP on one occasion
	Bile duct diameter > 10 mm
Type II	Biliary-type pain
	One of the other two criteria for type I
Type III	Biliary-type pain only

The approximate frequency of abnormal sphincter of Oddi manometry (SOM) is 65–85, 65, and 59 % for type I, II, and III respectively in the post-cholecystectomy patient presenting with presumed biliary pain [11]. Endoscopic biliary sphincterotomy has largely replaced open surgical sphincteroplasty. Regardless of whether SOM is normal or abnormal, 90–95 % of type I SOD patients experience pain relief. Therefore, in type I patients, endoscopic sphincterotomy is indicated. In type II SOD patients, the role of endoscopic sphincterotomy is controversial. In patients with suspected type II SOD with abnormal SOM results, 85 % will have pain relief with sphincterotomy, but in those with normal SOM results, only 35 % will experience pain relief. Regardless, most experienced biliary endoscopists will offer type II SOD a biliary sphincterotomy after discussion of the risks. In type III SOD patients, abnormal SOM has recently been shown not to be predictive of outcome, and empiric sphincterotomy (biliary with or without pancreatic) is not indicated and carries a significant risk. The equivalent pancreatic SOD classification has not been validated as an indication for pancreatic sphincterotomy, but in patients with unexplained recurrent pancreatitis, abnormal pancreatic and/or biliary SOM is often used as an indication for empiric dual sphincterotomy.

Ampullary Cancers/Adenomas

The major duodenal papilla, often interchangeably but erroneously called the ampulla of Vater, can be the source of different types of tumor including adenomas, adenocarcinomas, lipomas, leiomyomas, lymphomas, neuroendocrine tumors, and hamartomas. Adenomas occur sporadically in 0.04–0.12 % of the general population, but in those with hereditary polyposis

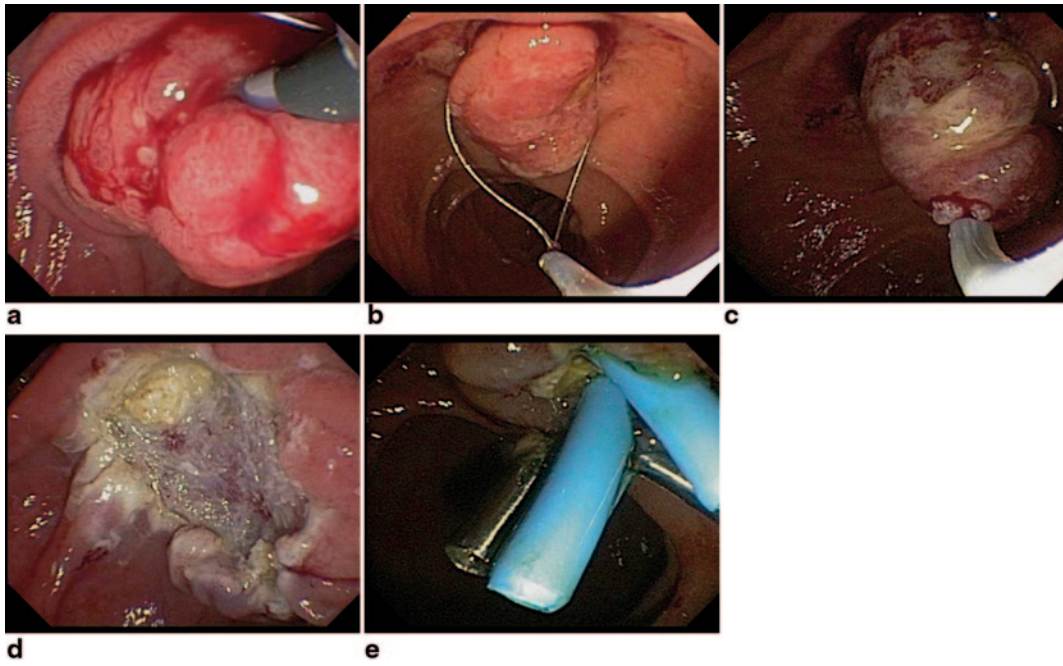

Fig. 2.6 Ampullectomy for adenoma sequence: **a** Cannula injecting pancreatic duct with friable adenoma visible; **b, c** Snare cautery en bloc resection of adenoma; **d** Postresection with biliary orifice visible in *upper left corner* (*yellow stain*); **e** Biliary and pancreatic duct stents inserted with clips visible placed for bleeding

syndromes, the incidence of ampullary adenoma increases to 40–90% [12]. Periampullary adenomas have the potential for malignant transformation into carcinoma at a rate of 30–50% [12] in sporadic cases but the risk in polyposis individuals is also high and this site represents the second highest incidence of cancer after the colon. Two decades ago, the primary treatment of periampullary adenomas was pancreaticoduodenectomy. Due to the increased morbidity and mortality associated with this procedure, especially for a benign disease, the surgery changed to a transduodenal approach with local excision. However, the recurrence rate ranged from 5 to 30% [12]. A review comprising 967 patients undergoing endoscopic ampullectomy reported a recurrence rate of 14% [12]. Endoscopic *en bloc* ampullectomy causes pancreatitis in an unpredictable manner. A prospective randomized controlled trial demonstrated that the placement of a prophylactic pancreatic duct stent conferred a protective benefit against pancreatitis after endoscopic ampullectomy (Fig. 2.6) and should be used in all cases when possible [13].

Cancers in this area can be palliated in the same way as malignant pancreatobiliary strictures (see below) (Fig. 2.7).

Biliary and Pancreatic Ductal Abnormalities

ERCP is of great utility in the diagnosis and management of biliary and pancreatic ductal abnormalities including leaks and strictures. ERCP serves as a platform to access the ductal systems, as it always has, for the purpose of ductography but also to allow sampling by brushing and biopsy. It also permits direct cholangioscopy and pancreatoscopy which further facilitates sampling by directed forceps biopsy and interrogation by confocal laser endomicroscopy and intraductal ultrasound.

Leaks

Leaks from the ductal systems can be treated endoscopically in carefully selected patients.

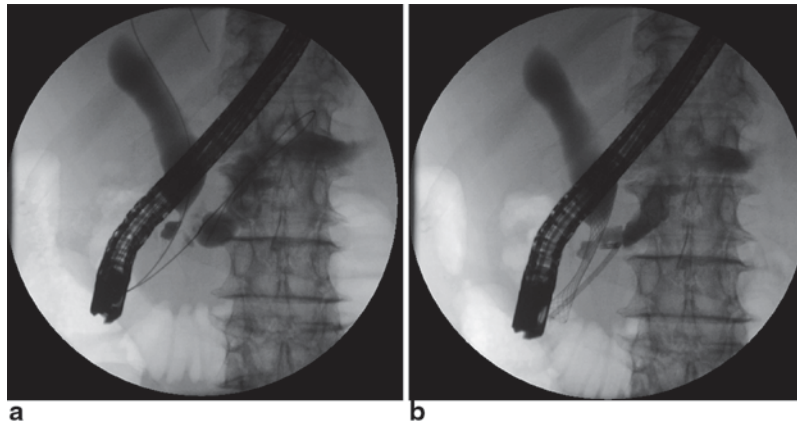

Fig. 2.7 **a** Two wires placed into dilated CBD and PD with distal strictures in patient with ampullary cancer. **b** Metal biliary stent and plastic pancreatic duct stent placed. *CBD* common bile duct, *PD* pancreatic duct

Continuity of the duct to be evaluated and treated is the most important factor determining the feasibility of managing the leak endoscopically [14, 15]. If the bile duct is completely transected or when there is no continuity between the injured segments, endoscopic management is usually not possible. Once duct continuity has been confirmed by cholangiography or pancreatography, the leak can be managed by deploying a stent either across the papilla to reduce intrabiliary pressure in the case of a postoperative biliary leak in an otherwise normal duct, or across the leak itself as in the case of a pancreatic disruption or injury (Fig. 2.8). The types of stent used in these situations continue to evolve as stent technology changes. Two studies performed by Traina et al and Kahaleh et al. reported resolution of the majority of bile leaks after the use of self-expandable metal biliary stents [16, 17]. However, there were instances of stent migration and stricture formation with the use of these metal stents and cost-effectiveness is questionable. It is hypothesized that the success of biliary stenting in the setting of leaks is attributed to the reduction of transpapillary biliary pressure gradient. The reduction in this pressure gradient diverts flow from the leak site to the intact biliary tree and ultimately into the duodenum. Pancreatic duct (PD) leaks are a result of acute or chronic pancreatitis, trauma, malignancy, and surgery. Varadarajulu et al. demonstrated that successful resolution of a PD disruption was dependent on the type of

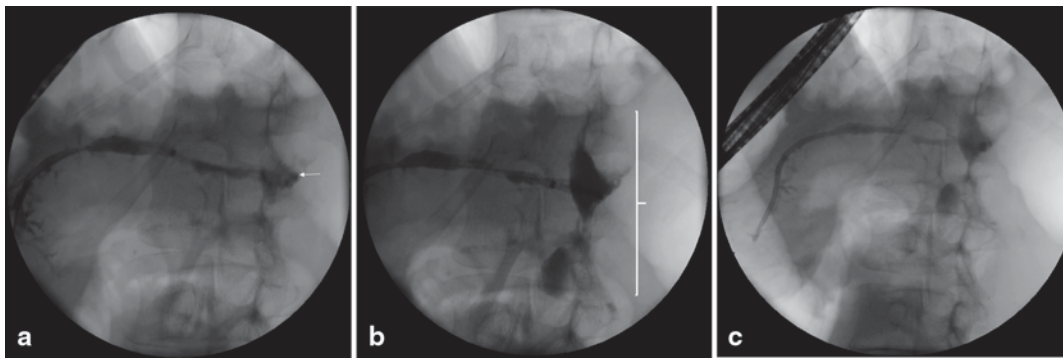

Fig. 2.8 **a, b** PD head stricture and tail disruption (*arrow* and *bracket*) with ascites, **c** treated by stent placement. *PD* pancreatic duct

disruption and the ability to bridge the disruption [18]. A study investigating the role of PD stenting in ductal disruption demonstrated that in 21 out of 28 patients with partial PD disruption who were treated with PD stent alone, the disruption resolved. In six out of eight patients with complete PD disruption, the disruption resolved with PD stenting alone as well [19].

Benign Strictures

The diagnosis of a benign stricture is not always straightforward and usually involves the implementation of the diagnostic sampling tools mentioned above. Once the stricture has been designated as benign and endoscopic therapy chosen as the management plan, either balloon dilation plus stenting or simply stenting alone may be employed. In the case of benign biliary strictures, placement of multiple large bore plastic stents side by side has resulted in good long-term outcomes, [20] but the outcome of self-expandable covered metal stents is being evaluated [21].

Pancreatic duct strictures in the setting of chronic pancreatitis or injury (Fig. 2.9) may also be amenable to endoscopic therapy using the same tools as in biliary applications, but the pancreatic duct does not necessarily respond in the same way and a plan of sequential pancreatic endotherapy needs to be discussed at the outset. Stents specifically designed for use in the pancreatic duct are available.

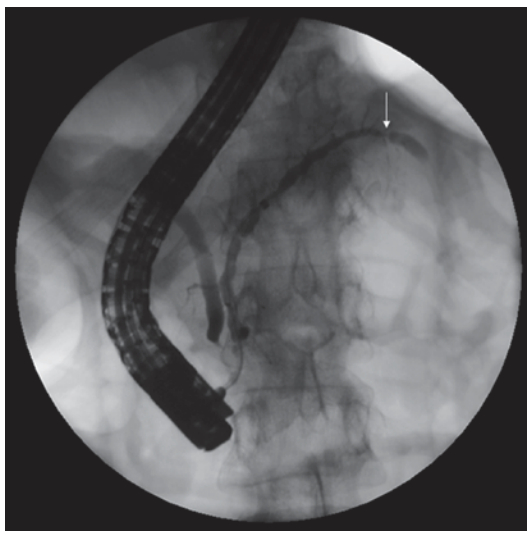

Fig. 2.9 Traumatic PD stricture (*arrow*) from seat belt injury with mild upstream dilation. *PD* pancreatic duct

Malignant Strictures

In the last 30 years, endoscopic decompression through stent deployment has emerged as the therapeutic procedure of choice in the temporary or permanent palliative management of malignant biliary obstruction (Figs. 2.10, 2.11 and 2.12). Lower hospital costs, shorter hospital stays, and lower morbidity when compared to surgical palliation of malignant biliary strictures have been demonstrated [22]. Biliary decompression can palliate the consequences of obstruction including jaundice, weight loss, cholangitis, secondary cirrhosis, and pruritus thus improving quality of life. Biliary stent therapy, however, has not been shown to have significant survival benefit [23, 24]. Although short-term preoperative biliary drainage with plastic stents is not indicated, metal stents may be cost-effective and, in the potentially resectable patient and/or those undergoing neoadjuvant chemoradiation therapy who have a significant delay between diagnosis and surgery, metal stent placement is indicated.

When is ERCP Not Indicated or Contraindicated?

Like any invasive procedure, there are circumstances in which ERCP should not be performed. Relative contraindications include:

1. Portal hypertension with esophageal and/or gastric varices
2. Acute pancreatitis except gallstone pancreatitis (this may change)
3. Recent myocardial infarction and/or severe cardiopulmonary disease unless the procedure is life-saving (e.g., cholangitis)
4. Repeated failed attempts at ERCP therapy when alternatives are available

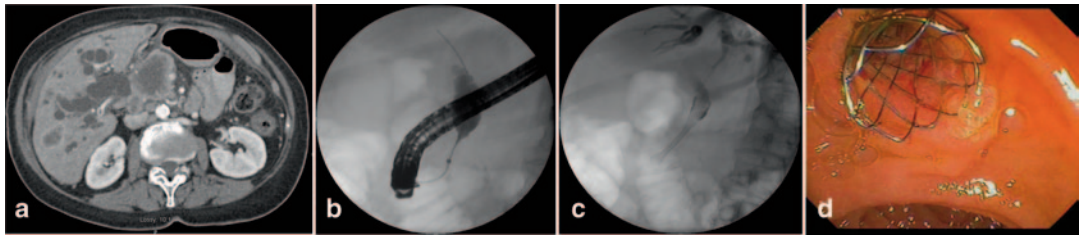

Fig. 2.10 **a** Pancreatic cancer with diffuse intrahepatic biliary dilation on abdominal CT, **b** confirmed by cholangiogram showing distal biliary stricture, **c, d** treated by metal biliary stent placement. *CT* computed tomography

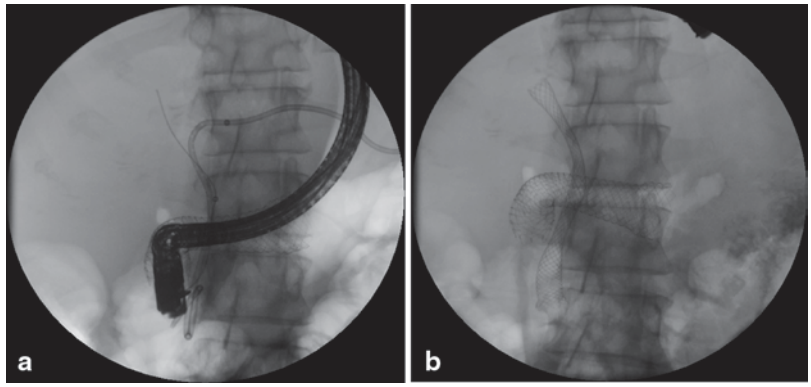

Fig. 2.11 **a** Malignant duodenal stricture treated by metal enteral stent placement and percutaneous biliary drain, **b** exchanged for metal biliary stent

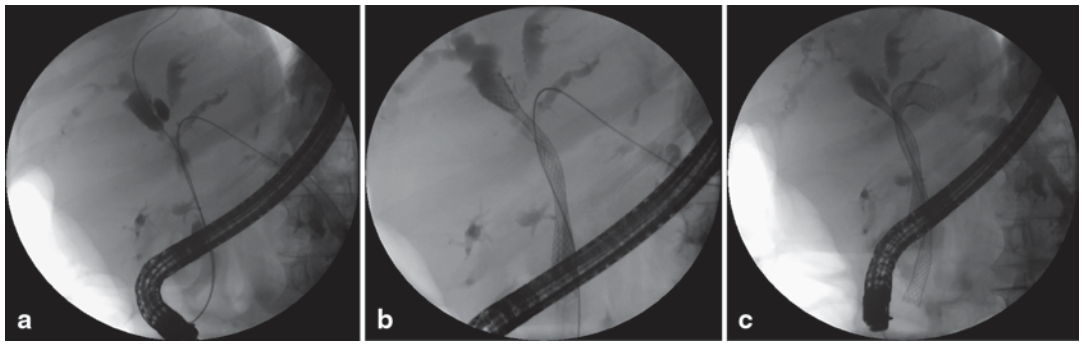

Fig. 2.12 Hilary malignancy treated by bilateral metal biliary stent placement. **a** Two wires advanced into bilateral hepatic ducts. **b** Metal stent placed into right main hepatic duct. **c** Second metal stent placed alongside into left main hepatic duct

5. Patient cannot be adequately sedated.
6. Anaphylactic reaction to radiographic contrast although this usually refers to reactions after intravenous contrast and there is little to no evidence that ERCP carries the same risk. Local policies will guide this.

Absolute contraindications are the following:

1. Pharyngeal or esophageal obstruction (unless these can be treated simultaneously)
2. Severe uncorrected coagulopathy
3. Inadequate indication, e.g., abdominal pain of unknown cause

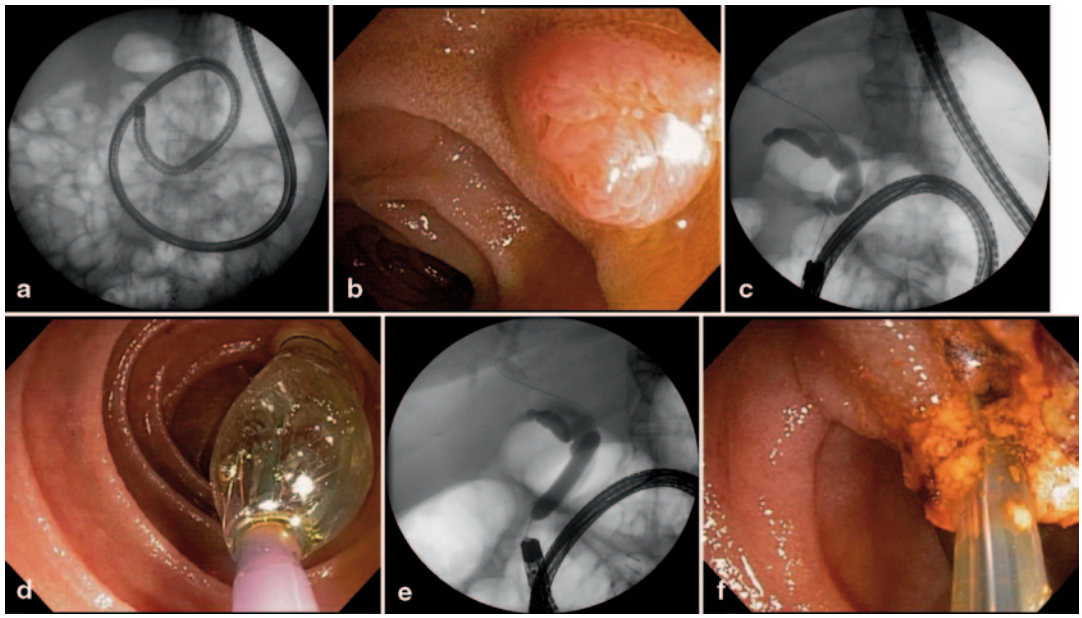

Fig. 2.13 **a** ERC after Roux-en-Y gastric bypass using a colonoscope, **b** showing a normal major papilla, **c** and stone in distal CBD with long guidewire placed. **d, e** Balloon dilation of the papilla performed, **f** followed by stone extraction using a biliary stone extraction balloon

4. Altered anatomy (Roux-en-Y, Billroth II, and pancreaticoduodenectomy) without the necessary skills and tools available (Fig. 2.13)
5. Known or suspected perforation
6. Consent cannot be obtained, unless deemed an emergency
7. The risks of the procedure outweigh the potential benefits

Where Do EUS and MRCP Fit in with ERCP?

EUS and MRCP have emerged as diagnostic modalities to aid, or in many cases, completely replace diagnostic ERCP. Both have become well accepted as less invasive and safer diagnostic procedures compared to ERCP that can provide the same information as ERCP without the risks.

MRCP, first developed in 1991, uses heavily T2-weighted sequences to return a high signal from fluid in the biliary and pancreatic ducts, which have long T2 relaxation times [25]. One of the advantages of MRCP is that there is no use of ionizing radiation nor iodinated contrast material [25]. Another advantage is that MRCP allows for visualization of ductal abnormalities extending into the smaller caliber intrahepatic ducts compared to EUS. Spatial resolution of MRCP compared with ERCP is, however, inferior. Therefore, pathology in nondistended pancreatic side branch or peripheral intrahepatic ducts may be missed [25]. Furthermore, early changes of conditions in chronic pancreatitis and primary sclerosing cholangitis may be missed on MRCP as opposed to ERCP [25].

Where EUS is not readily available, MRCP has become the test of choice in the diagnosis of choledocholithiasis. One study demonstrated that the sensitivity and specificity of diagnosing choledocholithiasis was 100 and 91 % in the EUS group while it was 90 and 100 % in the MRCP group, respectively [4]. Some studies suggest that MRCP is less accurate in detecting smaller diameter stones. For instance, one study reported that the sensitivity of MRCP in the detection of choledocholithiasis decreases from 71 to 33 % as stone diameters fell below 6 mm [2]. Kondo et al. corroborated this by stating that the performance of EUS was superior to

MRCP for detecting common bile duct stones < 5 mm in size [26, 27]. There has been a debate whether the accuracy of MRCP for the detection of choledocholithiasis varies with ductal diameter. This discussion needs further clarification as studies on this topic seem to contradict. For instance, one group concluded that there were no significant differences in the performance of EUS and MRCP in the diagnosis of malignancy and choledocholithiasis in patients with both dilated and nondilated bile ducts [4].

A systematic review of five randomized, prospective trials comparing EUS and MRCP in the diagnosis of pancreatobiliary diseases showed no significant differences in sensitivities, specificities, positive and negative predictive values, and likelihood ratios [28]. When choosing between the two modalities, one should consider other factors including resource availability, experience, costs, and patient requirements. For instance, in high-risk populations such as the elderly or severely ill patients, MRCP would be the better test due to the noninvasive nature of the test [28]. Nevertheless, MRCP is time consuming and requires a high level of patient cooperation. Furthermore, it is not well tolerated in up to 5 % of patients due to claustrophobia [28].

EUS combines both endoscopy and ultrasound to provide images of the pancreatobiliary system in radial or linear array without the interference of bowel air or subcutaneous fat [6]. Literature review comparing EUS to ERCP, intraoperative cholangiography and surgical exploration in the ability to detect choledocholithiasis have varied significantly with sensitivities reported from 71 to 100 % and specificities of 67–100 %. These variations were attributed to factors such as patient selection, operator expertise, and study design [6]. Nine studies including 601 patients have compared EUS to ERCP in the detection of choledocholithiasis. This review demonstrated that EUS was more sensitive and accurate than cholangiography in the detection of stones smaller than 4 mm. The diagnostic limitation of cholangiography in detecting small stones was partly explained by loss of sensitivity in dilated ducts [26, 28, 29]. EUS offers very high-resolution images (0.1 mm), thus allowing the detection of very small diameter stones [6]. In contrast to reports of CT and MRCP, the accuracy of EUS is not diminished in the setting of small stones or a nondilated bile duct [30].

EUS, where available, has become the test of choice in low to moderate suspicion of choledocholithiasis. If stones are detected on EUS, therapeutic ERCP can potentially be performed immediately while the patient is still sedated. This offers a convenient and safe management of these patients who would otherwise have undergone the risks of a diagnostic ERCP or the delay in proceeding to a therapeutic ERCP after a positive MRCP finding. In addition, when MRCP, CT, or ERCP studies are unable to identify the etiology of a bile duct or pancreatic duct stricture, EUS has also been used to exclude an underlying malignancy. If a mass is identified, EUS allows for sampling through fine needle aspiration. Furthermore, EUS is helpful in staging ampullary tumors to ensure that endoscopic ampullectomy is appropriate.

Despite the minimally invasive manner in which EUS provides valuable information for a variety of pancreatobiliary diseases, EUS has several limitations. EUS is not readily available in many community hospital settings, (1) and it is operator-dependent. If the echoendoscope cannot be advanced into the duodenum for reasons including pyloric stenosis, ulcer disease or surgically-altered anatomy, then EUS cannot be effectively considered an option for excluding choledocholithiasis, malignancy, and strictures of the distal CBD and ampulla. Furthermore, like any endoscopic procedure the risk of perforation, albeit small, is still present considering the larger diameter and oblique angle of the endoluminal view.

In addition, EUS has the great potential to provide therapy where ERCP is not possible or fails (Figs. 2.14 and 2.15 and see Chap. 34).

Complications

The best way to prevent or reduce post-ERCP complications is to avoid performance of unnecessary ERCP.

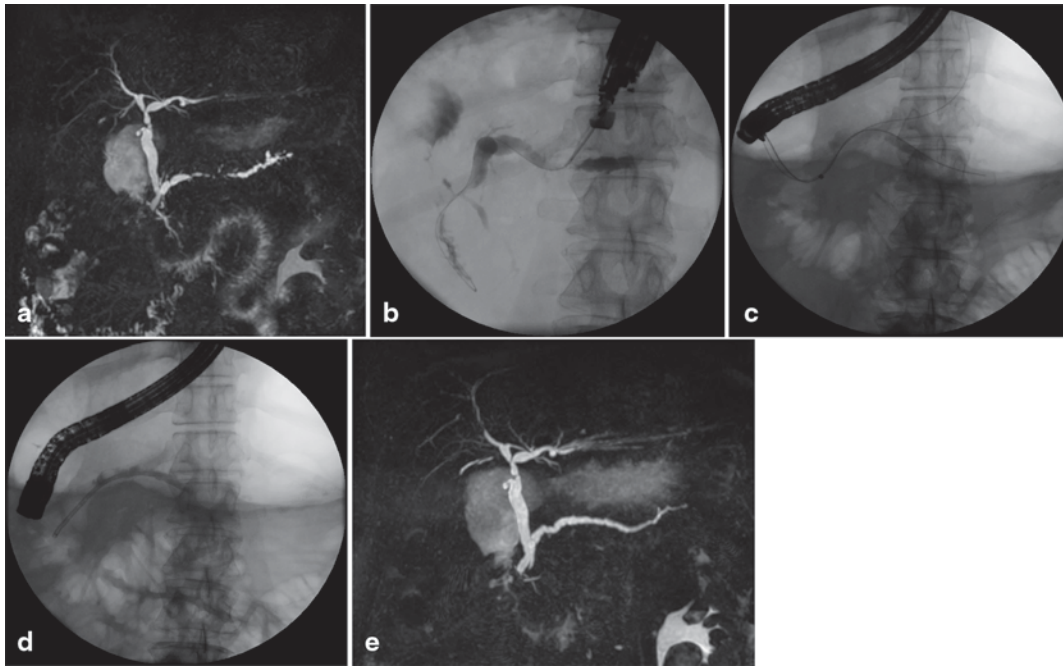

Fig. 2.14 **a** Sequence in a patient with pancreas divisum and postoperative stenosis, **b** showing antegrade access to the PD by EUS using a *19G* needle with guidewire placement, **c** rendezvous ERP, **d** and stent placement, **e** with follow-up MRCP demonstrating resolution of stricture. (Courtesy Dr Petros Benias)

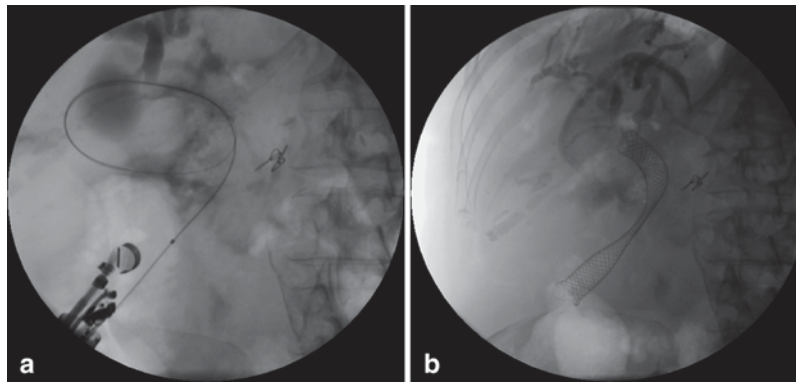

Fig. 2.15 **a** Direct EUS cholangiography through the duodenal bulb, **b** and metal biliary stent placement for malignant biliary obstruction. (Courtesy Dr Petros Benias)

Pre-ERCP Considerations

One of the most important aspects of performing ERCP is patient selection. An anesthesiologist may be the best consultant in this situation as cardiopulmonary depression is the most common complication associated with endoscopy. Up to 50 % of overall complications are associated with sedation [31]. Hypoxic events occurring at an incidence of 7–40 % and aspiration are associated with increased age, chronic illnesses, depressed mental status, supine positioning, and sedation [31].

Questions to ask prior to ERCP include:

1. Is this procedure justified?
2. Is SOD suspected? If so, am I ready to use methods for pancreatitis prophylaxis (pancreatic duct stent, rectal indomethacin)?

3. Is my patient optimized in terms of cardiopulmonary condition?
4. Should I recommend intubation versus conscious sedation?
5. When did the patient last eat and does the patient have a history of gastroparesis or gastric outlet obstruction?
6. What position is safest for the patient?
7. Is the patient of child-bearing age in which pelvic radiation protection must be provided?
8. Is the patient pregnant?
9. Does the patient have any allergies to medications including contrast?
10. Does the patient have any spontaneous or iatrogenic coagulopathies?
11. Does the patient have a history of post-ERCP pancreatitis or other complications?
12. Has this patient undergone a previous ERCP? If so, what were the difficulties and findings?
13. Is all necessary equipment ready to perform the planned ERCP?

Intra- and Post-Procedural Considerations

Complications during these stages include cardiopulmonary events, perforation, bleeding, drug reactions, pancreatitis, hemorrhage, cholangitis, cholecystitis, stent-related complications, and other miscellaneous adverse events. The major adverse events of ERCP are pancreatitis, bleeding, perforation, and infection which are briefly discussed below. See Chap. 3 for an extensive discussion on complications following ERCP. Appropriate management requires recognition of an adverse event, its accurate definition, and its prompt treatment.

Post-ERCP Pancreatitis

The pathophysiology of post-ERCP pancreatitis (PEP) is multifactorial including mechanical, chemical, hydrostatic, enzymatic, and thermal causes [31]. PEP is the most common adverse event with reported rates ranging from 1 to 40% [32]. The most cited rate of PEP is 5%. Multivariate analyses support the following risk factors for PEP: suspected SOD, young age, history of PEP, difficult or failed cannulation, pancreatic duct injection, pancreatic sphincterotomy, balloon dilation of intact biliary sphincter in the West and access papillotomy (precut sphincterotomy). The factors that "may" contribute to PEP include: female sex, normal bilirubin, pancreatic acinarization, absence of CBD stone, low ERCP case volume, and trainee involvement. Factors that do not cause PEP are: small CBD diameter, SOD manometry, and biliary sphincterotomy [32].

An array of technical methods is known to decrease the risk of PEP. A randomized trial showed significant reduction of PEP when a guidewire was used in conjunction with a papillotome compared to papillotome alone [33]. Pancreatic duct stent placement (Fig. 2.16) reduces the risk of PEP significantly and its severity in high-risk ERCPs, such as biliary sphincterotomy for SOD, SOD with normal manometry, pancreatic sphincterotomy, access papillotomy (precut sphincterotomy), ampullectomy, and difficult cannulation [13, 34–36]. Reduction in rate of post-ERCP pancreatitis from 17% in the control group to 9% in the treatment group using rectal indomethacin 100 mg suppositories has also been documented [37].

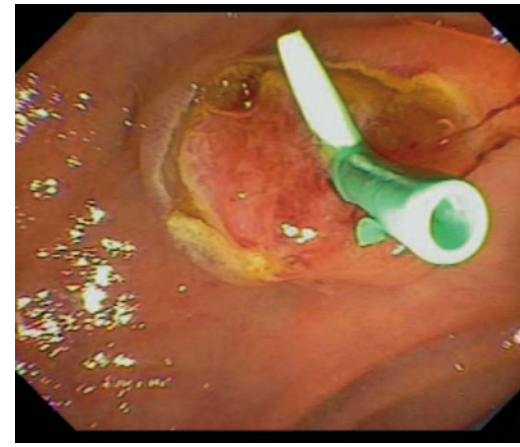

Fig. 2.16 Prophylactic pancreatic stent after sphincterotomy

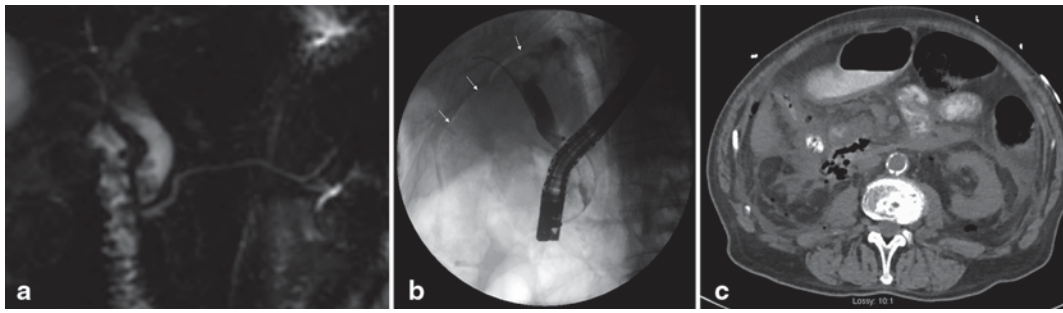

Fig. 2.17 **a** Sequence of MRCP showing multiple distal biliary stones, **b** followed by sphincterotomy and balloon extraction complicated by retroperitoneal perforation seen on fluoroscopy (**b**, *arrows* point to extraluminal air) and **c** abdominal CT scan treated conservatively

Post-ERCP Hemorrhage

Bleeding occurs in approximately 1–2% of patients during or after sphincterotomy [31]. If the bleeding site is visible, address the problem using either injection with epinephrine (1:10,000) and/or clip placement. Alternatively, one can also use balloon tamponade. The need for angiography and emergency surgery has diminished with the improved success of endoscopic management and appropriate patient selection.

Post-ERCP Perforation

Perforation is reported in less than 1% of ERCP and sphincterotomies [38]. Perforations range from micro-perforations after sphincterotomy to frank perforations of the gut and may be retroperitoneal, intraperitoneal, or both. Each perforation must be assessed and managed individually. Risk factors for perforation include: performance of sphincterotomy, presence of altered surgical anatomy, stricture dilation, and long duration of the procedure [39, 40]. The key to managing post-ERCP perforations is early detection and action in parallel with experienced surgical consultation (Fig. 2.17).

Post-ERCP Cholangitis

Adequate pancreatic and biliary drainage of obstructed and contaminated ducts is the key to treatment and avoidance of sepsis. Pre-ERCP planning by MRCP and EUS of obstructed ducts is now routine.

Medico-Legal Issues

The art and practice of medicine are not perfect. The goal of restoring human biology to its original state is often prohibited by adverse events as a consequence of treatment (iatrogenic) as briefly discussed earlier for ERCP. These complications result in decreased quality of life, disabilities, high medical costs, extended hospitalizations and an inability to partake in life's normal activities. Whether these complications are predictable or not, patients may place blame on the physician or facility and seek compensation [41]. Such lawsuits have widespread impact, not only on the accused but also on the criminal justice systems, the community, family members, and public health. The current medico-legal environment has changed the landscape of how we now provide healthcare. Each state has its own laws governing medical malpractice.

The Physician Insurers Association of America (PIAA) database from 1985 to 2005 showed that only 1.8% of claims involved gastroenterologists [41]. In more recent years, a large liability insurer showed that gastroenterologists ranked 5th out of 25 specialties in claims and outcomes [41]. ERCP is one of the more invasive procedures associated with more frequent adverse events. Therefore, it is easy to imagine that ERCP would account for a disproportionate number of legal claims. However, in 1995, the risk of litigation from ERCP was substantially less than other procedures [41]. The relative risk

of litigation from ERCP is less than twice that of simpler procedures including flexible sigmoidoscopy or gastroscopy [42]. In Canada, ERCP is only associated with 6% of GI-related lawsuits whereas in Japan, ERCP is the most common reason for endoscopy-related claims. In Peter Cotton's analysis of 59 ERCP lawsuits, the primary allegations in 32 cases were "marginal indications and poor communication" [43]. Hence it is essential to have firm evidence to justify the risks of performing ERCP as described here earlier.

Aside from having the correct clinical indications for ERCP, the endoscopist should also be properly trained and maintain a level of proficiency to provide the best possible outcome. Undertaking a dedicated advanced endoscopy fellowship has been suggested to decrease the risk of complications during ERCP, but this is controversial. Less than 200 ERCP procedures during training are not considered adequate to attain competence [5]. The ASGE has created guidelines to ensure adequate training. Data suggest that at least 180 to 200 cases is necessary to achieve competence in ERCP [44, 45]. Furthermore, hospitals also take responsibility since they grant privileges to endoscopists who wish to perform ERCP [46, 47].

Conclusion

In summary, when attempting to map out the biliary and pancreatic ductal systems, ERCP, although very sensitive and specific, carries significant risks. When the suspicion for choledocholithiasis is high, proceeding directly to ERCP should not be questioned. In a patient considered high risk with multiple co-morbidities, if she or he demonstrates clinical signs of deterioration secondary to presumed biliary obstruction (cholangitis, gallstone pancreatitis), ERCP can justifiably be undertaken [48]. In the low to moderate risk patient with low to moderate suspicion of choledocholithiasis, the clinician can choose between EUS and MRCP depending on availability followed by ERCP as indicated. For bile and pancreatic duct strictures, ERCP is the diagnostic and therapeutic procedure of choice. However, if ERCP is unable to identify the etiology of the stricture, MRCP and EUS are indicated. If both are available, one must consider what and where the possible pathology may be. If the suspicion is for an intrahepatic duct pathology, an MRCP would be best. If extrahepatic bile duct or pancreatic ductal abnormality is anticipated, EUS confers both diagnostic imaging and sampling benefits. EUS is also beneficial to staging ampullary lesions prior to endoscopic ampullectomy.

Key Points

- Always have a solid indication for performing ERCP and ask yourself: "What if this patient has a serious complication, can I justify what I/we did?"
- Ensure that the therapeutic indication is the best of all alternatives.
- Be familiar with all general and specific risks of ERCP.
- Know your own skill limitations and when to ask for help.
- Be prepared to manage complications as a team.
- Document what you do.
- Be aware that lawsuits mainly arise from situations where the indication was inappropriate or unclear, the consent was not informed, and/or where there was poor communication after the event.
- Utilize EUS and MRCP judiciously to complement ERCP.

References

1. Scheiman JM, Carlos RC, Barnett JL, Elta GH, Nostrant TT, Chey WD, Francis IR, Nandi PS. Can endoscopic ultrasound or magnetic resonance cholangiopancreatography replace ERCP in patients with suspected biliary disease? A prospective trial and cost analysis. Am J Gastroenterol. 2001;96:2900–4.
2. Roberts DN, Maple JT. The role of endoscopic ultrasonography (EUS) and endoscopic retrograde cholangiography (ERC) in diagnosing choledocholithiasis. Tech Gastrointest Endosc. 2009;11(1):2–12.
3. Berhns KE, Ashley SW, Hunter JG, Carr-Locke DL. Early ERCP for gallstone pancreatitis: for whom and when? J Gastrointest Surg. 2008;12(4):629–33.

4. Fernández-Esparrach G, Ginès A, Sánchez M, et al. Comparison of endoscopic ultrasonography and magnetic resonance cholangiopancreatography in the diagnosis of pancreatobiliary diseases: a prospective study. Am J Gastroenterol. 2007;102:1632–9.
5. Balmadrid B, Kozarek R. Prevention and management of adverse events of endoscopic retrograde cholangiopancreatography. Gastrointest Endosc Clin N Am. 2013;23(2):385–403.
6. Tse F, Liu L, Barkun AN, Armstrong D, Moayyedi P. EUS: a meta-analysis of test performance in suspected choledocholithiasis. Gastrointest Endosc. 2008;67(2):235–44.
7. ASGE Guidline. The role of endoscopy in the evaluation of suspected choledocholithiasis. Gastrointest Endosc. 2010;71(1):1–9.
8. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endscopic sphincterotomy versus conservative treatment of acute pancreatitis due to gallstones. Lancet. 1988;2(8618):979–83.
9. Fan S-T, Lai ECS, Mok FPT, Lo CML, Zheng SS, Wong J. Early treatment of acute biliary pancreatitis by endoscopic papillotomy. N Engl J Med. 1993;328:228–32.
10. Tenner S, Baillie J, DeWitt J, Vege SS. American college of gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013. doi:10.1038/ajg.2013.218.
11. Leung WD, Sherman S. Endoscopic approach to the patient with motility disorders of the bile duct and sphincter of Oddi. Gastrointest Endosc Clin N Am. 2013;23:405–34.
12. Laleman W, Verreth A, Topal B, Aerts R, Komuta M, Roskams T, Van der Merwe S, Cassiman D, Nevens F, Verslype C, Van Steenbergen W. Endoscopic resection of ampullary lesions: a single-center 8-year retrospective cohort study of 91 patients with long-term follow-up. Surg Endosc. 2013;27(10):3865–76.
13. Harewood G, 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(3):367–70.
14. Navarrete C, Gobelet JM. Treatment of common bile duct injuries after surgery. Gastrointest Endosc Clin N Am. 2012;22(3):539–53.
15. Tewani SK, Turner BG, Chuttani R, Pleskow DK, Sawhney MS. Location of bile leak predicts the success of ERCP performed for postoperative bile leaks. Gastrointest Endosc. 2013;77(4):601–8.
16. Traina M, Tarantino I, Barresi L, et al. Efficacy and safety of fully covered self-expandable metallic stents in biliary complications after liver transplantation: a preliminary study. Liver Transpl. 2009;15:1493–8.
17. Kahaleh M, Sundaram V, Condron SL, et al. Temporary placement of a covered self-expandable metallic stents in patients with biliary leak. Midterm evaluation of a pilot study. Gastrointest Endosc. 2007;66:52–9.
18. Varadarajulu S, Noone TC, Tutuian R, Hawes RH, Cotton PB. Predictors of outcome in pancreatic duct disruption managed by endoscopic transpapillary stent placement. Gastrointest Endosc. 2005;61:568–75.
19. Shrode CW, MacDonough P, Gaidhane M, Northup PG, Sauer B, Ku J, et al. Multimodality endoscopic treatment of pancreatic duct disruption with stenting and pseudocyst drainage: how efficacious is it? Dig Liver Dis. 2012;8:26–30.
20. Draganov P, Hoffman B, Marsh W, Cotton P, Cunningham J. Long-term outcome in patients with benign biliary strictures treated endoscopically with multiple stents. Gastrointest Endosc. 2002;55:680–6.
21. Baron TH, Davee T. Endoscopic management of benign bile duct strictures. Gastrointest Endosc Clin N Am. 2013;23(2):295–311.
22. 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.
23. Webb K, Saunders M. Endoscopic management of malignant bile duct strictures. Gastrointest Endosc Clin N Am. 2013;23(2):313–31.
24. Bakhru M, Tekola B, Kahaleh M. Endoscopic palliation for pancreatic cancer. Cancers (Basel). 2011; 3(2):1947–56.
25. Sahni VA, Mortele KJ. Magnetic resonance cholangiopancreatography: current use and future applications. Clin Gastroenterol Hepatol. 2008;6:967–77.
26. Thevenot A, Bournet B, Otal P, Canevet G, Moreau J, Buscail L. Endoscopic ultrasound and magnetic resonance cholangiopancreatography in patients with idiopathic acute pancreatitis. Dig Dis Sci. 2013; 58(8):2361–8.
27. Kondo S, Isayama H, Akahane M, et al. Detection of common bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography, and helical-computed-tomographic cholangiography. Eur J Radiol. 2005;54:271–5.
28. Verma D, Kapadia A, Eisen GM, Adler DG. EUS vs MRCP for detection of choledocholithiasis. Gastrointest Endosc. 2006;64:248.
29. Karakan T, Cindoruk M, Alagozlu H, Ergun M, Dumlu S, Unal S. EUS versus endoscopic retrograde cholangiography for patients with intermediate probability of bile duct stones: a prospective randomized trial. Gastrointest Endosc. 2009;69(2):244–52. doi:10.1016/j.gie.2008.05.023.
30. Romagnuolo J, Currie G. Calgary advanced therapeutic endoscopy center study group. Noninvasive vs. selective invasize biliary imaging for acute biliary pancreatitis: an economic evaluation by using decision tree analysis. Gastrointest Endosc. 2005;61:86–97.
31. Silviera ML, Seamon MJ, Porshinsky B, et al. Complications related to endoscopic retrograde cholangiopancreatography: a comprehencive clinical review. J Gastrointestin Liver Dis. 2009;18:73–82.
32. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc. 2004;59:845–64.

33. Freeman ML, Guda NM. ERCP cannulation: a review of reported techniques. Gastrointest Endosc. 2005;61(1):112–25.
34. 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.
35. Tarnasky PR, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. Gastroenterology. 1998;115:1518–24.
36. Freeman ML, OVerby C, Qi D. Pancreatic stent insertion: consequences of failure and results of a modified technique to maximize success. Gastrointest Endosc. 2004;59(1):8–14.
37. Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SM, Nicholson S, Fogel EL, U.S. Cooperative for Outcomes Research in Endoscopy (USCORE). A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366(15):1414–22. doi:10.1056/NEJMoa1111103.
38. Williams EJ, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. Endoscopy. 2007;39:793–801.
39. Loperfido S, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc. 1998; 48:1–10.
40. Enns R, Eloubeidi MA, Mergener K, Jowell PS, Branch MS, Pappas TM, et al. ERCP-related perforations: risk factors and management. Endoscopy. 2000;34:293–98.
41. Baron TH, Kozarek R, Carr-Locke DL. ERCP. 2nd ed. Philadelphia: Saunders; 2012.
42. Gerstenberger PD. Malpractice in gastrointestinal endoscopy. Gastrointest Endosc Clin N Am. 1995; 5(2):375–89.
43. Cotton PB. Analysis of 59 ERCP lawsuits; mainly about indications. Gastrointest Endosc. 2006;63(3): 378–82.
44. Jowell PS, Baillie J, Branch MS, et al. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. Ann Intern Med. 1996;125:983–9.
45. Freeman ML. Training and competence in gastrointestinal endoscopy. Rev Gastroenterol Disord. 2001;1(2):73–86.
46. Sundermeyer MS, Murphy PA. Prevention of hospital liability for granting privileges to unqualified physicians. Gastrointest Endosc Clin N Am. 1995;5(2):433–45.
47. Faigel DO, Baron TH, Lewis B, et al. (Editors). Ensuring competence in endoscopy, american society for gastrointestinal endoscopy. Oak Brook; 2005. p. 15–31.
48. Bendia E, Marzioni M, Benedetti A, Di Sario A. Endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy in acute pancreatitis: indications and technique. Surg Treat Pancreat Dis Update Surg. 2009;95–9.

Overview of ERCP Complications: Prevention and Management

3

Nalini M. Guda and Martin L. Freeman

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly performed procedure. Its role as a diagnostic procedure is obsolete and is largely replaced by other less invasive/noninvasive procedures. Ductography (images of pancreatic and bile ducts) can be obtained by magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) and endoscopic ultrasound (EUS). Detailed information of the pancreatic parenchyma and other structures surrounding the gastrointestinal (GI) lumen is readily obtainable by EUS and MRCP. ERCP still has a dominant role in therapeutic interventions and the scope of interventional procedures is expanding with increased understanding of the pathophysiology, available instruments, increasing expertise, awareness, and treatment of complications. The indications for the procedure, techniques, etc., are described elsewhere.

Adverse events, unplanned events, and complications are terms that are often used interchangeably. Whatever they are called, they result in significant morbidity and occasional mortality. Understanding and minimizing risk is the key with any interventional procedure, and especially with ERCP which has a significantly increased risk relative to other endoscopic techniques.

The most common complications of ERCP are pancreatitis, hemorrhage (especially postsphincterotomy), perforation, cholangitis, cholecystitis, and others (Table 3.1). These topics have been extensively investigated in various prospective studies [1, 2]. An aspect that has not been well studied are the consequences and costs associated with failed cannulation and hence failed intervention, therapeutic failure, and repeat interventions due to failures as well as the direct consequences of the complications. Also to be emphasized, although beyond the scope of this chapter, is the importance of qualification, training, and expertise to perform ERCP.

Post-ERCP Pancreatitis

Post-ERCP pancreatitis (PEP) is the most common complication of ERCP. It has been reported to occur after 5–30% of ERCP, depending on patients, procedures, study definitions, and

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Table 3.1 Complications of ERCP

Complication	Frequency
Pancreatitis	5–25%
Bleeding	1–2%
Perforation	<1%
Cholecystitis	<1%
Cholangitis	Rare
Death	Rare

ERCP Endoscopic retrograde cholangiopancreatography

methodology. Most studies report incidence of PEP of about 7% [3]. Risk factors for PEP have been well defined and are discussed below. When more than one risk factor is present the risk is typically compounded rather than simply additive. Understanding risk factors is a critical piece in reducing incidence of complications and improving outcomes.

Definition

Uniform standards in diagnosis of pancreatitis are essential. The Atlanta criteria-based definition of pancreatitis is widely accepted: [4] two of three criteria are required to diagnose pancreatitis, including (1) abdominal pain in the epigastric region with or without radiation to the back, (2) at least threefold elevation of serum amylase and or lipase, and (3) imaging features suggestive of pancreatitis. These criteria are very similar to the original Cotton criteria with the addition of greater than three times elevation of serum lipase. Some clinicians routinely check serum amylase and/or lipase following ERCP, and elevations of serum enzyme levels may occur in the absence of pain. This does not represent pancreatitis, and is often referred to as "biochemical pancreatitis"; clinically these patients generally do well with no further intervention. In the setting of postprocedure pancreatitis, routine cross-sectional imaging to confirm the diagnosis is not necessary unless imaging is required for other reasons. Severe pain in the absence of significant elevation of serum lipase and/or amylase should be carefully evaluated and prompt a search for other complications such as perforation. It is not uncommon for some patients to complain of postprocedural pain in the absence of any detectable complication. The most problematic to assess are patients with preprocedure pain and equivocal enzyme rises post-ERCP, such as more than three times lipase elevation and less than three times amylase elevation, which is a common scenario.

Post-ERCP pancreatitis can range from mild interstitial to severe necrotizing with multiorgan failure and even death. The severity of post-ERCP pancreatitis is graded according to consensus definitions depending on the duration of hospitalization and need for intervention [4, 5]. Pancreatitis is considered mild if hospitalized for 2–3 days, moderate for 4–10 days, and severe for >10 days hospitalization, development of necrosis or pseudocyst, and/or performance of a drainage procedure or surgery.

What are Potential Mechanisms of Post-ERCP Pancreatitis?

The exact mechanism by which the pathway of inflammation is initiated is unclear. There are several possible explanations and some of the strategies for prevention of postprocedural pancreatitis are based on these postulates. There is some indirect evidence that the following factors play a role:

1. Mechanical outflow obstruction: It is known from clinical data that instrumentation causes ampullary edema and likely mechanical outflow obstruction of pancreatic ductal drainage. This led to the concept of pancreatic duct stenting for prophylaxis which has resulted in significant reduction in post-ERCP pancreatitis.
2. Ductal injury/trauma: Pancreatic ductal manipulation including passage of guidewires into the main pancreatic duct or side branches results in increased risk of pancreatitis. Any pancreatic ductal intervention appears to increase the risk. It is likely that ductal injury triggers the inflammatory cascade.
3. Thermal injury: Pancreatic sphincterotomy increases the risk of pancreatitis. Access/precut sphincterotomy is also a risk factor, suggesting that thermal injury can initiate the inflammatory cascade.

4. Hydrostatic injury: There appears to be a relationship between the perfusion of the duct and pancreatic inflammation. Pancreatic duct manometry with a perfusion catheter and no aspiration carries a high risk of post-ERCP pancreatitis. Repeated duct injections, depth of pancreatic duct injections, forceful injections/"acinarization" have all been implicated.

Other causes that have been postulated include the introduction of gut flora into the pancreatic duct and hence the "infectious theory," and chemical injury or allergic response from contrast.

While the exact inflammatory pathway is unclear, there seems to be a significant interplay of mechanisms. Prevention of pancreatitis is aimed at halting one or more of these processes to reduce the severity, if not completely prevent pancreatitis. Pharmacological interventions target the blockage of inflammatory chemokines. One category of drug that has shown promising results is NSAIDs.

How Are Risk Factors Defined?

Several prospective studies have advanced our knowledge of risk factors for PEP. Risk has been stratified as definite, indefinite, or no risk based on the evidence. Definite risk factors have been confirmed by multivariate analysis in studies involving greater than 500 patients and proven statistically significant in more than one study or meta-analyses. Indefinite risk factors are those that were significant on univariate analysis in multiple studies or by multivariate analysis in a single study. If there is no evidence based on multivariate analysis and the data are inconsistent based on univariate analysis, these factors are thought to pose no additional risk (other than the baseline or background risk) [3].

What Are Risk Factors for Post-ERCP Pancreatitis?

1. Patient-related risk factors
2. Procedure-related risk factors
3. Operator-related risk factors

Patient-Related Risk Factors

There are certain groups of patients who are at the highest risk of developing pancreatitis after ERCP, as confirmed by multiple cohort studies. Most clearly at risk are women with abdominal pain in the absence of common duct stones or other identifiable pathology, fitting into the category of "suspected sphincter of Oddi dysfunction (SOD)." There is no evidence that type III SOD (pain only) are at any more risk than II or I SOD (those with dilated bile ducts or/and abnormal liver chemistries). Those with a prior history of post-ERCP pancreatitis also have a higher risk (Table 3.2).

Procedure-Related Risk Factors

Difficult cannulation is a known risk factor, probably because of induced papillary edema. Other risk factors include multiple pancreatic duct contrast injections. Data support that the extent

Table 3.2 Patient-related risk factors for post-ERCP pancreatitis

Definite[a]	Probable	No risk
Young age	Absence of CBD stone	Normal/small CBD diameter
Female	Normal serum bilirubin	Periampullary diverticulum
Suspected SOD		Pancreas divisum
Recurrent acute pancreatitis		Allergy to contrast medium
Absence of chronic pancreatitis		
History of post-ERCP pancreatitis		

SOD Sphincter of Oddi dysfunction; *CBD* Common bile duct; *ERCP* Endoscopic retrograde cholangiopancreatography
[a] See text for stratification of risk

Table 3.3 Procedure-related risk factors for post-ERCP pancreatitis

Definite	Probable	No risk
Pancreatic duct injection	Pancreatic acinarization	Intramural contrast injection
Pancreatic sphincterotomy	Pancreatic brush cytology	Diagnostic vs. therapeutic
Balloon dilation of intact sphincter	Pain during ERCP	Biliary sphincterotomy
Difficult/failed cannulation		Prior failed ERCP
Precut sphincterotomy		Sphincter of Oddi manometry (esp. aspiration catheter)

ERCP Endoscopic retrograde cholangiopancreatography

of injection corresponds to the incidence of pancreatitis. Deep passage of a guidewire into the pancreatic duct has been shown to be a powerful risk factor [6]. Certain high-risk procedures including precut sphincterotomy or access papillotomy, balloon dilation of the bile duct especially without a biliary sphincterotomy, pancreatic sphincterotomy, and any pancreatic duct interventions are consistently associated with increased risk by multivariable analyses. Although there has remained concern over increased rates of pancreatitis with metal biliary stent placement, several studies including a small randomized trial failed to confirm this with uncovered and partially covered metal stents, [7–9] and biliary sphincterotomy before stent placement did not impact PEP. Despite these data, concern remains over potentially increased pancreatitis with use of fully covered metal stents. A small retrospective series reported that nonpancreatic cancer and injection of the pancreatic duct were risk factors for pancreatitis in patients with partially and fully covered metal stents placed [10]. The strength or osmolarity of the contrast plays no significant role in increasing the risk of pancreatitis. Degree of pancreatic opacification has shown to increase the risk. Despite popular opinion, acinarization of the pancreas did not pose any significant risk by multivariate analyses (Table 3.3) [11, 12].

Physician (Operator)-Related Risk Factors

Data from various studies suggest that endoscopist case volume and experience is inversely proportional to the risk of complications [13]. One study showed that trainee involvement was associated with increased risk [14]. Presence of multiple risk factors in a single patient has a compounding effect on risk. Thus a young woman with suspected SOD, normal liver functions and normal common bile duct diameter would have the highest risk [15]. The odds ratios for post-ERCP pancreatitis of some common risk factors as calculated based on various prospective studies and meta-analyses are summarized in Table 3.4.

How to Prevent Post-ERCP Pancreatitis

Careful Patient Selection

Diagnostic ERCP or ERCP for "suspicion" of most diseases is now obsolete and should be avoided. As an example, noninvasive or less invasive techniques including MRCP, endoscopic ultrasound, and intraoperative cholangiography during cholecystectomy provide similar information, which may obviate the need for ERCP. On the other hand, if there is biochemical, radiological, and/or clinical support for choledocholithiasis, then an ERCP first followed by cholecystectomy is a reasonable approach.

Table 3.4 Common risk factors and odds ratios for pancreatitis based on available data

Risk factor	Odds ratio (95 % CI)
Female gender	2.23 (1.75, 2.84)
Suspected SOD	4.09 (3.37, 4.96)
History of recurrent acute pancreatitis	2.46 (1.93, 3.12)
Pancreatic duct injection	2.20 (1.60, 3.01)
Pancreatic sphincterotomy	3.10 (1.60, 5.80)
Precut sphincterotomy	2.71 (2.02, 3.63)
Balloon dilation of intact sphincter	4.50 (1.50, 13.5)

SOD Sphincter of Oddi dysfunction, *CI* Confidence interval

Appropriate Physician (Operator) Experience

The endoscopist should be familiar with his or her own limitations and the type of therapeutic procedure that is required. The endoscopist must be capable of recognizing and handling unplanned events. Ability to place prophylactic pancreatic stents is a prerequisite of ERCP [16]. Consistent placement of pancreatic stents often requires use of small diameter wires (0.018″, 0.021″, or 0.025″).

Careful Procedure Techniques

It is recommended to avoid or minimize the extent of pancreatic duct opacification. Any contrast injection should be done under fluoroscopic guidance, and contrast should be gently injected a small amount at a time especially if opacifying the pancreatic duct inadvertently or unintentionally (Table 3.5).

Guidewire Cannulation

Guidewire cannulation was proposed as a way to minimize contrast injection and reduce the risk of pancreatitis. Cannulation techniques have been described elsewhere in the book. By using the guidewire instead of contrast, one can advance the wire into the desired duct. If the wire crosses over the spine, it is thought to be in the pancreatic duct while if the wire advances up along the spine, it is believed to be in the bile duct. Once the wire is passed in the direction of the bile duct, the cannula is advanced into the duct and contrast injected. There are at least 12 randomized controlled studies comparing guidewire cannulation to the standard technique using contrast. A recent meta-analysis of these published trials suggests that the guidewire cannulation technique reduces the risk of PEP with a risk reduction ratio (RR) of 0.51 [95% confidence interval (CI) 0.32–0.82]. Cannulation success was also more successful with guidewire cannulation [17]. Guidewire cannulation appears to reduce risk of pancreatitis not only by avoiding contrast injection into the pancreatic duct but also by likely reducing papillary trauma owing to the smaller diameter of the wire compared to the cannula used for cannulation. The problem with the published studies of guidewire cannulation is that the control groups used a technique of cannulating and injecting contrast without use of a guidewire, which is long antiquated and does not represent a realistic alternative. Guidewire cannulation also does not ensure safety. There are concerns for intramural dissection, ductal injury, trauma, or perforation, especially of the side branches. Care should be taken not to push wires, especially if passage is difficult. It is reasonable to inject a small amount of contrast to delineate the duct when in doubt as to the location of the tip of the wire, rather than to cause ductal injury or dissection by forcefully advancing the wire [18, 19]. If biliary access is the goal, but repeated passage of the guidewire occurs into the pancreatic duct, or even perhaps once in a high-risk patient, it is ideal to leave the wire in the pancreatic duct and cannulate the bile duct alongside this wire (dual guidewire cannulation technique). Double wire access should be followed by prophylactic pancreatic duct stent placement, as shown in a randomized trial [20].

Table 3.5 How to minimize risk of post-ERCP pancreatitis [3]

Patient selection	Technical considerations	Pharmacological methods
Avoid ERCP for marginal/weak indication—consider alternatives including EUS/MRCP/IOC	Efficient cannulation (including judicious use of guidewires)	Rectal indomethacin/diclofenac[a]
	Avoid unintended pancreatic duct cannulation/opacification	
	Placement of pancreatic stents prophylactically (preferably small bore and soft stents) for high-risk patients	

ERCP Endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *MRCP* magnetic resonance cholangiopancreatography, *IOC* intraoperative cholangiogram

[a] No data at the current time to use rectal NSAID alone. Generally used in conjunction with pancreatic duct stents

Table 3.6 Pancreatic stent placement: when and when not

Indicated (based on evidence)	Not indicated
Sphincter of Oddi dysfunction (suspected or documented, regardless of manometry findings)	Lower-risk patients (older or with obstructed pancreatic duct) undergoing a low-risk procedure
Difficult cannulation involving pancreatic instrumentation or injection	Pancreatic duct not injected with contrast material and limited guidewire manipulation in low-risk patient
Aggressive instrumentation of pancreatic duct (e.g., brush cytology)	Needle-knife precut or fistulotomy starting above the orifice in absence of other risks
Pancreatic guidewire placement during biliary cannulation	Doubtful feasibility of successful pancreatic wire access and stent placement
Pancreatic sphincterotomy (major or minor papilla)	Biliary therapy in patients with pancreas divisum
Precut sphincterotomy starting at papillary orifice	
Balloon dilation of intact biliary sphincter	
Prior post-ERCP pancreatitis	
Endoscopic ampullectomy	

ERCP Endoscopic retrograde cholangiopancreatography

Prophylactic Pancreatic Duct Stent Placement

Pancreatic duct stents have been proven effective at reducing risk of post-ERCP pancreatitis. It is thought that papillary edema from ERCP can impede the flow of pancreatic secretions. The hypothesis is that placement of a stent across the pancreatic sphincter would preserve flow of pancreatic secretions and thereby minimize the risk of post-ERCP pancreatitis. Since the initial reports demonstrating the benefits of pancreatic duct stenting in high-risk patients, numerous well designed studies and meta-analyses have assessed the value of prophylactic stenting, and currently stenting has the best evidence as a strategy to reduce risk of PEP [21, 22]. In the latest meta-analysis including 14 studies, pancreatic duct stent placement was associated with a statistically significant reduction of PEP (RR 0.39; 95% CI 0.29–0.53; $p<0.001$). Subgroup analysis stratified according to the severity of PEP showed that a stent was beneficial in patients with mild to moderate PEP (RR 0.45; 95% CI 0.32–0.62; $p<0.001$) and in patients with severe PEP (RR 0.26; 95%CI 0.09–0.76; $p=0.01$) [23–25].

Patients shown to benefit from pancreatic stents include those with one of the following characteristics: sphincter of Oddi dysfunction (suspected or documented, regardless of manometry findings); difficult cannulation involving pancreatic instrumentation or injection; aggressive instrumentation of the pancreatic duct (e.g., brush cytology); pancreatic guidewire placement during biliary cannulation; pancreatic sphincterotomy (major or minor papilla); precut sphincterotomy starting at papillary orifice; balloon dilation of intact biliary sphincter; prior post-ERCP pancreatitis; and endoscopic ampullectomy (Table 3.6). While there is overwhelming evidence for placement of stents in those with patient- and procedure-related risk factors, there are only two studies to assess the utility of pancreatic duct stenting for low-risk patient and procedures: interestingly, both showed a positive effect [22].

There are clear downsides to pancreatic stent placement (Table 3.7). Not all endoscopists are trained or familiar with pancreatic duct stenting both in terms of indications and techniques. Training/simulation models for practicing place-

Table 3.7 Challenges to pancreatic duct stent placement

Education of endoscopists regarding indications and applications
Need for training in techniques of pancreatic stent placement
Familiarity with specialized guidewires and pancreatic stents
Enhanced understanding of pancreatic duct anatomy
Appropriate follow-up to ensure stent passage or removal
Awareness of potential complications
Failed placement
Guidewire/stent-related ductal perforation
Inward delivery or stent migration
Stent-induced pancreatic duct or parenchyma injury

ment and removal of pancreatic stents might be useful. Familiarity with specialized guidewires and pancreatic stents and enhanced understanding of pancreatic duct anatomy are required. The endoscopist must be aware of potential complications associated with either stent placement or failed attempts at prophylactic pancreatic stent placement. Failed placement is associated with increased risk. When placing pancreatic stents, guidewire or stent-related ductal perforation is possible. Inward delivery or stent migration may occasionally occur. Finally, stent-induced pancreatic duct or parenchymal injury may occur, even occasionally following short-term pancreatic duct stenting for prophylaxis [26].

Technique of Pancreatic Stent Placement

When placing a pancreatic stent, vigorous manipulation of the wire in the pancreas should be avoided, since it can lead to side branch perforation and thus increase risk of pancreatitis. Although many endoscopists use 0.035-in. wires for general use, many experts use a 0.018–0.021-in. guidewire for pancreatic stent placement, and these are a prerequisite for small-caliber (3F) stent placement. Although a randomized trial failed to demonstrate that 3F stents were superior to 5F stents [27], 0.018-in. wires necessary for 3F stent placement were only passed after randomization. In addition, 0.035-in. wires may not be suitable for tiny or tortuous pancreatic ducts. The authors do not recommend passage of large-bore wires and placement of large-bore stents especially in small-caliber or tortuous pancreatic ducts.

Stents are made of different materials with some stents being softer than others. Intuitively softer stents without inner flanges should conform to the ductal configuration and cause less trauma and ductal injury than rigid flanged stents, although they have never been formally compared. Data are clear that larger stent diameter is associated with a significantly higher risk of ductal injury [28]. For prophylactic stents in high-risk patients, the authors recommend either short (2–3 cm), soft 4–5Fr, inner flanged stents or long (9–11 cm) soft 3F or 4F unflanged stents with a single pigtail. Patients should have an abdominal radiograph within 2–4 weeks, which preferably should be checked by the gastroenterologist since inexperienced radiologists may not readily recognize small pancreatic stents. If a stent remains at follow-up, it should be removed endoscopically. There are rare reports of pancreatitis following removal of pancreatic stents but this occurred mostly with stents having internal flanges.

One special situation occurs when the pancreatic duct takes a 360° loop in the head of the pancreas, the so-called ansa loop. In these situations and similar difficult ductal configurations, it is not possible to pass the wire deep into the duct (Video 3.1). If one can use a small-caliber 0.018-in. guidewire and create a “knuckle” or a “j” shaped intentional hook to the wire which is inserted as little as 2 cm into the duct, a 2 cm long 4 or 5Fr stent, preferably of soft material with an inner flange to avoid immediate outward migration, can be inserted. Immediate removal or passage of a pancreatic stent at the end of the procedure does not protect against post-ERCP pancreatitis compared with a stent that remains within the duct for at least a few days [29].

Can a Pill Prevent Post-ERCP Pancreatitis?

Many pharmacologic agents have been tested that could potentially work at various stages of the inflammatory cascade leading to pancreatitis. To date, at least 48 randomized controlled studies have been reported utilizing 15 different agents with most studies including patients at average or mixed risk for post-ERCP pancreatitis. At least six studies included high-risk patient populations [30]. Drugs that have been evaluated and their efficacy are listed in Table 3.8.

Medications that have been tried include those aimed at reduction of sphincter spasm like calcium channel blockers, topical lidocaine, and nitroglycerin. Calcium channel blockers and topical lidocaine are ineffective. There are some data suggesting that topical nitroglycerin might be beneficial. Based on a recent network meta-analysis of very limited data involving diagnostic ERCP, topical epinephrine may reduce post-ERCP pancreatitis [30].

Table 3.8 Pharmacological prevention of post-ERCP pancreatitis

Effective	Ineffective	Possibly effective
Rectal NSAIDs	Calcium channel blockers	Topical nitroglycerine
Gabexate infusion (>12 h)	Topical liodcaine	Nafamostat
	Corticosteroids	Antibiotics
	Allopurinol	Somatostatin (12–24 h infusion)
	PAF inhibitors	Topical epinephrine[a]
	IL-10	
	Heparin derivatives	
	Octreotide	
	Ulinastatin	
	Risperidone + ulinastatin	

ERCP endoscopic retrograde cholangiopancretography, *PAF* platelet-activating factor, *NSAIDs* Nonsteroidal anti-inflammatory drugs

[a] Based on a neural network meta-analysis topical epinephrine is effective [26]. Original studies not done in high-risk population. No randomized controlled trials done in high-risk population

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent the most promising class of medications for prevention of post-ERCP pancreatitis. A number of randomized controlled trials, including one with high-risk patients, and several meta-analyses have shown significant risk reduction. Initial studies used rectal diclofenac, which is not available in the USA. Rectal indomethacin is now the best studied agent available in the USA. In a large, multicenter, randomized study it was administered as a 100-mg suppository immediately after ERCP with significant reduction in PEP [31]. High-risk patients in this study also had pancreatic duct stent placement (approximately 80% of all patients), and these patients experienced additional benefit from rectal indomethacin: 16.1–9.7% PEP with NSAID ($p=0.04$). About 20% of the patients did not have a prophylactic pancreatic stent either due to technical difficulties or endoscopist decision, and use of rectal indomethacin alone reduced pancreatitis: 20.6–6.3% ($p=0.049$). NSAIDs have also reduced the severity of pancreatitis, and the numbers needed to treat varied from 21 to 6 depending on the number or risk factors included.

NSAIDs Alone vs. Pancreatic Stent Placement + NSAIDs

Currently clearly two interventions have been shown to reduce post-ERCP pancreatitis. One is the rectal administration of indomethacin and the other is placement of a pancreatic duct stent. Placement of pancreatic duct stents is not without problems as discussed above. Pancreatic duct stent insertion requires facility with use of smaller diameter guidewires into the pancreatic duct and with placement of stents. In some cases ductal anatomy may render deep passage of a wire and placement of a stent very difficult. The consequences of failed stent placement after multiple attempts are not favorable as the risk of pancreatitis is significantly higher [32]. On the other hand, rectal NSAIDs are easy to administer with a reasonable safety profile, require no expertise, and are relatively inexpensive. A recent network meta-analysis [33] suggested that rectal NSAIDs alone are superior to pancreatic duct stents alone in preventing post-ERCP pancreatitis, and should be considered first-line therapy for selected patients. However, these findings were limited by the small number of studies assessed (only 29 studies), lack of inclusion of high-risk patients in most NSAID studies, potential publication bias, and the indirect nature of the comparison. For the time being, it is reasonable to use rectal NSAIDs in all patients at high risk, but not as a replacement for pancreatic stents until further data are available. Whether NSAIDS should be given to the average and low-risk population or whether higher doses are more effective are both under investigation.

Case 1

A 73-year-old female was admitted with cholangitis and findings of a large bile duct stone. She had recently undergone carotid artery stenting for a stenotic artery causing transient ischemic attacks (TIAs), and had been on aspirin, Plavix, and anticoagulation with Coumadin. Following normalization of international normalized ratio (INR) and holding of the heparin bridge, the patient underwent ERCP with sphincterotomy plus large balloon dilation and extraction of a 12-mm bile duct stone. After consultation with neurology and internal medicine, the decision was made to restart anticoagulation with Lovenox 48 h after sphincterotomy. The patient was discharged to a transitional care facility, but on day 5 post-sphincterotomy was readmitted with hypovolemic shock and hemoglobin 6 mg/dL. The patient was resuscitated, transfused, INR normalized with fresh frozen plasma, and emergent ERCP was performed under general anesthesia. Inspection of the sphincterotomy site showed active bleeding from under a fresh clot (Fig. 3.1). What should be done?

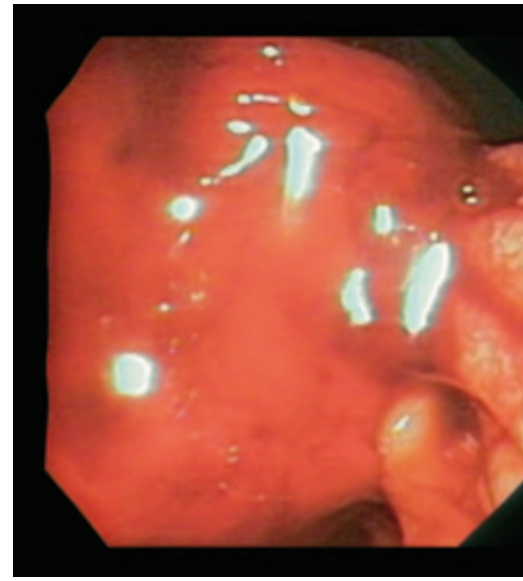

Fig. 3.1 Active bleeding at the sphincterotomy site

Bleeding

What Are the Risk Factors and How Should They Be Managed?

Bleeding may occur immediately during a procedure, but if controlled and without clinically significant blood loss, it is not generally considered to be a complication. Delayed or clinically significant hemorrhage is an increasingly rare complication of sphincterotomy which can occur up to a week or more after the procedure. Data from older large multicenter studies suggest that significant hemorrhage was typically seen in 1–2 % of cases postsphincterotomy [1, 34–36].

Risk factors for postsphincterotomy hemorrhage have been well defined. They include bleeding during the procedure, acute cholangitis, coagulopathy, and reinstitution of anticoagulation within 3 days after sphincterotomy (Table 3.9) [37].

Bleeding during sphincterotomy can usually be treated with injection of dilute epinephrine at the apex and edges of the sphincterotomy.

Table 3.9 Risk factors of postsphincterotomy bleeding

Definite[a]	Probable[b]	No added risk[c]
Coagulopathy	Cirrhosis	Aspirin/NSAID use
Anticoagulation <3 days of sphincterotomy	Dilated CBD	Ampullary tumor
Cholangitis prior to ES	Periampullary diverticulum	Long sphincterotomy
Low-volume center	Precut sphincterotomy	Extension of prior sphincterotomy
Bleeding during initial ES	Choledocholithiasis	

ES Endoscopic sphincterotomy; *CBD* Common bile duct; *NSAIDS* Non-steroidal anti-inflammatory drugs
[a] Significant by multivariate analysis
[b] Significant by univariate analysis
[c] Not significant by multivariate analysis

Injection is easiest to perform with a flexed papillotome or catheter impacted into the wall rather than a sclerotherapy needle although special needles designed for duodenoscopes are routinely available. Despite concerns for using epinephrine as monotherapy for hemostasis in treatment of bleeding from peptic ulcer disease, epinephrine injection alone for sphincterotomy bleeding is successful in 96–100% of cases [38, 39]. Injecting close to the pancreatic duct orifice should be avoided. If epinephrine injection fails to control bleeding, very careful use of bipolar coagulation or endoscopic clips is possible, but care must taken to avoid injuring the pancreatic orifice, causing perforation, and occluding the sphincterotomy or pancreatic orifice. Deploying clips through a duodenoscope can be challenging. If using a clip with an outer sheath, the clip should be advanced to the tip of the sheath before inserting it down the working channel to avoid kinking the sheath when it passes over the elevator. Some endoscopists routinely remove the outer sheath although this is not recommended by the manufacturers, and in our opinion prevents deployment through a duodenoscope. One should maintain a position as far away from the papilla as possible in order to visualize the clip. As the clip is advanced out of the duodenoscope, care should be taken to relax the elevator, and sometimes the scope dials need to be in a neutral position.

If bleeding is severe, balloon tamponade across the biliary sphincter may slow or stop bleeding and allow better visualization of the bleeding site. Temporary placement of fully covered self-expanding metallic stents is another option. If bleeding cannot be controlled by these techniques, hemostasis may be achieved by angiography and selective embolization of the feeding vessel. If a hemoclip was placed, this can often be used by the radiologist to identify the feeding vessel in the absence of significant ongoing bleeding. Bleeding can virtually always be controlled by the above techniques such that surgical intervention is rarely, if ever, needed. No data support the use of intravenous proton pump inhibitors to achieve hemostasis although this is often done. Similarly, no data confirm the utility of routinely using octreotide infusions to decrease splanchnic circulation and hence achieve hemostasis, though in rare instances this could be tried.

Case Continued

After vigorous irrigation and mechanical dislodgement of the clot using the papillotome, active oozing at the apex of the sphincterotomy, which was adjacent to a large diverticulum, was seen (Fig. 3.2). The bile duct was cannulated, and as the flexed papillotome was slowly withdrawn,

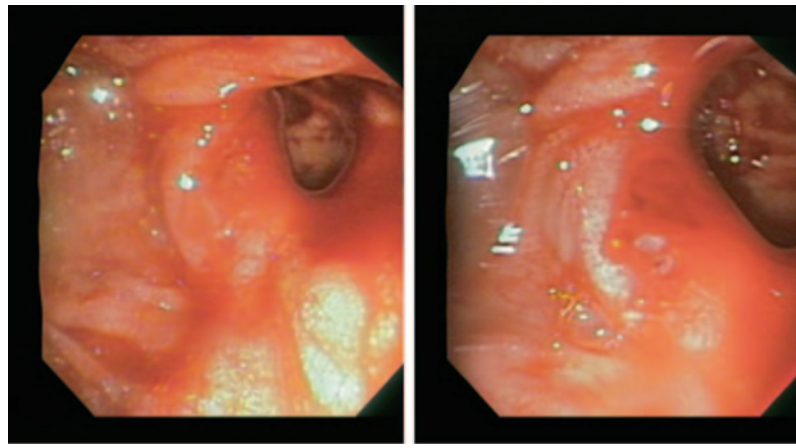

Fig. 3.2 Irrigation and visualization of the bleeding site adjacent to the diverticulum

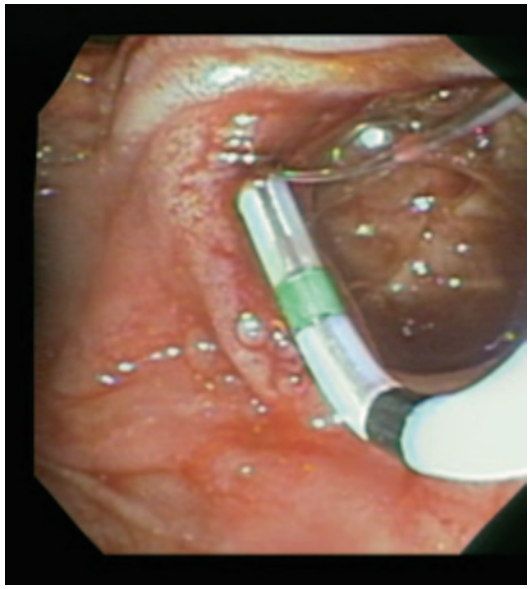

Fig. 3.3 Injection of epinephrine with the tip of the sphincterotome resulting in temporary hemostasis

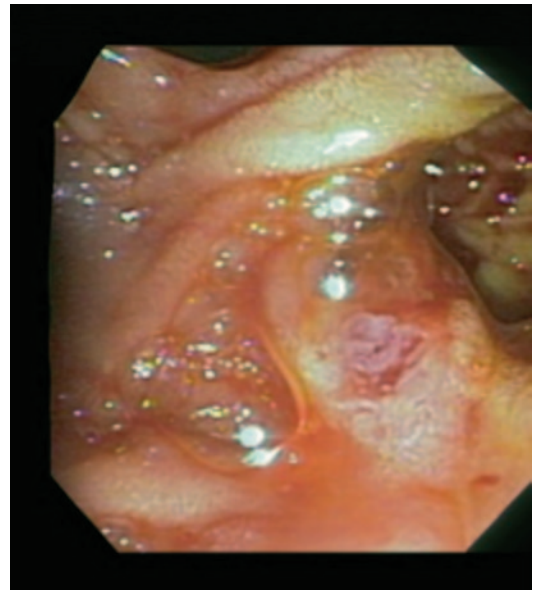

Fig. 3.4 Hemostasis following epinephrine injection

the site of bleeding at the apex was impacted and injected with 1:10,000 epinephrine until the bleeding stopped (Figs. 3.3 and 3.4). The sphincterotomy was gently dilated with an 8-mm wire guided balloon to better visualize and access the bleeding point, and separate the left and right walls of the sphincterotomy. This was performed to provide tamponade at the bleeding site and to better visualize the bleeding point since epinephrine injection would only provide temporary vasoconstriction and tamponade effect in this patient who had to resume anticoagulation. Additional mechanical hemostasis was achieved by placing a clip over the bleeding site around the left apex of the sphincterotomy, and deployed to avoid the pancreatic orifice (Fig. 3.5). The patient had no further bleeding but suffered a stroke 2 days later, despite reinstitution of Plavix.

How Can Bleeding Be Prevented?

As with any endoscopic intervention, preprocedure assessment of risk factors is essential. It is always advisable to discuss the risks and benefits with the patient. One should carefully evaluate the patient for any risk factors including the use of antiplatelet agents and anticoagulants. Risk factors for thromboembolism and management of anticoagulation have been described by the American Society of Gastrointestinal Endoscopy (ASGE) based on the current evidence. High-risk conditions for thromboembolic events include: atrial fibrillation associated with valvular heart disease, mechanical mitral valve, and history of prior thromboembolic event in the presence of any mechanical valve. Low-risk conditions include history or presence of deep vein thrombosis, bioprosthetic valve, mechanical aortic valve, and uncomplicated or paroxysmal atrial fibrillation. In high-risk cases, it is advisable to manage anticoagulants in conjunction with the cardiologist to assess and minimize risk. By ASGE guidelines, in high-risk patients warfarin should be discontinued 3–5 days prior to the procedure and heparin used as a bridge therapy while INR is below therapeutic level. Heparin may be resumed post-procedure with warfarin restarted 72 h post-sphincterotomy. In low-risk patients, anticoagulation can be stopped 72 h prior to the procedure and resumed 72 h post-procedure. Data on use of aspirin and NSAIDs

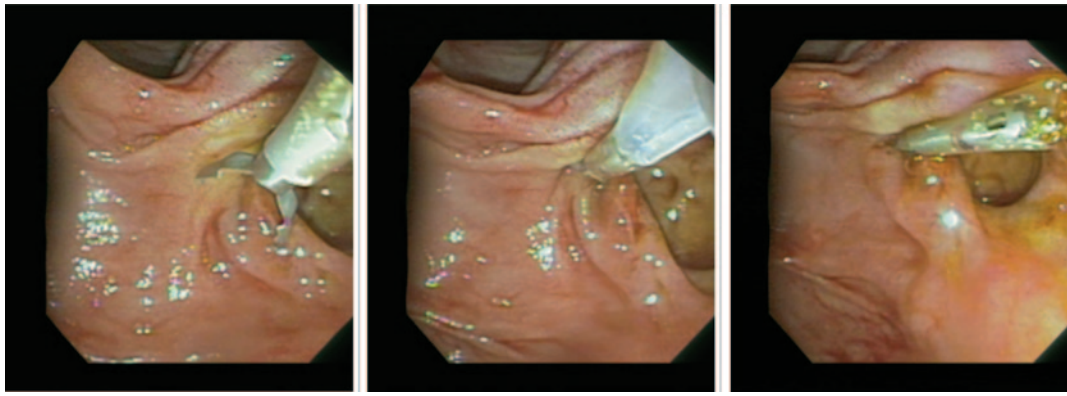

Fig. 3.5 Placement of a hemoclip over the left wall of sphincterotomy at site of the bleeding vessel. To deploy the clip, one should relax the elevator of the duodenoscope and sometimes gentle manipulation of the catheter should be done with back and forth motion of the sheath or clip. If a sheath is present, the clip should be advanced to the tip of the sheath so it does not bend when passing over the elevator. Newer clips are specifically designed to work well through a duodenoscope

suggest that these may be continued or resumed immediately postprocedure. However, data are unclear on the use of newer anticoagulants and antiplatelet agents including clopidogrel. Currently most clinicians hold these agents for 5–7 days. Patients with renal dysfunction tend to have an increased risk of bleeding. This risk is multifactorial and increased bleeding time is believed to correlate with platelet dysfunction. Clinically desmopressin acetate (DDAVP) or estrogens can be administered or hemodialysis performed to improve platelet function. Underlying anemia can be corrected with transfusion. One should be careful in patients with liver failure, malnutrition, or jaundice and check the prothrombin time. If prothrombin time is greater than 1.4, vitamin K or fresh frozen plasma can be administered to correct the coagulopathy. Ideally platelet count should be at least 50,000, and platelet transfusion considered for low counts [40]. Finally, in certain high-risk situations sphincterotomy can be avoided, substituting, balloon dilation ("balloon sphincteroplasty") to reduce the risk of bleeding. Balloon dilation without sphincterotomy should be accompanied by placement of a pancreatic stent, due to otherwise high risk of pancreatitis in the Western population.

Case 2

A 39-year-old woman was transferred to our center 1 day after ERCP with biliary sphincterotomy complicated by a retroperitoneal perforation at a community hospital. Initial indication for ERCP was recurrent post-cholecystectomy right upper quadrant pain associated with transiently abnormal liver chemistries. MRCP had shown no evidence of bile duct stone. During initial ERCP, pancreatic and bile ducts were both accessed with guidewires, a pancreatic duct stent was placed, and a biliary sphincterotomy was performed. After the sphincterotomy, the wire was lost from the bile duct, and the endoscopist had difficulty re-accessing the bile duct. The procedure was terminated. Shortly afterward, the patient developed severe abdominal pain. Serum lipase and amylase were mildly elevated, but CT scan of the abdomen showed extensive retroperitoneal and intraperitoneal air with some retroperitoneal fluid. The general surgeon on call took the patient to the operating room, found bile spillage, but despite extensive exploration could not find the source of the leak and placed retroperitoneal and intraperitoneal drains. The next morning, the patient was still draining substantial bile from the retroperitoneal drain. The local endoscopist was

approached to repeat ERCP for biliary stenting, but opted to transfer the patient to our center.

On arrival, the patient was hemodynamically stable. Hepatobiliary iminodiacetic acid (HIDA) scan showed extensive ongoing retroperitoneal bile leak. That day the patient underwent emergent ERCP.

Perforation

Mortality up to 10% has been reported with perforation, especially if not recognized and treated early. Mortality seems to be related to delayed recognition, onset of signs of peritoneal inflammation, and/or systemic inflammatory response [41]. Perforations can be caused by several mechanisms. The most common are endoscopic sphincterotomy, guidewire passing through the duct or duodenal wall, duodenoscope passage tearing the duodenal wall, or mechanical injury by stents. Several classifications have been proposed. The first system describes perforations as (1) duodenal wall perforation, (2) bile duct perforation, and (3) periampullary perforation [42].

A more recent classification takes etiology and location of perforation into account to help guide management. Type 1 perforations are related to trauma from the scope and occur away from the ampulla. These have traditionally required surgical repair, but are increasingly possible to close using endoscopic clips, stents, and/or sutures. CT with contrast is useful for diagnosis and also for monitoring closure of the leak. Type 2 perforations are periampullary and arise after sphincterotomy in the intraduodenal segment of the bile duct or rarely following balloon sphincteroplasty, especially if the ampulla is dilated beyond the size of the common bile duct or pancreatic duct. CT with contrast is useful for diagnosis. Type 3 perforations occur in the duct from either guidewires or catheters and can be managed conservatively by stenting beyond the leak or by decompressing the duct in other ways. Type 4 is the presence of free air without any obvious perforation or contrast extravasation on CT, and is managed conservatively [43, 44].

Early recognition of perforation is key to salvaging a reasonably good outcome. If perforation is suspected at the apex of a sphincterotomy, careful fluoroscopy searching for extraluminal gas, and injection of a small amount of contrast while pulling the catheter through the incision over a guidewire will confirm or reasonably exclude extravasation. If perforation is suspected, proactive treatment is essential. Endoscopic clipping may be attempted, but can be very difficult with a duodenoscope or a deeply retracted sphincterotomy [41]. In most cases, a biliary and if appropriate pancreatic stent or naso-ductal drains should be placed. For biliary sphincterotomy perforation, the most technically feasible approach is to place a fully covered self-expanding metallic stent to drain the bile duct and occlude the leak. Regardless of endoscopic therapy, the patient is generally treated with nasogastric suction, intravenous antibiotics, strict fasting, surgical consultation, and in-hospital observation. A CT scan of the abdomen should be obtained to assess for contrast leakage and any retroperitoneal or intraperitoneal air. If the leak is sizeable and ongoing as suggested by contrast extravasation or the patient's clinical condition deteriorates, prompt drainage via surgery or the percutaneous route is advisable. The importance of early recognition and endoscopic management of suspected perforations is supported by the observation that nearly all patients with immediate recognition and endoscopic drainage do well with conservative management compared with poor outcomes including multiple surgeries, complicated protracted hospital course, and increased mortality in patients with delayed recognition [42]. If the perforation is not discovered or suspected during the ERCP, but there is concern for a perforation following the procedure, a CT should be obtained. Plain films will miss small perforations because sphincterotomy-associated perforations are typically retroperitoneal and not intraperitoneal, and thus not visible under the diaphragm.

Risk factors for perforation include performance of sphincterotomy, presence of altered surgical anatomy, stricture dilation and long duration of the procedure [34]. An important tech-

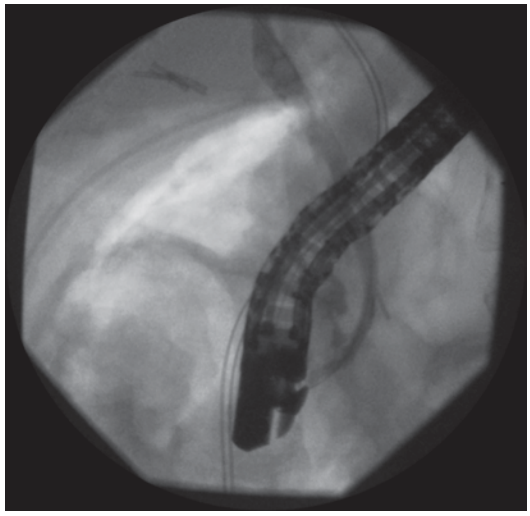

Fig. 3.6 Cholangiogram with extravasation of contrast outside the bile duct into the retroperitoneum (images courtesy of Rajeev Attam MD)

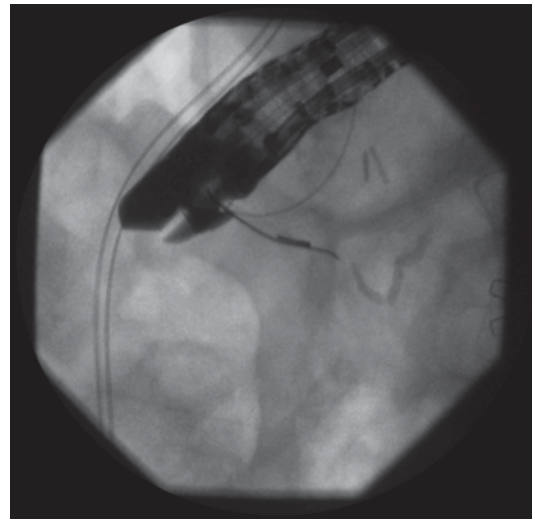

Fig. 3.7 With the wire in the bile duct, the pancreatic duct was cannulated alongside and a pancreatogram was obtained

nique during sphincterotomy is to use just the "nose" or only a small segment of the cutting wire in contact with the ampullary tissue. Prolonged contact with the cutting wire should be avoided. Automated current generators should be used to prevent a "zipper cut." Needle knife sphincterotomy should only be performed in a controlled fashion. Following larger sphincterotomies, it is advisable to perform a cholangiogram of the distal duct to look for any contrast extravasation. A scout film should be obtained before and after the procedure for such comparisons. Whether use of carbon dioxide insufflation would minimize visualization of or symptoms from a perforation is not known; it is possible that small or self-limited perforations are better tolerated with carbon dioxide than with room air.

Case Continued

ERCP was performed under general anesthesia using CO_2 insufflation. Scout film showed extensive retroperitoneal air; inspection of the major papilla showed a patulous sphincterotomy with a small rim of space just above the bile duct. Cholangiogram revealed a normal small caliber bile duct with active contrast leak into the retroperitoneum just inside the duct (Fig. 3.6). After a wire was placed into the bile duct, the pancreatic duct was accessed using a 4F tip papillotome (Fig. 3.7) and 0.018-in. guidewire; with difficulty, the knuckled wire was pushed around a tight ansa loop (Fig. 3.8) to the tail of the pancreatic duct (Fig. 3.9). With wires in both ducts, a 4F 11 cm soft material unflanged stent was placed into the pancreatic duct, and a 10 mm × 60 mm fully covered outer-flanged metallic stent was inserted into the bile duct and deployed across the biliary sphincter. Endoscopic views of the same sequence are shown in Figs. 3.10, 3.11, 3.12: bile duct accessed with the rim of space above the bile duct (Fig. 3.10), pancreatic stent in place (Fig. 3.11), and deployed metallic stent compressing closed the sphincterotomy with pancreatic drainage protected by the pancreatic stent (Fig. 3.12). Metallic biliary stent placement may be an independent risk factor for post-ERCP pancreatitis; this patient could ill afford an additional complication.

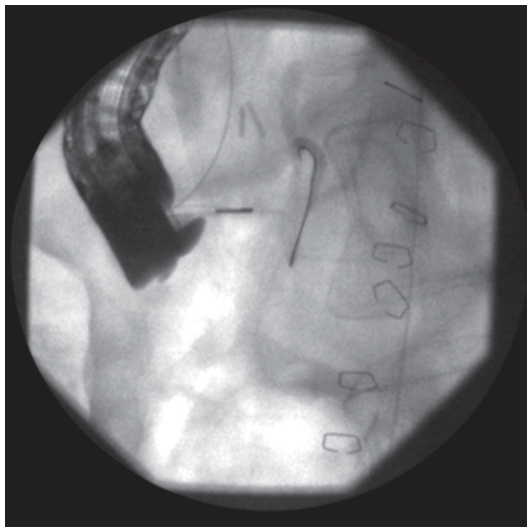

Fig. 3.8 Attempts were made to pass a guidewire deep into the pancreatic duct to place a pancreatic stent

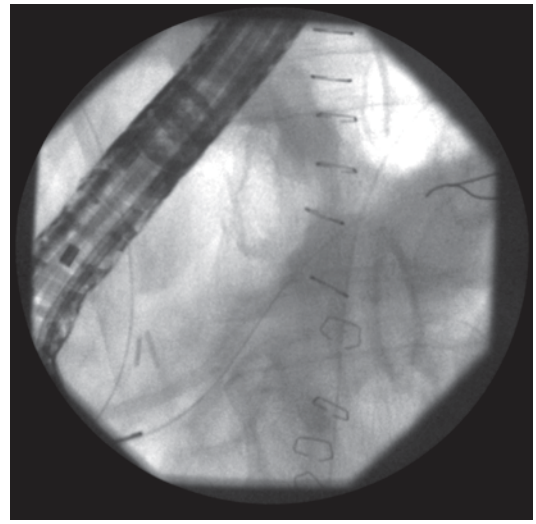

Fig. 3.9 The tip of the wire was "knuckled" and the loop advanced to the tail of the pancreas

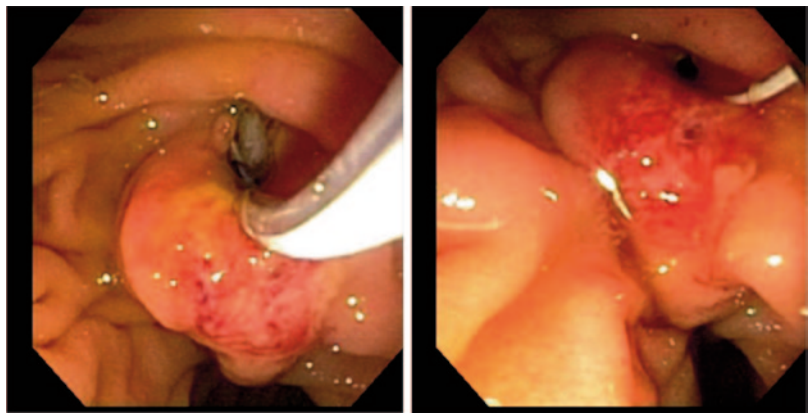

Fig. 3.10 Endoscopic image of biliary cannulation with a small rim around the sphincterotomy

She had immediate closure of the retroperitoneal leak and no post-ERCP pancreatitis, but she had a protracted hospital stay with the development of a retroperitoneal right flank abscess requiring prolonged percutaneous drainage. She required a peripherally inserted central catheter (PICC) line for hydration and several hospital admissions for failure to thrive and dehydration over the next 6 weeks. Eventually the biliary metallic stent and percutaneous drains were removed. The pancreatic duct stent migrated spontaneously.

Cholangitis and Cholecystitis

Cholangitis typically occurs after ERCP with incomplete biliary drainage or increasingly after intraductal cholangioscopy with continuous irrigation. A new and greatly concerning phenomenon is transmission of resistant bacteria from incompletely decontaminated duodenoscopes. Particularly prone to cholangitis are patients with previous colonization due to occluded stents and those with hilar strictures. In patients with suspected or known cholangiocarcinoma or hilar obstruction, a pre-procedure MRCP or at least

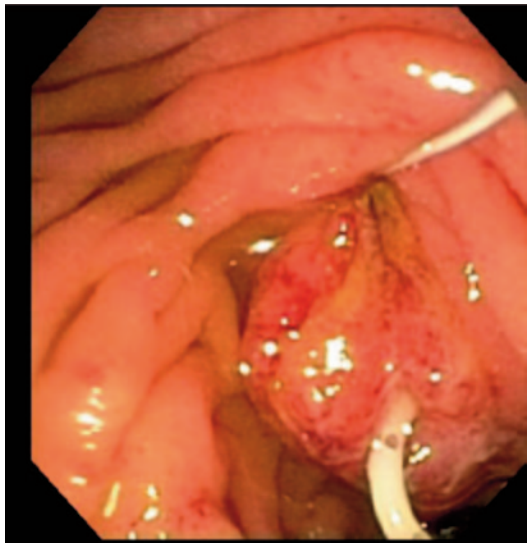

Fig. 3.11 Placement of 4Fr pancreatic duct stent while maintaining wire in the bile duct

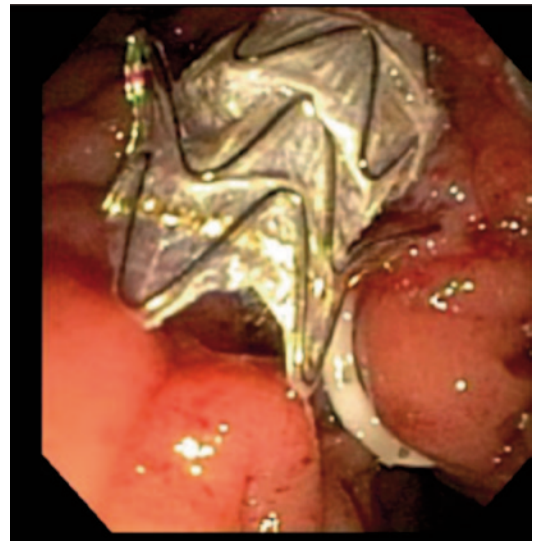

Fig. 3.12 Placement of fully covered metal biliary stent with pancreatic stent in place

coronal CT is advised to plan selective drainage, rather than opacifying the entire intrahepatic biliary system under pressure [45]. Cholangitis can generally be avoided by minimizing injection in patients with instrumented or stented ducts, providing complete clearance of stones, and if in doubt placing stents to allow complete biliary drainage. In cholangioscopy, minimizing irrigation is key. Although routine antibiotics are not recommended for all ERCP, prophylactic antibiotics are indicated with anticipated or definite incomplete biliary drainage (primary sclerosing cholangitis, hilar stricture, or retained contrast), cholangioscopy, presence of cyst communicating with pancreatic duct, pseudocyst drainage or necrosectomy, and posttransplant patients [46].

Cholecystitis is an uncommon complication and typically occurs after biliary stent placement, especially through tumors that involve the cystic duct takeoff. Data are conflicting as to whether fully covered metallic stents pose any greater risk than uncovered metal or plastic stents. For patients with distal biliary obstruction/stricture with gallbladder in situ, it is generally preferable to place an uncovered metal stent. For patients with biliary pancreatitis and simultaneous cholecystitis, ERCP should be done only if there is concern for cholangitis or ongoing biliary obstruction. In patients who are poor candidates for surgery, a long (up to 20 cm) gallbladder stent can be placed via a transpapillary route to treat acute cholecystitis.

A recently recognized and very concerning complication is infection resulting from incomplete cleaning of duodenoscopes. Recently, a number of serious and fatal infections resulting from incomplete disinfection of resistant bacteria, including CRE (Carbapenem-Resistant Enterobacteriaceae), as well as sporadic clusters of ESBL (extended spectrum beta-lactamase), VRE (vancomycin resistant enterococcus), and pseudomonas have been reported. These infections have occurred despite following manufacturers recommendations for cleaning, and are thought to be the result of difficulty removing particles of debris related to the elevator in duodenoscopes. The problem is being actively addressed by the FDA, the ASGE, the AGA, and duodenoscope manufacturers. In the meantime, careful attention to disinfection and quarantining of endoscopes thought to be involved in cases with nosocomial infection are recommended [47, 48].

Cardiopulmonary Complications

As with any intervention requiring sedation or anesthesia, there is a risk of cardiopulmonary complications. These are rare and in carefully selected patients should account for less than 1% of procedures. Unlike post-ERCP pancreatitis, risk of cardiopulmonary complications increases with age and comorbid conditions. With increasing complexity of therapeutic ERCP procedures often involving EUS, there is a rising trend to involve anesthesia to deliver monitored anesthesia care (MAC) or general anesthesia with endotracheal intubation [49, 50].

Air embolism is a very rare but often fatal complication with ERCP, and particularly endoscopic transluminal necrosectomy. At least 26 cases have been reported so far. The presenting symptom is usually a sudden change in cardiorespiratory or neurological status and often detected during or immediately after the procedure when the patient is turned from a prone to supine position. Most patients had a prior history of surgery, manipulation of the bile duct for stones, placement of metal stents, cholangioscopy, or endoscopic necrosectomy. Patients with prior shunts are particularly at risk. Immediate recognition is the key to salvaging the outcome. Bedside echocardiography can identify air in the right ventricle, which can be aspirated by using a central venous catheter [51]. The increasing trend towards using carbon dioxide instead of room air for insufflation may reduce risk and/or severity of air embolism.

Late Complications of ERCP

Most complications with ERCP occur within days or a week after the procedure. Delayed complications of the biliary tract include stent occlusion or perforation, formation of stones and debris around stents, restenosis of sphincterotomy, recurrent choledocholithiasis and others. Restenosis of the sphincter may result from incomplete sphincterotomy and fibrosis with healing. Pancreatic duct stents, especially when inadvertently left in place over extended periods, may be associated with ductal and parenchymal pancreatic injury [26].

Endoscopist Experience and Complications

Endoscopist experience is a critical factor in complications of surgical interventions and has been studied in surgical outcomes and certain endoscopic procedures. The data are mixed in terms of complications of ERCP and endoscopist experience. In an Austrian study by Kapral et al. [52] endoscopists were considered high volume if they performed more than 50 ERCPs a year. Their data demonstrated that high volume endoscopists had better diagnostic and therapeutic success (86.9 vs. 80.3%, $p<0.001$) with fewer complications (10.2 vs.13.6%, $p=0.007$) than lower volume endoscopists. These results are similar to a previous Italian study by Loperfido et al. in which complications were higher (7.1 vs. 2.0%, $p<0.0001$) in centers with low volumes (<200 ERCPs/year) [34]. In a US multicenter study, endoscopists who performed no more than one sphincterotomy per week had higher complication rates compared with their peers who carried out higher volumes of sphincterotomies each week [1]. These studies support the concept that a lower case volume affects outcomes adversely. In contrast, another recent large UK multicenter study assessing risk factors for ERCP complications found no difference in overall complications among endoscopists with differing caseloads or by hospital type [13]. The only difference found was a decrease in the risk of post-ERCP pancreatitis when the procedure was performed at a university hospital compared with a district hospital, which was interpreted to reflect perhaps the better support staff and environment available at university hospitals. Reasons for the striking difference in findings between this study and the Austrian study, which is quite similar in concept and design, are difficult to postulate.

Most studies of post-ERCP pancreatitis, the most common complication, have suggested that

case mix is at least as important as technical factors in determining risk; any difference in technical expertise is overshadowed by the difference in patient mix, which tends to be more complex and high risk at more specialized centers. Taken together, these studies demonstrate that each endoscopist must perform a certain number of ERCPs and sphincterotomies in order to both minimize the risk and improve outcomes. Endoscopist experience appears to be an underappreciated risk factor. There are no harder data on outcomes outside large multicenter studies where, again, bias in reporting, complexity of the case mix, and definitions of complications all play a pivotal role in study results [13].

Key Points

- ERCP is associated with risk of complications including pancreatitis, perforation, post-sphincterotomy bleeding, cholangitis, and cholecystitis.
- Any adverse event should be immediately investigated and supportive therapy initiated to minimize sequelae.
- ERCP should not be performed solely for diagnostic purposes in most cases. Other less or noninvasive modalities are recommended for initial evaluation.
- Risk factors are defined as patient-related, procedure-related (types of intervention) and physician/operator-related (case volume, expertise).
- Pancreatic duct stenting and rectal indomethacin reduce the risk of post-ERCP pancreatitis significantly.
- Cholangitis is usually iatrogenic and often due to occluded stents. Prophylactic antibiotics should be used only in select patients including those with incomplete biliary drainage, undergoing cholangioscopy, and a cyst communicating with the pancreatic duct.
- To minimize postprocedural bleeding, patients should be risk stratified and care individualized. Careful attention should be paid to sphincterotomy and ERCP technique to prevent bleeding, and knowledge of endoscopic techniques to treat bleeding is critical.
- If perforation is suspected, obtain a CT scan rather than or in addition to a conventional plain radiograph, which can miss retroperitoneal air.

Video Caption

Video 3.1 Placement of prophylactic small caliber pancreatic stent in patient with tiny, tortuous pancreatic duct using 0.018-in. guidewire and 4F 2-cm inner-flanged soft stent

This young woman had recurrent abdominal pain associated with abnormal liver function tests (LFTs) suggestive of sphincter of Oddi dysfunction type II. MRCP showed a normal bile duct but a very tortuous small caliber ventral pancreatic duct. The plan was for ERCP with biliary sphincterotomy and a protective pancreatic stent. This type of pancreatic ductal anatomy leads to virtual impossibility of stent placement using conventional guidewires, as the wire will exit side branches and potentially lead to ductal perforation, while not allowing stability to place a protective stent. Therefore, the case was started with a 5-4-3 cannula (Boston Scientific) loaded with an 0.018″ Roadrunner wire (Cook Medical). The major papilla was very small, adding to technical challenge. The pancreatic duct was cannulated and a very limited amount of contrast injected, which showed the sharp angular turn in the main pancreatic duct. The 0.018″ wire was intentionally knuckled inside the duct, so that the platinum tip would remain intraductal and avoid entering side branches. Normally, we would leave a pancreatic wire and cannulate the bile duct with a second wire. However, the stability of this pancreatic wire was very precarious. As a result, we placed the pancreatic stent before attempting biliary access. With the wire pushed only as far as the first turn, a 4F 2-cm soft material, inner-flanged pancreatic stent (Hobbs Medical) was placed. The inner flange is critical to avoid immediate outward migration. Then, using the guidewire technique, an 0.025-in. wire was

used to cannulate bile duct beside the pancreatic stent, and a biliary sphincterotomy performed.

This approach prioritizes early and safe placement of a protective pancreatic stent in a high-risk patient with a very tortuous, small-caliber pancreatic duct in whom conventional guidewire techniques are very risky for ductal perforation or failure to place a pancreatic stent. Additionally, this video demonstrates use of a soft material atraumatic stent to avoid pancreatic ductal injury [32, 53].

References

1. Freeman ML, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med. 1996;335(13):909–18.
2. Kahaleh M, Freeman M. Prevention and management of post-endoscopic retrograde cholangiopancreatography complications. Clin Endosc. 2012;45(3):305–12.
3. Freeman ML, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. Gastrointest Endosc. 2004;59(7):845–64.
4. 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(1):102–11.
5. Cotton PB, Lehman G, Vennes J, et al. Endoscopic sphincterotomy complications and their management: an attempt at consensus. Gastrointest Endosc. 1991;37(3):383–93.
6. Wang P, Li ZS, Liu F, et al. Risk factors for ERCP-related complications: a prospective multicenter study. Am J Gastroenterol 2009;104(1):31–40.
7. Artifon EL, Sakai P, Ishioka S, et al. Endoscopic sphincterotomy before deployment of covered metal stent is associated with greater complication rate: a prospective randomized control trial. J Clin Gastroenterol. 2008;42(7):815–9.
8. 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.
9. Wilcox CM, Kim H, Ramesh J, Trevino J, Varadarajulu S. Biliary sphincterotomy is not required for bile duct stent placement. Dig Endosc. 2014;26(1):87–92.
10. 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.
11. Cheon YK, Cho KB, Watkins JL, et al. Frequency and severity of post-ERCP pancreatitis correlated with extent of pancreatic ductal opacification. Gastrointest Endosc. 2007;65(3):385–93.
12. Johnson GK, Geenen JE, Bedford RA, et al. A comparison of nonionic versus ionic contrast media: results of a prospective, multicenter study. Midwest Pancreaticobiliary Study Group. Gastrointest Endosc. 1995;42(4):312–6.
13. Guda NM, Freeman ML. Are you safe for your patients—how many ERCPs should you be doing? Endoscopy. 2008;40(8):675–76.
14. Cheng CL, Sherman S, Watkins JL, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. Am J Gastroenterol. 2006;101(1):139–47.
15. Freeman ML, DiSario JA, Nelson DB, et al. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. Gastrointest Endosc. 2001;54(4):425–34.
16. Freeman ML. Pancreatic stents for prevention of post-ERCP pancreatitis: for everyday practice or for experts only? Gastrointest Endosc. 2010;71(6):940–4.
17. Tse F, Yuan Y, Moayyedi P, Leontiadis GI. Guide wire-assisted cannulation for the prevention of post-ERCP pancreatitis: a systematic review and meta-analysis. Endoscopy. 2013;45(8):605–18.
18. Freeman ML, Guda NM. ERCP cannulation: a review of reported techniques. Gastrointest Endosc. 2005;61(1):112–25.
19. Kobayashi G, Fujita N, Imaizumi K, et al. Wire-guided biliary cannulation technique does not reduce the risk of post-ERCP pancreatitis: multicenter randomized controlled trial. Dig Endosc. 2013;25(3):295–302.
20. Ito K, Fujita N, Noda Y, et al. Can pancreatic duct stenting prevent post-ERCP pancreatitis in patients who undergo pancreatic duct guidewire placement for achieving selective biliary cannulation? A prospective randomized controlled trial. J Gastroenterol. 2010;45(11):1183–91.
21. Tarnasky PR. Mechanical prevention of post-ERCP pancreatitis by pancreatic stents: results, techniques, and indications. J Pancreas. 2003;4(1):58–67.
22. Freeman ML. Pancreatic stents for prevention of post-ERCP pancreatitis: for everyday practice or for experts only? Gastrointest Endosc. 2010;71(6):940–4.
23. Mazaki T, Mado K, Masuda H, Shiono M. Prophylactic pancreatic stent placement and post-ERCP pancreatitis: an updated meta-analysis. J Gastroenterol. 2014;49(2):343–55.
24. Sofuni A, Maguchi H, Itoi T, et al. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. Clin Gastroenterol Hepatol. 2007;5(11):1339–46.
25. Tsuchiya T, Itoi T, Sofuni A, et al. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial. J Hepatobiliary Pancreat Surg. 2007;14(3):302–7.
26. Bakman YG, Safdar K, Freeman ML. Significant clinical implications of prophylactic pancreatic stent placement in previously normal pancreatic ducts. Endoscopy. 2009;41(12):1095–98.

27. Chahal P, Tarnasky PR, Petersen BT, et al. Short 5Fr vs. long 3Fr pancreatic stents in patients at risk for post-endoscopic retrograde cholangiopancreatography pancreatitis. Clin Gastroenterol Hepatol. 2009;7(8):834–9.
28. Rashdan A, Fogel EL, McHenry L, Jr, Sherman S, Temkit M, Lehman GA. Improved stent characteristics for prophylaxis of post-ERCP pancreatitis. Clin Gastroenterol Hepatol. 2004;2(4):322–9.
29. Conigliaro R, Manta R, Bertani H, et al. Pancreatic duct stenting for the duration of ERCP only does not prevent pancreatitis after accidental pancreatic duct cannulation: a prospective randomized trial. Surg Endosc. 2013;27(2):569–74.
30. Akshintala VS, Hutfless SM, Colantuoni E, et al. Systematic review with network meta-analysis: pharmacological prophylaxis against post-ERCP pancreatitis. Aliment Pharmacol Ther. 2013;38(11–12):1325–37.
31. Elmunzer BJ, Scheiman JM, Lehman GA, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366(15):1414–22.
32. Freeman ML, Overby C, Qi D. Pancreatic stent insertion: consequences of failure and results of a modified technique to maximize success. Gastrointest Endosc. 2004;59(1):8–14.
33. Akbar A, Abu Dayyeh BK, Baron TH, Wang Z, Altayar O, Murad MH. Rectal nonsteroidal anti-inflammatory drugs are superior to pancreatic duct stents in preventing pancreatitis after endoscopic retrograde cholangiopancreatography: a network meta-analysis. Clin Gastroenterol Hepatol. 2013;11(7):778–83.
34. Loperfido S, Angelini G, Benedetti G, et al. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. Gastrointest Endosc. 1998;48(1):1–10.
35. Masci E, Toti G, Mariani A, et al. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. Am J Gastroenterol. 2001;96(2):417–23.
36. Rabenstein T, Schneider HT, Hahn EG, Ell C. 25 years of endoscopic sphincterotomy in Erlangen: assessment of the experience in 3498 patients. Endoscopy. 1998;30(9):A194–201.
37. Freeman ML. Adverse outcomes of ERCP. Gastrointest Endosc. 2002;56(6 Suppl):S273–82.
38. Leung JW, Chan FK, Sung JJ, Chung S. Endoscopic sphincterotomy-induced hemorrhage: a study of risk factors and the role of epinephrine injection. Gastrointest Endosc. 1995;42(6):550–4.
39. Wilcox CM, Canakis J, Monkemuller KE, Bondora AW, Geels W. Patterns of bleeding after endoscopic sphincterotomy, the subsequent risk of bleeding, and the role of epinephrine injection. Am J Gastroenterol. 2004;99(2):244–8.
40. Van Os EC, Kamath PS, Gostout CJ, Heit JA. Gastroenterological procedures among patients with disorders of hemostasis: evaluation and management recommendations. Gastrointest Endosc. 1999;50(4):536–43.
41. Jin YJ, Jeong S, Kim JH, et al. Clinical course and proposed treatment strategy for ERCP-related duodenal perforation: a multicenter analysis. Endoscopy. 2013;45(10):806–12.
42. Howard TJ, Tan T, Lehman GA, et al. Classification and management of perforations complicating endoscopic sphincterotomy. Surgery. 1999;126(4):658–63.
43. Machado NO. Management of duodenal perforation post-endoscopic retrograde cholangiopancreatography. When and whom to operate and what factors determine the outcome? A review article. J Pancreas. 2012;13(1):18–25.
44. Stapfer M, Selby RR, Stain SC, et al. Management of duodenal perforation after endoscopic retrograde cholangiopancreatography and sphincterotomy. Ann Surg. 2000;232(2):191–8.
45. Freeman ML, Overby C. Selective MRCP and CT-targeted drainage of malignant hilar biliary obstruction with self-expanding metallic stents. Gastrointest Endosc. 2003;58(1):41–9.
46. Banerjee S, Shen B, Baron TH, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc. 2008;67(6):791–8.
47. Epstein L, Hunter JC, Arwady MA, Tsai V, Stein L, Gribogiannis M, Frias M, Guh AY, Laufer AS, Black S, Pacilli M, Moulton-Meissner H, Rasheed JK, Avillan JJ, Kitchel B, Limbago BM, MacCannell D, Lonsway D, Noble-Wang J, Conway J, Conover C, Vernon M, Kallen AJ. New Delhi Metallo-β-Lactamase–Producing Carbapenem-Resistant Escherichia coli Associated With Exposure to Duodenoscopes. JAMA. 2014;312(14):1447-55.
48. ASGEcommunication.http://www.informz.net/informzdataservice/onlineversion/ind/bWFpbGluZ2luc3RhbmNlaWQ9MTkwMjY5NCZzdWJzY3JpYmVyaWQ9OTMyNjcxMjU=doi:10.1001/jama.2014.12720.
49. Garewal D, Powell S, Milan SJ, Nordmeyer J, Waikar P. Sedative techniques for endoscopic retrograde cholangiopancreatography. Cochrane Database Syst Rev. 2012;6:CD007274.
50. Goudra BG, Singh PM, Sinha AC. Anesthesia for ERCP: impact of anesthesiologist's experience on outcome and cost. Anesthesiol Res Pract. 2013;2013:570518.
51. Donepudi S, Chavalitdhamrong D, Pu L, Draganov PV. Air embolism complicating gastrointestinal endoscopy: a systematic review. World J Gastrointest Endosc. 2013;5(8):359–65.
52. Kapral C, Duller C, Wewalka F, Kerstan E, Vogel W, Schreiber F. Case volume and outcome of endoscopic retrograde cholangiopancreatography: results of a nationwide Austrian benchmarking project. Endoscopy. 2008;40(8):625–30.
53. Freeman ML, Gupta K. Biliary access techniques for ERCP: from basic to advanced. Instructional DVD #035, American Society for Gastrointestinal Endoscopy, 2007 (63 min). www.asge.org

ERCP from Soup to Nuts: Evaluation, Preparation, Execution, and Follow-Up

4

John Baillie

Introduction

There are many sources of information about ERCP equipment and techniques. It is not my goal to duplicate these readily available documents. Instead, I would like to take the reader through the whole ERCP "experience," from clinic or inpatient evaluation through preparation, execution of the procedure, and follow-up afterwards. I tell my trainees that the ERCP procedure itself is sometimes the least important part of the patient's management. Certainly, without other considerations being addressed, it can be a meaningless and dangerous undertaking. As a former mentor of mine used to say, "ERCP is not a game: it is dead serious." ERCP should never be undertaken lightly or hurriedly, because—literally—lives are at stake. ERCP is arguably the most demanding of all the procedures performed on a routine basis by gastrointestinal endoscopists. Book chapters and articles can frame the subject for you, but there is absolutely no substitute for hands-on experience, and preferably plenty of it. Since the landmark Duke University ERCP training study published in 1996 [1], the "bar" for basic competence in ERCP has been set at around 200 procedures. However, much has changed in almost 20 years: in 1996, half the ERCPs were diagnostic; in 2014, almost 100% of ERCP is therapeutic, requiring a broad spectrum of skills with endoscopes and accessories [2]. Real competence likely begins somewhere around 400–500 cases, and expertise may emerge around 1000 cases. It has been suggested that there should be two tiers of ERCP training: a basic level of training for "average" endoscopists who intend to confine their practice to "basic" therapeutics and an advanced level for specialists who are expected to manage the full range of hepatobiliary and pancreatic disorders. Unfortunately, the difficulty of ERCP cases cannot reliably be predicted ahead of time: difficult anatomy can be encountered in the most straightforward appearing cases.

At the present time, there are too many endoscopists learning ERCP [and endoscopic ultrasound (EUS)] in fellowship programs in the United States, many with relatively low procedure volumes. The days when every gastroenterology fellow could expect to be trained in ERCP are gone, although this is a relatively recent change. There is still great pressure on program directors to provide each fellow at least 25–50 ERCP procedures during their 3 years of general gastroenterology fellowship. Unfortunately—but predictably—this small experience is all-to-often parlayed into credentials at community hospitals to perform ERCP. For many years, just 25 was the average number of cases required by hospital credentialing committees to prove expertise and obtain credentials to perform ERCP. Community hospitals are under pressure from their surgeons who want accessible ERCP when a problematic—usually post-cholecystectomy—case arises. The inevitable consequences of inexperience

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in this area are failed cases and complications. Having to perform a second or subsequent ERCP when the first attempt fails is expensive and likely accompanied by increased morbidity. *At the very least, a competent community endoscopist should be able to access the duct of choice at least 80% of the time*. It is often stated—correctly—that skill at needle knife papillotomy (NKP) is necessary to approach 100% success at accessing the desired duct at ERCP. However, NKP training has been restricted to the chosen few favored by their skilled mentors. In a recent commentary, I suggested that this has been an unfair barrier to success for a large group of ERCP hopefuls [3].

Additionally, ERCP is not just about cannulating the duodenal papilla. The endoscopist should be able to perform safe and effective biliary and pancreatic sphincterotomy to access stones, pass dilators, and place stents. Competence in ERCP requires the ability to decompress an obstructed biliary tree in a patient with acute cholangitis by means of sphincterotomy, stone removal and/or biliary stent or nasobiliary drain placement. A competent ERCP endoscopist should also be able to insert a biliary stent to manage post-cholecystectomy bile leaks, and brush a biliary stricture for cytology. In the past, many ERCP endoscopists avoided pancreatic endotherapy, limiting their efforts to diagnosis and treatment of biliary disorders. As *placing a guidewire in the main pancreatic duct (PD) and inserting a temporary plastic stent over it has been shown to reduce the risk of post-ERCP pancreatitis (PEP)* [4], all ERCP endoscopists need to be comfortable working in the pancreas. Passing a small caliber pancreatic stent usually requires familiarity and dexterity with thin caliber guidewires, some as thin as 0.018 in. in diameter. Finally, ERCP endoscopists cannot work in a vacuum, but must be part of a multidisciplinary team managing hepatobiliary and pancreatic disorders.

Evaluation

Patients who are being considered for ERCP should undergo unhurried evaluation before the procedure. In a busy academic center where I worked many years ago, it was common for the fellows to see "add-on" ERCP patients between procedures, or during a lunch break. They would report their findings to the faculty member running the endoscopy list, and if he or she agreed the patient would be made an "add-on." This meant that the first time these patients saw the endoscopist was in a preparation bay in the endoscopy unit. Consent for the procedure was often left to the trainees, further limiting pre-procedure contact between the patient and the endoscopist. If relatives were not on site to accompany the patient to Endoscopy, there was no opportunity to meet them and answer questions. This rush to ERCP was often justified by the urgency of the case, although in truth the urgency was usually more for convenience (e.g., to improve patient turnover) than to address a truly urgent problem. So, what's wrong with this picture? It is a scenario that is still common in busy academic endoscopy units. Actually, there are several potential problems with this model of same-day ERCP scheduling. Let's look at some specific issues:

1. The endoscopist receiving highly selective, second-hand information about the patient's need for ERCP risks missing "the big picture." Perhaps the trainee left out some small, but important, detail, like the patient's near-fatal anaphylaxis after receiving intravenous contrast medium for a computed tomography (CT) scan in the past, or a history of technically difficult endotracheal intubation following radiation therapy for a throat cancer. In this situation, the endoscopist is literally at the mercy of the trainee regarding the quality of the medical information provided. *The endoscopist should personally see the patient and review the relevant records (including radiology images) before agreeing to proceed with ERCP*.
2. *Consent for ERCP ideally should be obtained well before the procedure, to allow the patient and/or the family, legal guardian, etc. time to process the information and ask questions*. Obtaining consent from an anxious patient 15 min before the procedure may meet the legal requirement, but it is far from ideal that the patient be expected to comply with strangers' expectations to proceed with the ERCP. Indeed, a patient who declines to proceed at this stage would likely be considered a dif-

ficult patient. In a true emergency like acute cholangitis in a confused and hypotensive patient, we do not have the luxury of discussing the pros and cons of the procedure in a calm and relaxed environment. But such emergencies are few and far between. Whenever possible, patients being scheduled for inpatient ERCP should be seen the evening before the test, and those coming as outpatients, 24 h or more ahead of time. Understanding of the procedure and its risks and benefits is greatly aided by pamphlets and other written materials, which are inexpensive and can be purchased in bulk from our professional societies. It is important for all of us, but especially trainees, to understand that a hurried consent may be considered worthless in a court of law at a later date, should the patient suffer an adverse outcome and litigation follow. It has often been said, and it bears repeating, that *a well-executed informed consent is the physician's best defense in a court of law when disputes arise regarding the appropriateness of a procedure and the risk of a complication*. In many states in the United States, there is no legal requirement for informed consent to be in writing, but as lawyers like to say, "if it's not in writing, it wasn't done." As medicolegal cases may take several years to reach trial, neither the patient nor the physician will remember specifics of the consent discussion. Therefore, all informed consent should be documented in writing, and ideally witnessed by an independent observer. Obtaining informed consent should not be delegated to nurses or other physician extenders. *It is the responsibility of the physician doing the procedure to obtain the consent*. Particular care must be taken when obtaining consent for ERCP to identify the indication, explain the alternatives, and list the common complications. These would include post-ERCP pancreatitis, infection, bleeding, and perforation. Anesthetic risks are usually addressed in separate consent forms now that the majority of cases are being done using monitored anesthesia care (MAC) or general anesthesia. However, if ERCP is being performed under moderate sedation with intravenous conscious sedation, the endoscopist should include the risks of the agents used as part of the informed consent for the whole procedure. Emergency exceptions exist to allow urgent procedures to proceed without the consent of the patient or relatives (typically, two physicians must agree that the procedure is necessary to save a life), but these circumstances are rare. *If a next-of-kin or designated power-of-attorney cannot be identified at short notice, the procedure should be delayed, if it is safe to do so, until a suitable signatory is identified*.

3. Rushing to do a procedure usually means that pre-anesthetic evaluation has to be abbreviated. One of the great advances in ERCP in the last decade has been the recognition that it is safer and more comfortable for the patient to have the procedure done under MAC sedation or general anesthesia, typically with an anesthesia provider present. Pre-anesthetic evaluation allows reversible problems, ranging from bronchospasm in chronic obstructive airways disease and poorly controlled cardiac dysrhythmias to previously unrecognized conditions, such as sleep apnea, heart failure, carotid stenosis, and hyperglycemia, to be investigated and treated before a procedure requiring sedation. The pre-anesthetic assessment should include an estimate of the patient's risk as determined by the American Society of Anesthesiologists (ASA) classification (grade I-IV).
4. Pre-procedure fasting may result in the patient being significantly dehydrated by the time they arrive for ERCP. *In many endoscopy units, ERCP patients routinely receive 500–1000 cc of intravenous fluid (provided they are not at increased risk from fluid overload) as a pre-procedure maneuver to compensate for this*. There may not be time to do this if the preparation period is curtailed.
5. *The patient's pre-procedure evaluation should include review of the need for intravenous antibiotics as prophylaxis for infection risk (e.g., when instrumenting an obstructed bile duct). The need for steroid prophylaxis for contrast (iodine) allergy is guided by local policies and should be identified at least the day before ERCP for maximal benefit*. Anticoagulation status also needs to be addressed, especially in

this era of aggressive anti-platelet therapy with, for example, clopidogrel bisulfate (Plavix™) and dabigatran etexilate (Pradaxa™). Endoscopic sphincterotomy carries increased risk of bleeding when performed with the patient fully anticoagulated with these agents or warfarin (Coumadin). For an urgent procedure in a patient who is fully anticoagulated, alternative strategies are necessary. For example, a biliary stent can be placed to allow bile to flow past biliary stones into the duodenum, relieving infection and jaundice. In the non-emergency setting, when required anticoagulation must be reversed to allow sphincterotomy or other therapy, the antiplatelet agent can be stopped for 7 days, or warfarin withdrawn 3–5 days before ERCP with or without daily injection of a short-acting agent like enoxaparin sodium (Lovenox™) to allow a period of time during which the patient's coagulation reverts to normal. Aspirin is often substituted for the stronger antiplatelet agents. *The risk of thrombotic events is considered minimal if the anticoagulation is fully reversed for no longer than 24 h*. Over-anticoagulated patients may require administration of fresh frozen plasma to normalize their prothrombin time. Concentrated platelets can be administered to reverse platelet aggregation-inhibiting drugs, such as clopidogrel, but as platelet transfusions are expensive, they should be used sparingly. For detailed recommendations on the management of anticoagulation in patients requiring therapeutic procedures, such as ERCP, readers should consult the recent excellent guidelines promulgated by the American Society for Gastrointestinal Endoscopy (ASGE) and consult with the patient's cardiologist or neurologist [5].

Preparation

Fasting is required to ensure that the patient's stomach is empty of food and liquid before sedation or anesthesia. Prolonged fasting is unpleasant for the patient. *For routine ERCP, a fast of 4–6 h before the procedure is typical. Patients with known or suspected gastroparesis (especially diabetics and chronic narcotic users) may require a longer fast*, and if doubt exists regarding the possibility of retained gastric contents, a nasogastric tube may need to be placed pre-procedure to check. If the procedure is delayed, the patient's hydration should be addressed with intravenous fluid replacement. Mouth discomfort from dryness may benefit from sucking on a moist sponge on a stick, and some anesthesia providers will allow the patient to chew ice chips to avoid a sore throat. The alert endoscopist always assesses for gastric fluid retention as he or she passes the endoscope, and will make aspirating that fluid through the endoscope a priority before proceeding with ERCP. To reduce the risk of intentional or unintentional consumption of liquids and/or solids during the fasting period, you should explain to the patient and family why fasting is necessary.

Positioning Before the patient is placed on the fluoroscopy table for ERCP, the patient's position should be agreed upon and understood by the anesthesia provider, the endoscopist and the nurses and/or technical assistants. Historically, the standard position for ERCP has been face-down (prone), which creates a favorable orientation for X-rays to pass through the patient between the fluoroscopy source and the detector. However, this may be a difficult position for anesthesiologists to maintain a patent airway. *A compromise that works for both the endoscopist and the anesthesia provider is a semi-prone position, with the right chest elevated off the table using a rubber bolster (aka "jelly roll")* (Fig. 4.1). The patient's

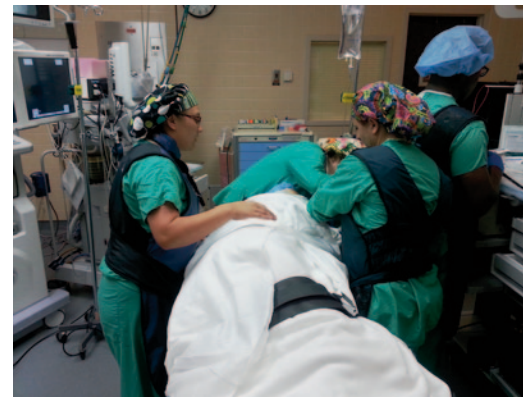

Fig. 4.1 Patient being positioned semi-prone in the operating room for ERCP

arms should be positioned to avoid interference with the endoscopist's access; this often involves taping arms to brackets (padded extensions of the fluoroscopy or operating table).

Other positions that are used for ERCP include left lateral and supine. *Although the left lateral position is preferred for esophagogastroduodenoscopy, it is not ideal for ERCP due to the unusual projection of the radiologic image obtained during fluoroscopy*. The directions taken by the opacified bile and pancreatic ducts are unfamiliar in the left lateral projection; the author confesses to once having placed a stent in the bile duct when he thought it was in the main pancreatic duct. The left lateral position has one particular use that is worth remembering: if a large, J-shaped stomach makes it difficult to access and intubate the pylorus with the duodenoscope, repositioning the patient to the left lateral position will often work. After the tip of the scope is safely in the second part of the duodenum and the control wheels locked to maintain that orientation, the patient should be returned to the previous semi-prone/prone position for a more familiar view of the papillary fold. The supine position is the most difficult position in which to access the descending duodenum for ERCP. The supine position may be requested by the anesthesia provider for a morbidly obese patient because in the event of respiratory depression or a code, it is difficult to roll a very obese patient from prone to supine quickly for resuscitation. With the patient supine, and the endoscopist facing the patient and the endoscopy monitor in the usual fashion, the control section of the duodenoscope is rotated 180° from its normal position, which is an unfamiliar and uncomfortable way to do ERCP for many. However, if the endoscopist rotates 90 degrees to the right (i.e., away from the patient), he or she can hold the duodenoscope in the more familiar and comfortable position. If the patient is undergoing surgery immediately before ERCP, then the supine position is inevitable. However, if ERCP is performed first, the option exists to position the patient as you prefer. This requires the agreement and cooperation of the operating room staff, including the surgeon. In my experience, the best results are obtained when the patient undergoes ERCP in the semi-prone position.

If the patient is having a prolonged procedure under anesthesia, hypothermia may be a problem, especially if the room is cold as many operating rooms are intentionally kept cool. A heating blanket helps prevent this problem. If the patient is under general anesthesia, the endotracheal tube (ET) may be conveniently routed through a side hole in the bite block, which slides over it. For this maneuver, the ET is briefly disconnected from the bag or machine being used to ventilate the patient. The ET should not apply pressure to the lip or the corner of the mouth. Your patient will not thank you for a swollen lip or another sore place in their mouth after ERCP! Care should be taken to ensure the correct positioning of the bite block, so that the teeth are gently holding it in place. The pre-procedure evaluation should have included careful inspection of the teeth, but this should be repeated at the time of placing the bite block. Loose, usually carious, teeth create a risk for aspiration should they be dislodged during instrumentation. *If loose teeth are detected at preprocedure screening in clinic, the patient should be asked to have them removed by a dentist before returning for ERCP*. Unfortunately, patients with poor dentition may be uninsured and unable to pay for dental extractions. A social worker or other patient advocate may help identify indigent dental care locally to address this problem. Complete or partial dentures that are not "cemented" in place should be removed before endoscopy. Finally, many anesthesia providers like the patient's head supported by a foam block.

The electrocautery grounding pad should be applied to an area of skin well away from any metallic implants like a hip prosthesis or pacemaker and connected to the electrosurgical unit in preparation for use during the procedure. It is recommended that the active cord (often a red or black cord linking the electrosurgical unit to the accessory) not be connected until the endoscopist is ready to use the device. This reduces the risk of unintended activation of electrocautery by, for example, the endoscopist stepping on a foot pedal that he or she thinks controls fluoroscopy rather than electrocautery.

Until 1990, when the author and colleagues from Duke University published the first small case series of pregnant women undergoing ERCP [6, 7], this procedure was considered too risky to attempt (Chap. 19). There was concern that complications of ERCP, especially pancreatitis, could put the lives of both the mother and fetus at risk. In the last 25 years, *it has been demonstrated repeatedly that if the patients are chosen carefully, for appropriate indications, ERCP in pregnancy is safe and effective*. Appropriate precautions must be taken to screen the fetus from X-rays used for fluoroscopy. This is achieved by shielding the mother's abdomen with a lead apron, which needs to be pulled up at least to the level of the top of the uterine fundus. Minimal fluoroscopy is used to confirm positioning of the catheter in the bile duct, and taking pictures is avoided as this will add to radiation exposure. A radiation dosimeter can be placed over the uterus under the lead apron to measure fetal exposure during ERCP; this should be minimal. Pregnant women in the second and third trimesters should NOT be placed in the supine position for ERCP. Lying on the gravid uterus may compress the inferior vena cava, reducing venous return to the heart, and result in supine hypotension syndrome that causes syncope and sometimes seizures (Fig. 4.2) [8]. It is best to perform ERCP with the mother in the left lateral position during the second and third trimesters, which is not ideal for imaging but a necessary compromise for safety and comfort.

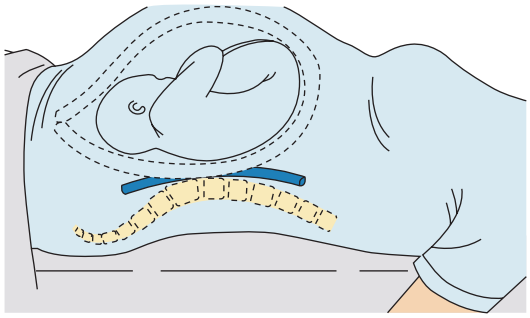

Fig. 4.2 Inferior vena cave (*IVC*) compression by third trimester gravid uterus in supine position (*schematic*)

Equipment All the equipment required for the procedure should be available at the beginning. It is inefficient, time-consuming and frustrating for all concerned when your assistants must leave the room to find missing accessories. Time-outs are invaluable, but planning for ERCP has to start well before the endoscope is passed. *You should meet with your ERCP room staff at the beginning of a list of procedures to discuss the cases and identify specific needs you anticipate*, such as having a mechanical lithotripter or a metal stent available. Where I currently work, we have a mobile cart for endoscopic accessories that is easily moved from room to room. Your cannula of choice should be removed from its package and prepared for use by flushing with contrast medium that has already been drawn up. In addition to having an automated water jet (activated by a foot pedal) connected to the duodenoscope, I like to have a 60 cc syringe with a metallic tip that fits snugly in the instrument channel for applying high pressure lavage. The ERCP nurse or technician should ensure that the duodenoscope is fully functional before handing it to you. If necessary, they should use a check list to ensure that a suction source is attached and operating, air and water are available for insufflation and lens cleaning, the light source has been switched on, and the elevator is functional. It is also important that electrocautery connections are checked before the start to avoid delays when sphincterotomy is needed. Accessories that *may* be used, but not definitely, should be nearby in their packaging. As most ERCP accessories including catheters, wires, baskets, stents are expensive and single-use, opening but not using them is a waste of money. Some devices are reusable, but must be re-sterilized first. Ensure that equipment you use is replaced. Many endoscopic accessories are expensive enough that they are often bought one at a time to avoid large inventories. The use of an expandable metal stent (or a nasobiliary drain or a needle knife papillotome, etc.) should trigger a same-day order preferably by overnight or 2-day express delivery for replacement. Most accessory manufacturers are happy to set up a reordering mechanism to accommodate these requests. It

is helpful to review the ERCP accessory inventory regularly with your endoscopy staff. *Most endoscopists have a relatively small number of accessories that they use on a regular basis*. Although it is necessary to have a range of stent lengths and calibers to address different uses and types of strictures, maintaining a large inventory is wasteful and expensive. When devices reach their sell-by date, they can no longer be used for patient procedures or be returned for credit. It is common practice now in larger endoscopy units for new devices and accessories to undergo committee review before they are approved for purchase. A new device that is significantly more expensive than the existing one must demonstrate some additional benefit in terms of safety and/or efficacy to justify the added expenditure. Many endoscopists find such restrictions irksome, as they like to have the latest and greatest equipment available. However, the fiscal reality is that ERCP frequently loses money for institutions, making financially responsible choices imperative when it comes to purchasing equipment.

Special tools for ERCP, such as choledochoscopes, intraductal ultrasound probes, and biliary manometry systems, are expensive items. It is difficult to justify their purchase if they will only be used a few times each year. In the community, who has the latest ERCP technology appears more important than the skill level of the operator when it comes to directing referrals. Tertiary centers with deep pockets (a rarity these days) may have the volume of challenging cases to justify these purchases, especially if their use generates additional revenue.

The middle of a complex procedure is not the time for assistants to learn how to deploy a new (unfamiliar) stent, or assemble a lithotripsy device for the first time. If an experienced assistant cannot be available, it is wise to request an in-service from the equipment company representative *ahead of time*. Unfortunately, in my experience one in-service may be inadequate as it may take your assistants repeated use of a new device to become familiar and comfortable using it. *It is very important to develop a cadre of experienced assistants for ERCP work*. If you have to perform ERCPs in a surgical operating room with duty surgical technicians assisting, at certain times of day and especially during weekends, no one with ERCP experience may be on duty. In that event, it may be better to transfer a sick patient requiring urgent ERCP to a referral center which is suitably staffed rather than attempt a difficult procedure without experienced support staff.

An important piece of equipment for all endoscopy units is an electronic reporting system to generate endoscopy reports. A number of these are available for purchase, several through major endoscope suppliers. Electronic record keeping is here to stay, especially with the introduction of the Affordable Care Act. However, many small endoscopy units still rely on physician dictations and printouts of endoscopic images. This is not a sustainable mechanism for producing medical records. Not only is it difficult to search these records, but prospective or retrospective review of large numbers for quality assurance becomes a daunting task. *Carbon dioxide (CO2) used for insufflation during endoscopy reduces gaseous distension of the bowel from prolonged procedures and hastens recovery* [7]. It is common for patients who have undergone long ERCP procedures to have significant gaseous distention of the bowel, resulting in post-procedure pain and delayed recovery. This pain may masquerade as PEP in evolution. Substituting CO2 for air for insufflation effectively addresses this problem, as unlike air CO2 rapidly diffuses across the bowel wall into the circulation for rapid excretion by the lungs. For a relatively small investment in a CO2 tank connected to the air pump, post-procedure recovery times after endoscopy can be significantly shortened. Early concerns that CO2 insufflation of this type might lead to problems with hypercapnia have proved groundless. When ERCP is performed in the operating room immediately before laparoscopic cholecystectomy for suspicion of a retained bile duct stone, gaseous distension of the small bowel can create problems for the surgeon. CO2 insufflation prevents this problem.

Execution: The Procedure

Passing the Duodenoscope

Modern duodenoscopes are sophisticated devices that have undergone considerable evolution since ERCP was first introduced in the late 1960s. The current duodenoscopes are much more flexible with a smaller external diameter but a larger caliber instrument channel than their predecessors. The "quantum leap" in endoscopic imaging arrived with the change from fiberoptics to electronic [charge coupled device (CCD)] technology [8]. The only part of a modern endoscope that employs fiberoptics is the light guide used for illumination. It may be a cliché, but it is not an exaggeration to say that the original duodenoscopes were primitive and crude compared to the precision tools of today (in terms of automotive development, Model T Fords compared to Rolls Royces!) Part of the unavoidably long learning curve required for ERCP involves gaining familiarity and comfort handling duodenoscopes, which are decidedly differently from all other endoscopes. Detailed descriptions of the modern duodenoscope are available elsewhere [9]. What matters most when passing the duodenoscope into the duodenum is an understanding of the various axes of motion of the scope, and how they are used to obtain the best position for cannulating. The axes of motion are push-pull, twist (torque on the shaft) right and left, and tip deflection (up/down and right/left, controlled by the dials on the control head). In addition, the "angle of attack" of the catheters and other accessories passed through the instrument channel can be varied using the elevator, a small moveable ramp at the bottom of the instrument channel controlled by a lever on the control head. Positioning the duodenoscope tip in front of the papillary fold on the medial wall of the second part of the duodenum is achieved by advancing it through the hypopharynx into the esophagus, through the stomach, exiting out of the pylorus and passing into second/third part of the duodenum. At this point the duodenoscope is in the long position, which is unfavorable for cannulation. To achieve correct orientation, the right–left control wheel is locked in the full-right position and the scope gently pulled back to remove the gastric loop. When done correctly, the major duodenal papilla almost always pops into view directly ahead with this shortening maneuver. Small adjustments are usually necessary to fine tune the position, and a motility-control agent, such as glucagon, may have to be administered to inhibit peristalsis.

Passing the duodenoscope through the patient's mouth into the hypopharynx and then through the upper esophageal sphincter (UES) into the esophagus merits further review. *The tip of the duodenoscope is rounded, so it can be passed "blind" with modest pressure*. Experienced ERCP endoscopists can interpret the side-viewing images during intubation, but they usually confuse beginners, who are determined to see where the duodenoscope is going. I tell my trainees not to overthink the process. *Provided that the lubricated duodenoscope tip is passed over the back of the tongue and maintains a posterior track, it will almost always pass smoothly through the UES into the esophagus*. Some endoscopists teach their trainees to lock the tip controls for intubation to maintain curvature on the end of the duodenoscope, but I consider this a potential risk for injury and discourage it. Modest—but not major—forward pressure on the duodenoscope shaft is needed to advance the instrument. If resistance is encountered, it is always best to pull back and try again rather than risk traumatizing the fragile hypopharynx. Neck positioning may influence the ease or difficulty of scope passage, and occasionally cervical spine bone spurs may provide resistance. *If a few gentle attempts to pass the duodenoscope fail, I recommend passing a standard gastroscope to assess the local anatomy*. If no obvious cause for failing to pass the duodenoscope is identified, you can try to advance it over a guidewire. A long 0.035-in. guidewire can be placed into the stomach using the gastroscope, which is then removed while maintaining the wire position. The wire is captured into a cannula advanced down the instrument channel of the duodenoscope, and finally the duodenoscope is advanced over the wire into the esophagus. I have used this technique successfully a number of times. Another option is to pass the duodeno-

scope using the blade of a laryngoscope for visualization and guidance. Anesthesia providers are happy to assist you with a laryngoscope. *Patients who have had prior head and neck surgery for cancer (and often radiation therapy) require particular care, as they often have altered anatomy that makes passing adult caliber duodenoscopes difficult or impossible*. Unsuspected esophageal webs, rings, and strictures can all interfere with duodenoscope passage, as well as the possibility of a Zenker's diverticulum catching the duodenoscope tip.

Negotiating the pylorus is often an adventure too! In patients with a large, J-shaped stomach, it is usual to run out of duodenoscope before reaching and traversing the pylorus due to the formation of a large loop in the stomach. The way to manage this is first to remove as much air as possible (consistent with maintaining an adequate view) in order to collapse the stomach. If this does not allow the duodenoscope tip to access the pylorus, move the patient from semi-prone into the left lateral position (warning: this may make you unpopular in the operating room, where the patients are usually taped or strapped tightly in position, but it is necessary!). In most cases, this maneuver allows you to intubate the duodenum through the pylorus. The patient can then be repositioned semi-prone and the shortening maneuver undertaken to visualize the major papilla.

Accessing the major duodenal papilla is rendered difficult by benign or malignant stenoses of the gastric outlet or duodenal sweep, as may occur in cancers of the duodenum and head of the pancreas (Fig. 4.3). Dilation of strictures with or without subsequent metal stenting may be necessary to access the papilla. EUS-guided biliary access techniques may be used to overcome stenoses involving the vicinity of the major duodenal papilla: for example, a dilated bile duct may be accessed through the duodenal bulb by EUS-guided needle puncture and subsequent guidewire placement (Fig. 4.4a, b, c, d and Chap. 34) [10]. However, this remains an experimental technique for experts only at present, due to the risk of retroperitoneal leaks and perforations [11]. It is anticipated that EUS-guided biliary access will become more widely available when

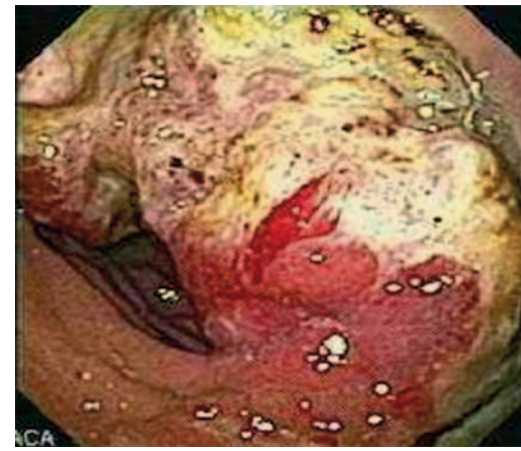

Fig. 4.3 Malignant stenosis at junction of 1st and 2nd part of duodenum preventing access to duodenal papilla for ERCP

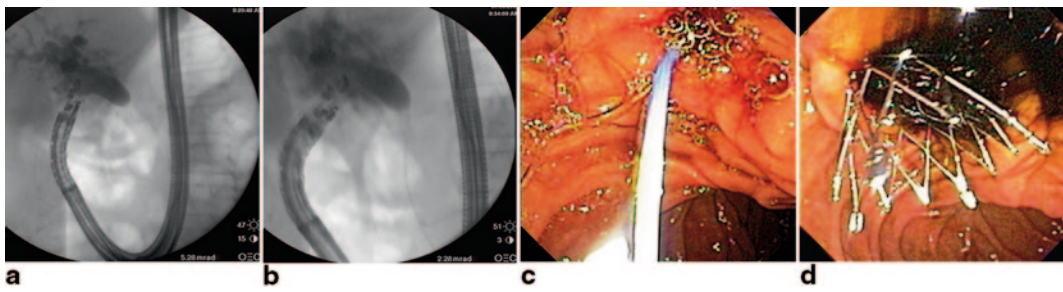

Fig. 4.4 Endoscopic ultrasound (*EUS*) access for difficult biliary cannulation. **a** After needle puncture through the posterior duodenal bulb, a contrast cholangiogram is obtained. **b** Using the same needle, a 0.025-in.-diameter guidewire is passed down the bile duct and into the duodenum. **c** Endoscopic view of the papillary area showing the guidewire exiting. **d** Using the guidewire, which is grasped with a basket and pulled up the instrument channel of the EUS scope, an expandable metal mesh biliary stent was placed in the standard fashion

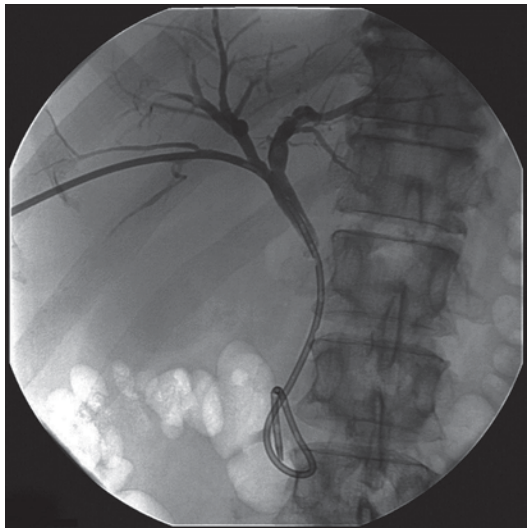

Fig. 4.5 External-internal biliary drain placed as prelude to a combined radiologic-endoscopic ("*rendezvous*") procedure

suitable tools have been developed to minimize these risks. Combined radiologic-endoscopic procedures ("rendezvous") were used to deal with difficult cannulation situations 20 years ago, but have gone out of fashion due to the increased morbidity associated with them (Fig. 4.5) [12]. Endoscopists try very hard to avoid subjecting their patients to percutaneous biliary procedures, because of the inevitable inconvenience and discomfort associated with them. Unfortunately, these combined procedures were frequently used as an alternative to skill at biliary cannulation, to the patients' detriment.

Altered surgical anatomy, including Billroth II (BII) partial gastrectomy and Roux-en-Y diversions, creates other difficulties (Chap. 17). Provided that the afferent limb of the BII anatomy is relatively short, most experienced ERCP endoscopists have little difficulty finding it. This requires a special technique for retrograde (compared to the usual route) access to the papilla up the blind-ending afferent limb. The major duodenal papilla is upside down from the perspective of the endoscopist, which requires modification of cannulation technique. If the tip of the duodenoscope cannot be torqued into a position in which a papillotome, which has a gently curved tip, can be advanced into the duct of choice, a straight catheter may work better. The need to access a surgical Roux limb of small bowel has increased considerably recently with the introduction of bariatric surgery. The most common type of Roux diversion currently in vogue creates considerable difficulty for ERCP, as the Roux limb is usually too long for a standard duodenoscope. Even when the papilla is reached using a colonscope or enteroscope and special long accessories, it can be technically very difficult to perform the standard therapeutic ERCP maneuvers using an endoscope without an elevator. An alternative approach involves shortening the distance needed for duodenoscope insertion by bypassing the esophagus. This can be accomplished by creating a gastrostomy track with percutaneous endoscopic gastrostomy (PEG) [13] or using a laparoscopic trochar. The disadvantage of the PEG technique is that 6 weeks are required to allow the gastrostomy track to mature, so this approach does not help when the patient needs urgent ERCP. A more elegant approach is to combine laparoscopic access to the gastric remnant with ERCP performed through the laparoscopy trochar [14]. Following laparoscopic puncture of the gastric remnant by the surgeon, the cannula of the trochar is removed and replaced with the duodenoscope, which is just small enough in caliber to pass through it. The papilla can be reached through the pylorus after which ERCP is performed in the standard fashion. I have performed this procedure on numerous occasions and found it a nice solution to a difficult problem in patients with post-bariatric surgery anatomy needing urgent ERCP.

So I'm at the Papilla: Which Tool for the Job?

There is a dizzying array of catheters, guidewires, and guidewire retention devices available to the ERCP endoscopist. Detailed description and comparison of individual devices is beyond the scope of this chapter. Interested readers should consult the excellent ASGE Technology Committee reviews on ERCP cannulation and sphinc-

terotomy devices [15] and Short-Wire ERCP Systems [16]. Short guidewire-based systems were introduced to address perceived and actual limitations of long wires for ERCP procedures. The most widely used devices used in the US are FUSION™ (Cook Medical, Bloomington, IN), the V-System™ (Olympus Corporation, Tokyo, Japan), and the Rx System™ (Boston Scientific, Marlborough, MA). All short-wire systems have three elements in common: a mechanism to lock the guidewire in position during accessory exchanges, the short guidewire itself (decreasing standard wire length by as much as 270 cm) and some open or closed "tear-away" mechanism on compatible accessories. One of the many benefits of short-wire systems touted by the manufacturers is improved physician-controlled guidewire cannulation of the desired duct at ERCP. However, doubt has recently been cast on the supposed reduction in risk of PEP when guidewires are used for cannulation rather than contrast injection. Are endoscopists who cling to long-wire techniques, which require skilled nursing or technician assistance, ERCP dinosaurs? I certainly understand the reluctance of those who have honed their skills over many years using long-wire systems to make changes just for the sake of change. Skilled ERCP assistants contribute significantly to the success of complex procedures, and without exception they take great pride in doing so. But the reality is that increasingly endoscopists find themselves working with shared support staff who lack experience with catheter exchanges and other important ERCP skills. For endoscopists who do not have the luxury of experienced assistants for their procedures (e.g., community gastroenterologists doing ERCP in the operating rooms of small hospitals), short-wire technology confers undoubted benefits. Training programs should provide their ERCP fellows experience with short-wire systems that they will likely encounter in community practice. Equipment representatives are always pleased to provide bench-top demonstrations of these and other devices for potential future customers. Although short-wire ERCP systems have been touted as reducing procedure times, fluoroscopy exposure, physician fatigue, and cost, these outcomes have not been consistently confirmed in clinical studies.

The duodenal papillae are delicate structures and must be treated with care and respect. Ill-considered poking and other amateurish attempts to cannulate the papilla often fail, and may be complicated by acute pancreatitis, the most feared complication of ERCP. It is my personal preference to use a papillotome with a tapered tip to cannulate both the main and accessory duodenal papillae. However, *a straight metal-tipped needle cannula (ERCP-1-Cramer™, Cook Endoscopy, Bloomington, IN) may be the most effective tool to access the minor papilla when rendered necessary by a challenging duodenoscope position (Video 4.1). When using a straight catheter to cannulate the bile duct, a rounded (ball) tip is preferable, as this is less traumatic to the papilla*. Straight catheters are also useful with aberrant or post-surgical anatomy, such as the "upside-down" papilla found in Billroth II gastrectomy.

Papillotomes come in many varieties with different length cutting wire, number of lumens, tip length (distance from tip of papillotome to distal attachment of the cutting wire); some having a rotatable tip, and some having a protective coating on the proximal end of the cutting wire. Some commercially available papillotomes now come pre-loaded with a guidewire in the 0.021–0.035 -in.-diameter range. However, all papillotomes allow sphincterotomy to be performed via electrical current through the cutting wire and flexing the cutting wire enables manipulation of the tip direction to facilitate cannulation.

Cannulas also come in different varieties with different diameter of the tip, tip configuration, and number of lumens (single, double, and triple). Specialty cannulas include the swing tip cannula with a wire running the entire length of the cannula and connected to the control handle, thereby allowing tip deflection; ultra tapered tip cannulas accepting only 0.018 or 0.025 in. wires; and the blunt metal-tipped needle cannula specifically used for minor papilla cannulation. This latter cannula only allows contrast injection.

Guidewire-assisted cannulation increases the success rate, and positioning the wire deep in the biliary tree ensures that cannulation is

not lost if the catheter slips out. Many different guidewires are available that vary in diameter (0.018–0.038 in.), length (260–600 cm), tip design (straight, angled, J-shaped, or tapered), inner core material (stainless steel or nitinol), and outer coating (Teflon, PTFE, polyurethane, hydrophilic coating). The electrically neutral coating, which is often colored for ease of identification, is required when performing electrocautery. Barbershop striped pole design of the coating makes it obvious when the wire is in motion: if the stripes are not moving, the wire is locked in position. Many guidewires have a radiopaque tip to enhance visualization during fluoroscopy. A torque device, which is clamped onto the wire outside the duodenoscope, can be used with angled wires to change the direction of the tip. Several wires only have hydrophilic coating at the tip. Hydrophilic wires can be difficult to use because they must be kept continuously moist to avoid drying and sticking which prevents exchanges from occurring; however, some prefer the "feel" of these wire when cannulating.

Large-caliber guidewires (e.g., 0.035-in. diameter) tend to be stiff. While this is an advantage when placing large stents and negotiating some strictures, it is a distinct disadvantage when trying to advance the wire around bends. On the other hand, the thinnest commercially available guidewire, 0.018 in. in diameter, is very floppy and is easily displaced from catheters and ducts. The tip is sharp and can cause trauma, especially when used in the pancreatic ducts. Great care should be taken to avoid side-branch trauma (often at the genu of the main PD) from the guidewire tip during stenting for post-ERCP pancreatitis prophylaxis. The smallest stents used for this purpose are 3 French (Fr) gauge (just under 1 mm internal diameter) and require the 0.018-in. wire. Side-branch perforation results in leakage of corrosive pancreatic juice and almost guarantees that the patient will develop post-procedure pancreatitis! ERCP endoscopists should become familiar and comfortable with a few different guidewires that address their needs.

Cannulate like a Pro(fessional)

Setting the scene for an expert cannulation starts with good sedation and appropriate patient positioning on the fluoroscopy table. Comfort with passing the duodenoscope and positioning it in front of the main duodenal papilla is next. With experience, the landscape of the medial wall of the duodenum becomes very familiar. Subtle—often subliminal—clues make it increasingly easy with experience to recognize the papillary fold, and the biliary and pancreatic orifices. This applies to the minor duodenal papilla as well, which can be highlighted with supravital staining (Video 4.1) or caused to swell and exude fluid by intravenous secretin injection [17]. The optimal position for biliary cannulation is a little below the major papilla which allows the catheter to curve up in the direction of the bile duct, whereas the PD is more easily cannulated (especially with a papillotome) from at or slightly above so that the cannula tip ends up meeting the orifice "head on" as the pancreatic duct usually courses straight in. When positioned en face before the papilla, the bile duct lies in the left upper corner of the papilla and courses to the left and up along the direction of the intraduodenal portion of the bile duct. Mentally, the projected path of the bile duct should be traced from the papilla along the intraduodenal segment, and subsequent cannulation efforts should focus on aligning the catheters and wires along this line. The pancreatic duct, on the other hand, lies between 1–5 o'clock on the papilla and runs to the right in a more straight direction.

Taking the time to inspect and position in front of the main duodenal papilla prior to instrumentation pays dividends. The rush to cannulate as quickly as possible should be resisted. Poking blindly at the papilla is unlikely to result in successful cannulation, and risks causing bleeding and PEP. Catheters with sharp, pointed tips are more likely to cause trauma and should generally be avoided. Rounded (ball) tip catheters are less traumatic. If the orifice of the bile or pancreatic duct is not apparent, gentle probing with a blunt catheter tip can expose it. Blind injection of contrast into the papilla in the hope of opacifying a

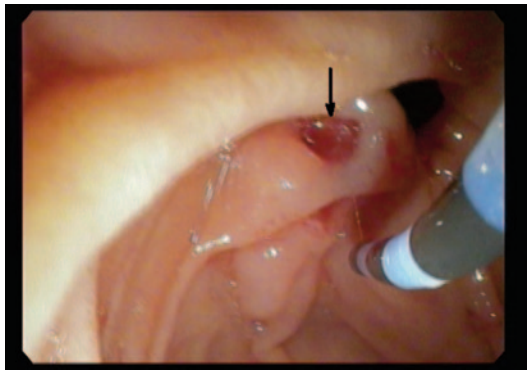

Fig. 4.6 Suprapapillary fistula: small opening (*arrow*) above main duodenal papilla

duct should be avoided, because an unintended submucosal injection will render subsequent deep cannulation more difficult, or impossible, and increase the likelihood of PEP. Biliary cannulation is made easier by finding a suprapapillary fistula (Fig. 4.6), which may result from spontaneous stone passage or (more often) dilator trauma during common bile duct exploration at the time of laparoscopic cholecystectomy. Prior biliary and/or pancreatic sphincterotomy also makes cannulation easier, which is why the guidelines of several national societies require ERCP on native papillae only for credentialing purposes. Following sphincterotomy, the biliary orifice is located superiorly while the pancreatic orifice is usually inferior and to the right.

The only type of cannulation that counts is deep cannulation with the placement of the catheter and often subsequently a guidewire deep in the desired duct, usually with the intention of performing a therapeutic intervention. Typically cannulating close or moderately close to the papilla is recommended. If too close though and using a sphincerotome, the cutting wire cannot be advanced far enough out from the accessory channel for bowing to occur. If too far away, the mechanical advantage of the accessories will be diminished. Deep cannulation is assisted by gentle probing of the orifice of the desired duct using the tip of a guidewire. Every endoscopist seems to have his or her own trick for doing this, such as using an angled wire, or one of the thinner caliber varieties. As indicated elsewhere, jabs with the wire tip ("poking") should be avoided because these are traumatic. Instead, gentle probing and pressure with a centimeter or two of wire protruding from the catheter tip are more likely to achieve the desired outcome. Once the wire and/or catheter tip are superficially seated, deeper biliary cannulation can be achieved by remembering that the bile duct curves in a more upward direction. This may be facilitated by turning the large knob towards you, pulling the scope out a little, and/or partially relaxing the sphincterotome. Fluoroscopy may help with angling the catheter in the projected direction of the desired duct.

If biliary cannulation is desired, but the PD is repeatedly entered, consider using the guidewire already there to place a small caliber (e.g., 5 Fr) plastic stent in the PD, over which biliary cannulation can be attempted. The orientation of the stent may help determine the direction of the bile duct, and the stent may occlude the opening to the PD to prevent ongoing unintentional pancreatic cannulation. Alternatively, two wires can be passed through the instrument channel, one left in the PD and the other maneuvered into the common bile duct over it. Cannulation over a wire or a stent placed for this purpose is frequently successful when the standard technique fails (Video 4.2). I favor stent placement because it adds a layer of protection against PEP, especially in high-risk settings including needle knife papillotomy, snare papillectomy, and biliary manometry for possible sphincter of Oddi dysfunction. As already stated, basic pancreatic endotherapy, such as PD stent placement, is part of the skill set necessary for the modern practice of ERCP. Needle knife papillotomy is another technique for gaining access to the bile duct, which will be discussed further in the next section.

Sphincterotomy/Papillotomy

Access to the biliary tree and pancreatic ductal systems is facilitated by sphincterotomy, a basic therapeutic skill for all ERCP endoscopists. Strictly speaking, incision of a true sphincter is sphincterotomy, whereas incision of the pa-

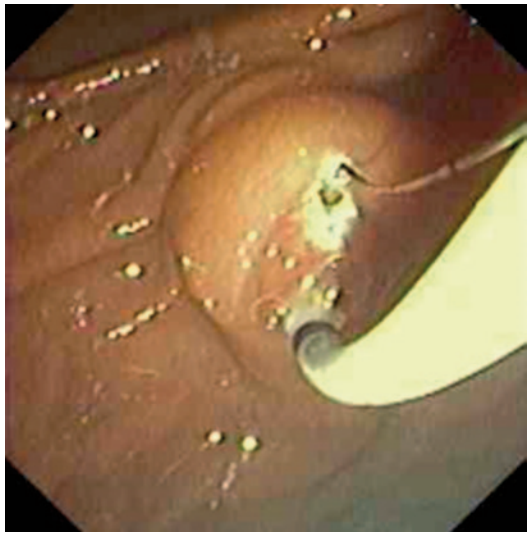

Fig. 4.7 Pull papillotome or sphincterotome

pilla (major or minor) is papillotomy. The terms sphincterotome and papillotome tend to be used interchangeably. The commonest type of sphincterotome is the so-called pull variety (sometimes also referred to as an Erlangen catheter, for its city of origin in Germany) (Fig. 4.7). There are long- and short-wire pull sphincterotomes; however, 20 mm is generally the preferred length. The longer wire will allow greater flexion, but needs to be advanced further out of the scope channel. It is important to realize that only a small length of wire is needed to perform sphincterotomy (Video 4.3). The current density at the point of contact is inversely related to the length and area of wire in contact with tissue. A common mistake is to have too much wire inside the duct when starting biliary or pancreatic sphincterotomy. When not much appears to be happening, turning up the power is a mistake. This may still not result in effective cutting. If the wire is intentionally or accidentally pulled back at this point, there will be an exponential increase in current density during power application, often resulting in a large, very rapid cut (a so-called "zipper cut"). This is dangerous because it risks both perforation and bleeding. *Pick one setting for your sphincterotomies and do not change this*. Biliary sphincterotomy should occur in the 11–1 o'clock direction which may be difficult to achieve as the cutting wire often naturally orients towards 3 o'clock. Turning the small knob all the way towards you in addition to applying counterclockwise torque and pushing the duodenoscope into a slightly long position may help achieve the correct direction.

Modern electrosurgical generators provide options for delivering pure cutting current, pure coagulating current, and a variety of blended waveforms that combine cutting and coagulation. Which type of electrocoagulation should be used for sphincterotomy? Despite over 40 years of experience, the ERCP community has still not reached a consensus on the optimal approach. Pure cutting current, a sawtooth waveform, creates a rapid cut with minimal coagulation. The theoretical advantage is less risk of acute pancreatitis from sphincterotomy, but at the cost of an increased risk of bleeding. A pure coagulating current (a sinusoidal waveform) causes a "slow cook" with blanching of the tissue. While this is desirable when removing a pedunculated polyp in the colon before complete transection with a snare, "cooking" the duodenal papilla runs the risk of provoking acute pancreatitis. Blended currents provide a middle-of-the-road alternative to these two extremes and are popular for this reason. Certain electrosurgical generators are designed to provide regular pulses of current that take the guesswork out of sphincterotomy; in particular, they prevent the occurrence of an overly rapid cut with pure cutting current, the rightly feared "zipper" effect. For the record, I like to use pure cutting current alone for small (access) sphincterotomies, and a combination of pure cutting followed by blended current for larger ones. The use of blended current some distance from the ampulla of Vater keeps heat away from the pancreas, and in my experience appears to reduce the risk of pancreatitis.

Regarding standard biliary sphincterotomy, how far should one cut? It is notoriously difficult to accurately measure the length of a sphincterotomy cut using the naked eye. The size of the incision must bear some relation to the size of the duct: a 15-mm incision that is safe when the bile duct measures 20 mm in diameter may risk perforation when applied to a 5-mm-diameter bile

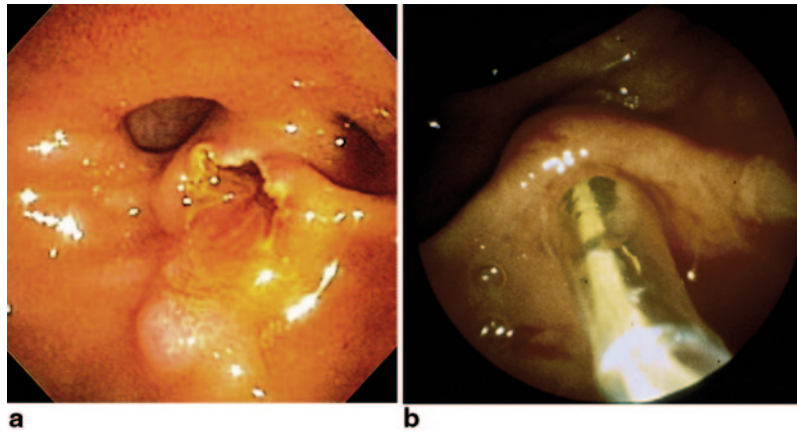

Fig. 4.8 **a** It is safer to perform a small sphincterotomy first (*shown here*) before extending the opening with gentle balloon dilation. **b** Balloon sphincteroplasty for biliary access to retrieve stones

duct. A 15-mm incision is generally considered the upper limit for safe biliary sphincterotomy. For removing stones, you want the opening to be as big as—or bigger than—the diameter of the largest stone, unless you plan to perform lithotripsy to fragment the stones before pulling them out. A small sphincterotomy may suffice before stent insertion.

If you have to choose just one accessory for your ERCP, a pull papillotome is probably the most cost-effective. Get comfortable with one or two types and stick with them. *Do not change power settings during sphincterotomy: the need to do this usually reflects poor technique rather than a problem with power transmission*. Adjusting the length of wire within the papilla to increase current density is more effective. *Never cut a sphincter in a hurry. Small, incremental cuts allow more control than a single rapid cut*, which risks perforation and bleeding. Do not perform sphincterotomy in a fully anticoagulated patient. Take particular care in patients on platelet aggregation inhibitors like dabigatran etexilate (Pradaxa™) and clopidogrel (Plavix™). I have seen more significant post-sphincterotomy bleeding in patients on these agents than in those fully anticoagulated with warfarin.

Other techniques may achieve biliary sphincterotomy. *Needle knife papillotomy is a useful tool in experienced hands*. Formerly, it was reserved for failed cannulation, but increasingly it is employed as a quick way to access the duct of choice if cannulation difficulty is anticipated [20]. The needle knife is a bare wire exiting from a plastic sleeve through which electrocautery is applied to tissue (Fig. 4.10). NKP is considered a relatively uncontrolled cutting procedure due to the catheter not being seated within a duct before the cut. The current density at the tip of the needle knife is huge due to the small area in contact with tissue, so light strokes are used and never pressure to make a cut. Indeed, the optimal technique for NKP has been compared to strokes with a paint brush on a canvas. NKP should be taught under supervision and not self-taught, as has been the tradition in the past. Recognizing what the bile duct wall looks like when it is exposed by incising the overlying mucosa is a skill rarely taught, but actually the key to your success (Fig. 4.11). Have a skilled mentor show you the relevant structures during some NKPs.

Before beginning NKP, as with cannulation, the direction of the bile duct should be visualized and even traced with the needle knife before initiating the cut. One approach with NKP is to insert the needle knife into the papillary orifice and cut in the 11 o'clock direction with superficial cuts repeated in the same direction until the biliary orifice is exposed which appears whitish. If oozing occurs, epinephrine can be sprayed to the area as maintaining visualization is important.

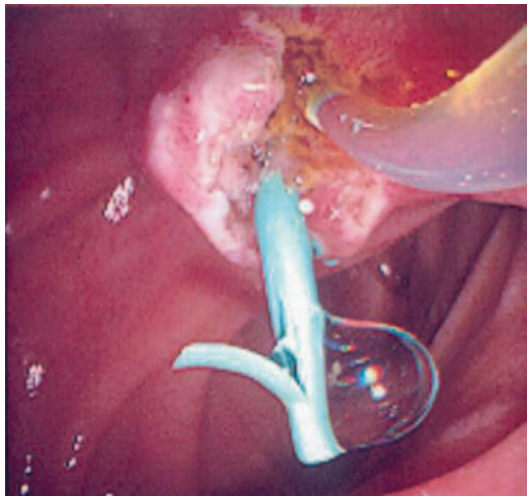

Fig. 4.9 Needle knife papillotomy (*NKP*): cutting down on to a plastic stent

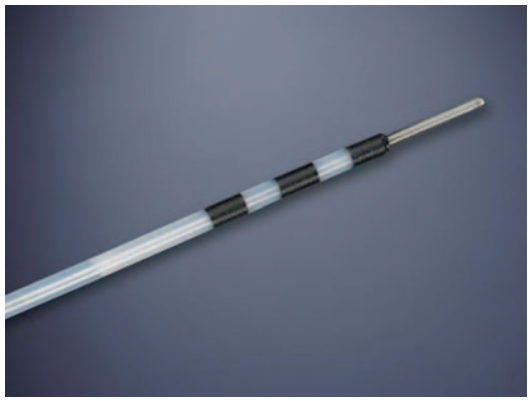

Fig. 4.10 One model of needle knife papillotome

NKP down on to a biliary or pancreatic duct stent can be used to perform biliary sphincterotomy. This is a quick and relatively safe way to perform NKP when there is already a stent in place (e.g., if a patient had a stent placed to manage bile duct stones that could not be removed during the initial procedure, perhaps due to unreversed coagulopathy). The plastic stent protects the pancreas beneath from unintentional burns or incisions (Fig. 4.9). After papillotomy, the biliary stent is removed and stone retrieval conducted in the usual fashion. A pancreatic stent may be left in place as prophylaxis against PEP.

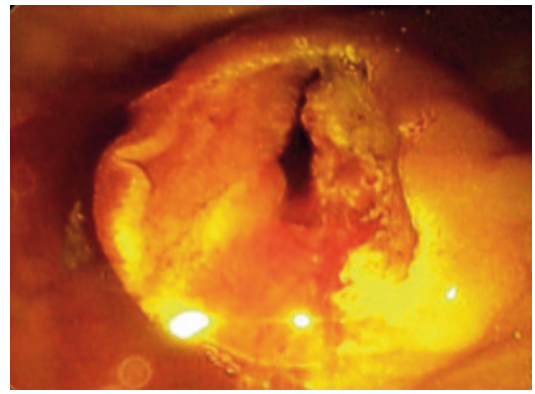

Fig. 4.11 Recognizing the bile duct when it is revealed by NKP

Fistulotomy is the creation of an opening into a duct, usually the bile duct and preferably a dilated one, above the papillary orifice (Fig. 4.12a, b). A fluctuant ("pillowy") duodenal papillary fold is a tempting target for fistulotomy if standard sphincterotomy fails. Provided it is performed sufficiently cephalad to the papillary opening, the risk of PEP is low. *If you are performing fistulotomy, you should be nowhere near the sphincter muscle*. Prior imaging with CT, MRI, and/or EUS to confirm the presence of a dilated bile duct increases the endoscopist's confidence that this is a suitable environment for needle knife fistulotomy. Once the opening is created (usually heralded by a sudden burst of bile flow), it may be extended cephalad using the needle knife, although it is safer to do this with a standard wire-guided papillotome which provides more directional control.

The Goff Technique [19] (named for US endoscopist, Dr John Goff) or transpancreatic septotomy is a cutting procedure with the tip of the sphincterotome in the pancreatic duct over a guidewire and the cutting wire oriented in the direction of the bile duct at about 11–12 o'clock. The cut begins in the roof of the pancreatic duct, extending through the septum and continuing through the roof of the bile duct. The sphincterotomy is extended through the septum between the pancreatic duct and bile duct until both are exposed. There were concerns when this technique was first reported that it would be associ-

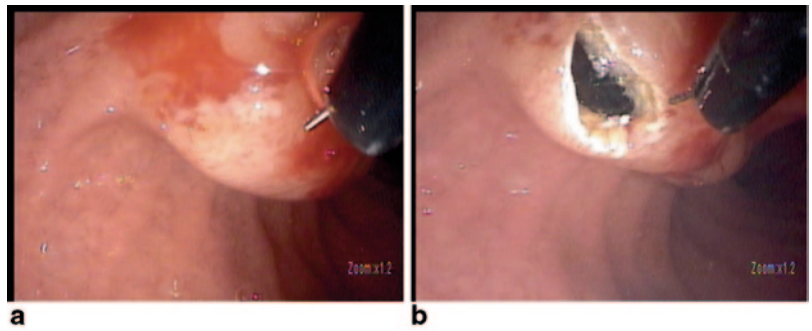

Fig. 4.12 **a**/**b** Fistulotomy of a choledochocele (*Type III choledochal cyst*) using a needle knife

ated with a high risk of pancreatitis, but this has not consistently proven true. Making the cut over a small caliber stent placed in the main PD may further reduce the risk.

Stone Removal After Sphincterotomy

When removing a column of bile duct stones with a basket or balloon catheter, try to capture the most distal one first. Attempting to pull out numerous stones all at once may cause them to bunch up and impact at the sphincterotomy site. It is important to estimate whether or not the sphincterotomy site is large enough to remove the stones without prior lithotripsy. Options include leaving a temporary stent and coming back another day, using mechanical, electrohydraulic or laser lithotripsy (with or without choledochoscopy), or performing balloon dilation. Combined sphincterotomy and balloon sphincteroplasty has been used with good effect for removing large bile duct stones. With this technique, a small (5–10 mm) initial incision is enlarged using a dilating balloon (Fig. 4.8a, b) [18]. Generally, dilating a biliary or pancreatic sphincter without prior incision should be avoided, as this carries increased risk of pancreatitis. However, gentle dilation of the biliary orifice for access may be justifiable when a patient with unreversed coagulopathy needs therapeutic access.

A study from Racine, Wisconsin, USA, almost 30 years ago found that softening the surface of bile duct stones with the choleretic agent, ursodiol (Actigall™), for some weeks facilitated subsequent stone extraction [21]. This has not been everyone's experience, and certainly not mine, with oral bile acid treatment. Presumably, the results are best with predominantly cholesterol stones.

Follow-Up: Post-Procedure Care

Following ERCP, the patient must be carefully monitored for potential complications, including pancreatitis, bleeding, perforation, sepsis, and respiratory depression. Typically, outpatients are kept no longer than 1–2 h for observation after ERCP. Unfortunately, *one third of patients who develop post-ERCP pancreatitis develop the signs and symptoms of this condition more than 2 h post-procedure*. If the patient develops acute abdominal pain, nausea, and/or vomiting hours after leaving the hospital, he or she may end up in the emergency room of a hospital 100 miles away, with all of the attendant disadvantages. In the days when I was doing a lot of outpatient ERCP, I routinely encouraged patients who had traveled a considerable distance for their procedure to book a hotel room for the night after as their insurance would not pay for overnight observation in the hospital. This ensured that they would still be in town and near our hospital if they became unwell. Patients and their relatives need oral and written instructions about what to do in the event of becoming ill after ERCP. These instructions should include an accessible pager or cellphone number of the gastroenterologist covering for emergencies. The signs and symptoms of the ERCP complications identified above should be described, and the patient or their relatives encouraged to call to discuss any concerns,

day or night. A printed copy of the ERCP report should be given to the patient—with the endoscopist's contact number—in case they end up in an emergency room elsewhere. I have a low threshold for admitting patients for overnight observation after ERCP. Patients who are slow to awaken from sedation should be kept until they are fully alert; this may require transfer to a short-stay unit in the hospital. Repeated requests for narcotic analgesia and/or antiemetic agents in the recovery period suggest that the patient may be developing PEP. Persistent or worsening abdominal pain despite narcotic analgesia should be investigated with a non-contrast abdominal CT scan to rule out perforation. A 2-h serum amylase level > 1000 iu/l is strongly predictive of the onset of PEP, with increasing sensitivity at 4 h. Urine amylase levels can also be used, but these take longer to become positive and are less sensitive than serum values. In keeping with the latest guidelines for management of acute pancreatitis, *patients suspected of developing PEP should receive a 500–1000 cc bolus of Ringers Lactate solution intravenously followed by 250–300 cc/hr for the first 24 h, to reduce the risk of necrotizing pancreatitis* [22]. Their urine output should be carefully monitored, if necessary using a urinary catheter, to ensure the production of at least 50–100 cc of urine per hour. *If you admit a post-ERCP patient for inpatient observation, it is essential to communicate your management recommendations to the responsible physician if that is not you*. Many hospital inpatient services are now run by hospitalists working shifts. A busy hospitalist, especially one single-handedly responsible for a large number of patients overnight, may not have sufficient time (or interest) to manage a patient becoming severely ill after ERCP. For this reason, you should plan your ERCP schedule so that you will be in town and available for after-hours calls about your patients. *Remember, no one cares as much about your patients as you do!* An overloaded or disinterested colleague covering your patients is your worst enemy. I have cancelled trips out of town and missed family vacations in order to personally monitor sick patients after ERCP. If you cannot postpone or cancel your trip, and your ERCP patient is sick, formulate and document a management plan with the responsible physician before you leave, and call in for daily updates. Write your cellphone number in the progress notes and clearly indicate that you are available "24/7" for consultation. Not only will this help your less-experienced colleagues manage a potentially complex problem, but it will be evidence later of your interest in the patient should a negative outcome lead to litigation.

A Final Word: The Prevention of Post-ERCP Pancreatitis

PEP is rightly the most feared complication of ERCP (Chap. 3). Every effort should be made to minimize the risks. It has been said that those most at risk from ERCP are those who need it least [23]. These include young women with non-specific abdominal pain, normal liver enzymes, and a non-dilated bile duct being investigated for supposed sphincter of Oddi dysfunction. ERCP endoscopists should review the literature on risk factors for PEP and memorize the high-risk categories. Of course, the best way to prevent PEP is not to perform ERCP in the first place. When ERCP *is* necessary, multiple studies have demonstrated that the placement of a prophylactic, small-caliber pancreatic stent in high-risk situations significantly reduces the risk of PEP and almost eliminates severe necrotizing PEP (Fig. 4.13) [4]. Failure to consider placing such

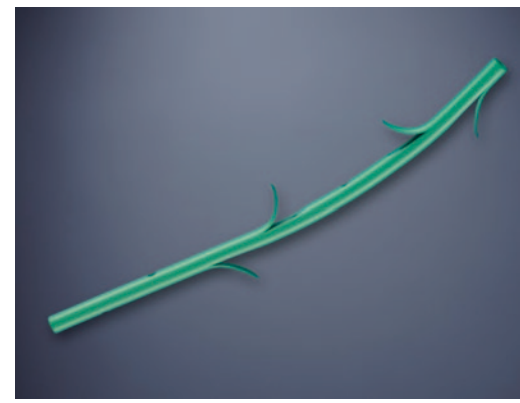

Fig. 4.13 5 French gauge, dual-flanged, plastic pancreatic duct stent

a stent in a high-risk situation may invite litigation in the event of an adverse outcome. Another intervention that is relatively simple, but potentially effective, for reducing PEP is the administration of indomethacin 100 mg by suppository at the end of the procedure [24]. Whether this treatment should be given to all ERCP patients or only to a select few with high risk for PEP has not been established, but as there is so little downside to using this inexpensive drug, like many of my colleagues I use it routinely.

Key Points

- A competent community endoscopist should be able to access the duct of choice at ERCP at least 80% of the time.
- The ability to place a guidewire in the main pancreatic duct and position a temporary plastic stent over it is key to limiting the risk of post-ERCP pancreatitis (PEP) in high-risk cases.
- Patients being considered for ERCP should undergo unhurried evaluation before the procedure.
- The endoscopist should personally see the patient and review the relevant records, including imaging, before agreeing to proceed with ERCP.
- Consent for ERCP should be obtained well before the procedure, to allow time for reflection, discussion with loved ones, and the opportunity to ask questions.
- If the patient has had a prolonged fast before ERCP, consider fluid loading with a 500–1000 cc bolus of Ringers Lactate solution to address dehydration close to the start of the procedure as this may reduce the risk of post-ERCP pancreatitis.
- Patients with gastroparesis may require a longer-than-normal fast before endoscopic procedures, including ERCP, to reduce the risk of aspiration.
- The semi-prone position is preferred for ERCP, but this should be modified for special situations, such as morbid obesity, pregnancy, and ERCP during surgery.
- If gentle attempts to pass the duodenoscope fail, stop and evaluate the local anatomy with a gastroscope to ensure that a web, ring, stricture, or Zenker's diverticulum is not the problem.
- The major and minor duodenal papillae are delicate structures and must be treated with care and respect!
- Blind injection of contrast into the papilla in the hope of identifying a duct that you have failed to cannulate deeply should be avoided. The only type of cannulation that counts is a deep cannulation.
- One third of patients who develop post-ERCP pancreatitis present the signs and symptoms more than 2 h after the end of the procedure. Prophylactic pancreatic stenting and post-procedure NSAID suppositories have been shown to reduce PEP.

Video Captions

Video 4.1 a straight metal-tipped needle cannula (ERCP-1-Cramer™, Cook Endoscopy, Bloomington, IN) may be the most effective tool to access the minor papilla when rendered necessary by a challenging duodenoscope position

Video 4.2 Cannulation over a wire or a stent placed for this purpose is frequently successful when the standard technique fails

Video 4.3 It is important to realize that only a small length of wire is needed to perform sphincterotomy

References

1. Baillie J, Cairns SC, Putnam WS, Cotton PB. Endoscopic management of choledocholithiasis during pregnancy. Surg Gynec Obstet. 1990;171(1):1–4.
2. Rolhauser C, Johnson M, Al-Kawas FH. Needle knife papillotomy: a helpful and safe adjunct to endoscopic retrograde cholangiopancreatography in a selected population. Endoscopy. 1998;30:691–6.
3. Baillie J. Reflections on needle knife papillotomy (with videos). Gastrointest Endosc. 2014;79(5):822–7.

4. Freeman ML. Pancreatic stents for prevention of post-ERCP pancreatitis: the evidence is irrefutable. J Gastroenterol. 2014;49(2):369–70.
5. ASGE Standards of Practice Committee. Management of antithrombotic agents for endoscopic procedures. Gastrointest Endosc. 2009;70(6):1060–70.
6. Baillie J, Cairns SC, Putnam WS, Cotton PB. Endoscopic management of choledocholithiasis during pregnancy. Surg Gynec Obstet. 1990;171(1):1–4.
7. Brethauer M, Seip B, Aasen S, Kordal M, Hoff G, Aabakken L. CO2 insufflation for more comfortable endoscopic retrograde pancreatography: a randomized, controlled, double-blind trial. Endoscopy 2007;39(1):58–64.
8. Baillie J. The endoscope (Part I of the "under the hood" series) (invited review). Gastrointest Endosc. 2007;65(6):886–93.
9. Ahlawat SK, Al-Kawas FH. Endoscopes, guidewires and accessories. In: Baron TH, Kozarek RA, Carr-Locke DL, Editors. ERCP. 2nd edn. Elsevier-Saunders: Philadelphia; 2013. p 32–45.
10. Sarkaria S, Sundararajan S, Kaheleh M. Endoscopic ultrasound access and drainage of the common bile duct. Gastrointest Endosc Clin N Am. 2013;23:435–52.
11. Varadarajulu S, Hawes RH. Endoscopic ultrasound-guided biliary drainage: taxing and not ready. Gastrointest Endosc. 2013;78:742–3.
12. Calvo MM, Bujanda L, Heras I, Cabrianda JL, Bernal A, Orive V, Miguelez J. The rendezvous procedure for treatment of choledocholithiasis. Gastrointest Endosc. 2001;54(4):511–3.
13. Gutierrez JM, Lederer H, Krook JC, Kinney TP, Freeman ML, Jensen EH. Surgical gastrostomy for pancreaticobiliary and duodenal access following Roux-en-Y gastric bypass. J Gastrointest Surg. 2009;13(12):2170–5.
14. Saleem A, Levy MJ, Petersen BT, Que FG, Baron TH. Laparoscopic-assisted ERCP in Roux-en-Y gastric bypass (RYGB) surgery. J Gastrointest Surg. 2012;16(1):203–8.
15. DeBenedet AT, Elmunzer BJ, McCarthy ST, Elta GH, Schoenfeld PS. Intraprocedural quality in ERCP: a meta-analysis. Am J Gastroenterol. 2013;108(11):1696–704.
16. ASGE Technology Committee. Short wire ERCP System. Gastrointest Endosc. 2007;66(4):650–7.
17. Devereaux BM, Lehman GA, Fein S, Phillips S, Fogel EL, Sherman S. Facilitation of pancreatic duct cannulation using a new synthetic porcine secretin. Am J Gastroenterol. 2002;97(9):2279–81.
18. Binmoeller KF, Schafer TW. Endoscopic management of bile duct stones. J Clin Gastroenterol. 2001;32(2):106–18.
19. Goff JS. Long-term experience with the transpancreatic sphincter pre-cut approach to biliary sphincterotomy. Gastrointest Endosc. 1999;50(5):642–5.
20. Baillie J. Difficult biliary access for ERCP. Curr Gastroenterol Rep. 2012;14(6):542–7.
21. Johnson GK, Geenen JE, Venn RP, Schmalz MJ, Hogan WJ. Treatment of non-extractable common bile duct stones with combination ursodeoxycholic acid plus endoprostheses. Gastrointest Endosc. 1993;39(4):528–31.
22. Tenner S, Baillie J, Dewitt J, Vege SS. American college of gastroenterology guidelines: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400–15.
23. Cotton PB. Analysis of 59 ERCP lawsuits; mainly about indications. Gastrointest Endosc. 2006;63(3):378–82.
24. Baron TH, Irani S. Prevention of post-ERCP pancreatitis. Minerva Med. 2014;105(2):129–36. Review.

Part II
Biliary Cases

Biliary Stones

5

Hemanth K. Gavini and John T. Cunningham

Introduction

Choledocholithiasis is a frequently encountered problem and is potentially associated with complications such as cholangitis, sepsis, and death. About 5–10 % of patients undergoing cholecystectomy for cholelithiasis and 18–33 % of patients with acute biliary pancreatitis have choledocholithiasis.[1]. Management is determined by risk stratification for the likelihood of finding common bile duct (CBD) stones using clinical parameters, liver tests, and imaging. Patients with very high or high probability of stones are managed by endoscopic retrograde cholangiopancreatography (ERCP). Patients with intermediate probability are further evaluated by magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) to determine the need for ERCP.

The natural history of choledocholithiasis is not well known. Approximately one out of five stones pass spontaneously within 1 month. Small stone size (< 5 mm) was determined to be an independent factor for spontaneous passage of the stone [2]. On the other hand, stones that do not pass spontaneously can cause further complications including acute pancreatitis, acute biliary colic, cholangitis, secondary biliary cirrhosis with subsequent sequelae of sepsis, portal hypertension, and possibly death. Hence, suspected choledocholithiasis should be further investigated and once confirmed, stones should be extracted.

Most stones can be extracted using conventional techniques involving sphincterotomy, balloon dilation, and balloon or basket extraction with high success rates averaging 90–95 %. However, factors increasing the difficulty of stone management include abnormal and postsurgical anatomy, large stones (greater than 15–20 mm), cystic duct stones with Mirizzi's syndrome, and intrahepatic stones. Development of instruments and techniques such as endoscopic sphincterotomy with large balloon dilation of the sphincter (ESLBD), mechanical lithotripsy, electrohydaulic lithotripsy, laser lithotripsy has enabled successful clearance of the biliary tract in difficult cases with rates ranging from 77 to 98 %. Intraductal ultrasound (IDUS) can be a valuable tool to ensure complete clearance of the CBD of stones in equivocal cases where the cholangiogram is not definitive.

Case Study

A 45-year-old female presented with RUQ pain and jaundice. Labs were notable for total bilirubin 7.8 mg/dl, AST 80 IU/L, ALT 60 IU/L, and alkaline phosphatase 235 IU/L. An abdominal ultrasound showed multiple gallstones within the gallbladder. The CBD measured 8 mm but no

Electronic supplementary material The online version of this chapter (doi: 10.1007/978-1-4939-2320-5_5) contains supplementary material, which is available to authorized users. Videos can also be accessed at http://link.springer.com/chapter/10.1007/978-1-4939-2320-5_5.

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stones were seen in the CBD. What is the next best step?

How Are Patients Risk Stratified for Possible Choledocholithiasis?

The initial workup for suspected choledocholithiasis should be least invasive and cost-effective and consequently includes liver biochemical tests and a transabdominal ultrasound (US). Liver biochemical tests have a low positive predictive value (15%) but a high negative predictive value (95%) and hence are useful in ruling out choledocholithiasis [3]. Higher levels of bilirubin and alkaline phosphatase occur with longer duration and severity of biliary obstruction, and thus are more predictive of the presence of CBD stones. The US has a low sensitivity (less than 50%) but a very high specificity (100%) in the detection of choledocholithiasis. Thus, the presence of a stone confirms the diagnosis but the absence of a stone does not rule out choledocholithiasis. However, the US finding of a normal sized CBD (<6 mm in patients with intact gallbladder) has a high negative predictive value of 95% and is consequently helpful in excluding stones [4]. Thus, the combination of normal liver biochemical tests and a normal sized CBD on US with a negative predictive value of 95% are useful in ruling out choledocholithiasis.

Risk stratification to determine the presence of choledocholithiasis helps avoid unnecessary procedures and streamlines the management in an efficient manner. The ASGE standards of practice committee has guidelines to risk stratify patients with symptomatic cholelithiasis into three groups based on the probability of choledocholithiasis: high risk (>50%), intermediate (10–50%), and low risk (<10%) [1]. The presence of any very strong clinical predictor (clinical ascending cholangitis, ultrasound showing a stone, or total bilirubin >4 mg/dl) or both strong predictors (US showing a dilated CBD and total bilirubin 1.8 mg/dl-4 mg/dl) places the patient at high risk of having choledocholithiasis with recommendations to proceed with ERCP for further management. The absence of any clinical predicators places the patient at low risk of having choledocholithiasis. These patients can proceed with cholecystectomy with no further testing. All other patients have an intermediate risk of having choledocholithiasis and should proceed with either EUS or MRCP preoperatively or an intraoperative cholangiogram (IOC) during cholecystectomy. In a recent study, IOC, when attempted routinely in patients undergoing cholecystectomy, was successful in 95% with a sensitivity of 97% and specificity of 99% [5]. However, IOC is highly operator dependent, adds to procedure time, and may not be feasible in cases of severely inflamed gallbladder. If a stone is confirmed on the IOC, it can be removed via laparoscopic CBD exploration (LCBDE) or via postoperative ERCP. An advantage of performing preoperative confirmatory studies (EUS/MRCP) in this group is that the stone can be removed during preoperative ERCP, and if ERCP is unsuccessful, LCBDE can be performed to remove the stone during cholecystectomy. However, proceeding with a cholecystectomy and IOC would not be unreasonable when surgical expertise is available, thus avoiding the risk of possible complications associated with ERCP which may delay the cholecystectomy.

EUS in selected patients has been shown to decrease the need for ERCP by 70% and adverse events related to the ERCP by 65% [6]. EUS has been compared to MRCP for the detection of choledocholithiasis and has a higher sensitivity (93 vs 85%), specificity (96 vs 93%), positive predictive value (93 vs 87%), and negative predictive value (96 vs 92%) but the differences were not statistically significant [7]. The sensitivity of MRCP decreases with smaller stone size and approaches 70% when evaluating for stones <5 mm but has the advantage of being noninvasive [8]. Thus, the choice between these modalities should be based on local availability, expertise, patient characteristics, and preference.

Tips for Preparation and Technique of Cholangiogram During ERCP

Obtaining a comprehensive history and review of previous imaging and records is essential for providing optimal care and avoiding unanticipated

roadblocks during the procedure. Reviewing previous diagnostic imaging also provides a roadmap for performing the ERCP. Antibiotics are continued in patients with acute cholangitis until the procedure and after if complete drainage is not achieved. Patients with sepsis related to the cholangitis should be resuscitated prior to the procedure. After cannulation of the bile duct and deep advancement of the wire, aspiration of bile prior to injecting contrast helps minimize the hydrostatic pressure of injection and over distension of the bile duct, thereby decreasing the risk of bacteremia in the setting of cholangitis. A good cholangiogram should be obtained to identify the stone burden, location and size of the stones, size of the duct, and any strictures that will have an impact on the stone extraction strategy as will be discussed further below. We inject half strength contrast starting at the distal aspect of the CBD and carefully evaluate for any filling defects as the contrast extends proximally into the bifurcation of the right and left hepatic ducts. Care should be taken not to overdistend the biliary system as it predisposes to cholangitis. The cystic duct is opacified to ensure patency. The gallbladder should not be overfilled as this causes pain and may predispose to cholecystitis. A balloon occlusion cholangiogram is performed after removal of all stones to ensure complete clearance. Nonopacification of the cystic duct during the occlusion cholangiogram is evidence of cyst duct blockage and makes a case for cholecystectomy.

Case Continued

Because the patient was at high risk for CBD stone, an ERCP was performed which revealed a smooth narrowing in the distal biliary tree. A sphincterotomy was performed but a balloon sweep showed no stone and a stent was placed (Fig. 5.1a, b). A laparoscopic cholecystectomy was then performed. She returned for a second ERCP, which revealed a persistent narrowing, and the stent was replaced. She was then referred for further management.

How Are Uncomplicated Stones Retrieved During ERCP?

Among other factors, stone size is an important determinant of successful endoscopic removal after a sphincterotomy (Fig. 5.2). As a general rule, stones smaller than 10 mm can be successfully removed following a sphincterotomy [9].

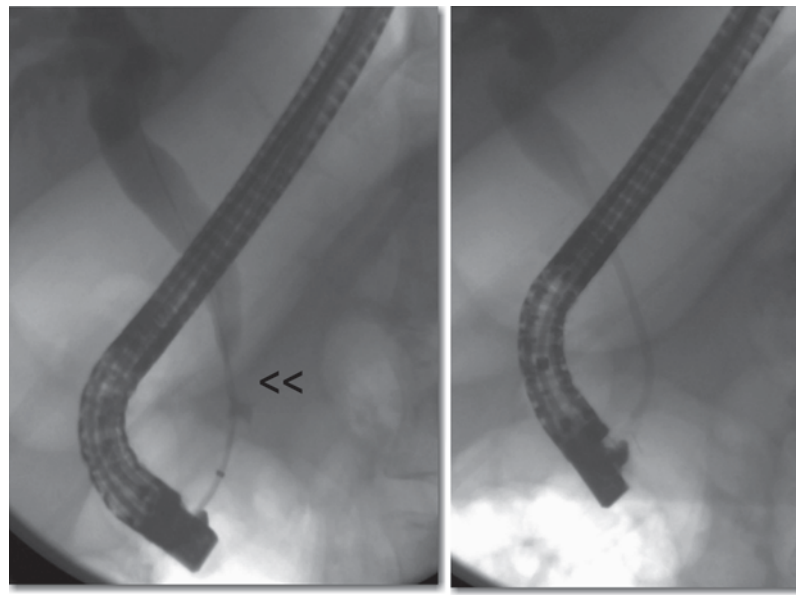

Fig. 5.1 **a**. ERCP with a smooth eccentric narrowing (*arrows*) in the distal biliary tree without evidence of a mobile filling defect or a distinct stone. **b**. Stent is placed

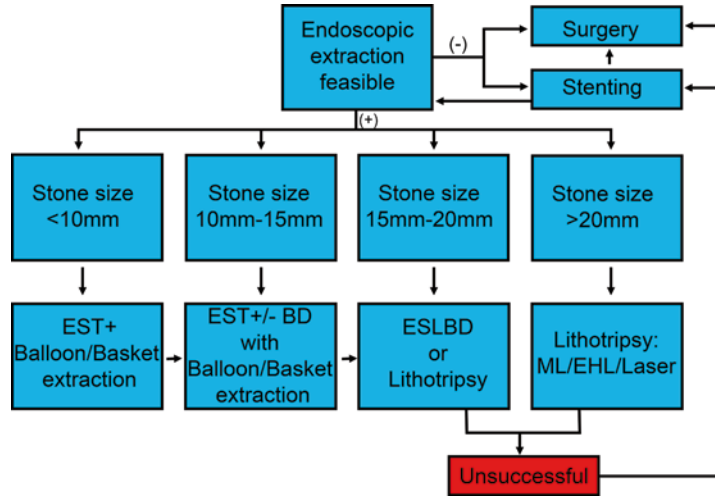

Fig. 5.2 Algorithm for management of established bile duct stones. *EST* = endoscopic sphincterotomy; *BD* = balloon dilation; *ESLBD* = endoscopic sphincterotomy and large balloon dilation; *ML* = mechanical lithotripsy; *EHL* = electrohydraulic lithotripsy

As such if a stone appears smaller than the diameter of the scope, it can be extracted with a balloon catheter or a basket without difficulty after sphincterotomy. In the setting of a dilated bile duct with small stones, a basket is more helpful in extraction as the stones tend to slide by the balloon within the large duct during removal. Any stones impacted in the lower CBD should be pushed up into the proximal duct to avoid inadvertent rupture of the duct. During retrieval of stones using a basket, the stone is first engaged within the basket by to and fro motion around the stone, and the stone is extracted without closing the basket. This is to prevent inadvertent impaction of the stone within the basket and subsequent inability to remove the basket containing the stone through the papilla due to a mismatch between the size of the stone and the papillary orifice. When multiple stones are present, they should be removed one at a time starting with the most distal stone first to avoid impaction. As a general rule, the balloon or basket containing the stone is withdrawn until at the papilla and locked in this position at the biopsy port with the left hand while simultaneously pushing the big dial away and gently advancing the scope using clockwise torque with the right hand. This technique of stone removal aligns the vector of the extraction force with the axis of the bile duct while maintaining visualization of the papilla to confirm stone extraction.

Some factors which make stone extraction difficult include the following:

1. Large stones (> 1.5–2 cm)
2. Impacted stones
3. Cystic duct stones causing Mirizzi's syndrome
4. Stones in the intrahepatic ducts
5. Concomitant presence of a downstream stricture.

When to Perform Sphincterotomy, Balloon Dilation or Both?

Endoscopic sphincterotomy (EST) has a high success rate of stone extraction approaching 85–98%, but can be associated with a risk of bleeding, perforation and pancreatitis [10]. The risk of postsphincterotomy bleeding is increased in patients with coagulopathy either due to intrinsic liver disease or from the use of anticoagulants and antiplatelet agents [11]. EST also leads to permanent loss of the sphincter function with a theoretical risk of free bacterial access to the bile duct leading to recurrent stone formation [12]. Endoscopic balloon dilation of the native papilla (EBD) was initially developed as an alternative to EST to minimize the risk of adverse events and also preserve the sphincter function [13]. Balloon dilation of the papilla can be performed using balloons ranging from 4 to 8 mm. Although one meta-analysis showed lower efficacy of stone

clearance with EBD compared to EST [14], other studies have demonstrated high success rates of 91–97% for stone extraction with EBD, comparable to that of EST [15–17]. Equal efficacy of EST and EBD for extraction of small to medium-sized stones up to 8 mm has been shown in randomized controlled trials (RCT) [15, 16]. A meta-analysis by Baron et al confirmed comparable efficacy for stone removal with both techniques, albeit with a lower risk of pancreatitis in patients undergoing EST [17]. A few studies have reported an increased risk of serious complications including severe pancreatitis with EBD, with one RCT terminated prematurely due to complications and two deaths related to severe pancreatitis in the EBD group [15]. Thus, EBD has fallen out of favor as a primary choice for stone extraction. With its lower risk of bleeding and perforation, EBD has been recommended as an option for stone removal in patients with coagulopathy [15–17]. Therefore, for small to medium-sized stones, EST would be the preferred method to facilitate stone extraction with EBD used sparingly in patients with coagulopathy that cannot be corrected, altered anatomy where sphincterotomy cannot be achieved, or periampullary diverticulum that makes sphincterotomy difficult.

Large stones (>1.5 cm) may require lithotripsy to deliver the stone following EST or EBD. An alternative combines an initial small to less than maximal sphincterotomy followed by large balloon dilation (10–20 mm), which is termed endoscopic sphincterotomy with large balloon dilation (ESLBD) and was first described by Ersoz et al. [18]. Subsequently, several studies have demonstrated successful extraction of complex stones with this procedure [19, 20]. This technique of initial sphincterotomy separates the biliary and pancreatic sphincters and helps direct the controlled tear of the sphincter by the large balloon dilation away from the pancreatic duct, thus theoretically minimizing the risk of pancreatitis [21]. A meta-analysis by Feng et al comparing ESLBD with EST to facilitate removal of large stones showed fewer complications and decreased need for mechanical lithotripsy in the ESLBD group [22]. A RCT comparing mechanical lithotripsy following EST to ESLBD demonstrated equal efficacy in stone removal but a higher rate of complications in the lithotripsy group [23]. ESLBD also decreases the need for mechanical lithotripsy, fluoroscopy time, total procedure time, [24], and total hospital cost [25]. The rate of pancreatitis following ESLBD is lower than 5%, which is comparable to EST and lower than EBD [26]. Rare but serious perforations and occasional bleeding have occurred following ESLBD. Care should be taken to match the size of the balloon with the diameter of the native distal CBD to avoid perforation.

The currently available balloons for large dilation were intended for use in the luminal GI tract, and due to their length may present some problems if the CBD has numerous stones (Fig. 5.3). The stones need to be either pushed upstream or the balloon placed very distal in the CBD just enough to dilate the papilla without lying beside stones (Fig. 5.4a, b). This is important as inflating the balloon beside a stone may carry a risk of perforation, especially if the stone is angulated rather than smooth. Regarding how long to dilate, a nonblinded RCT comparing 1 versus 5 min dilation of the papilla without EST showed

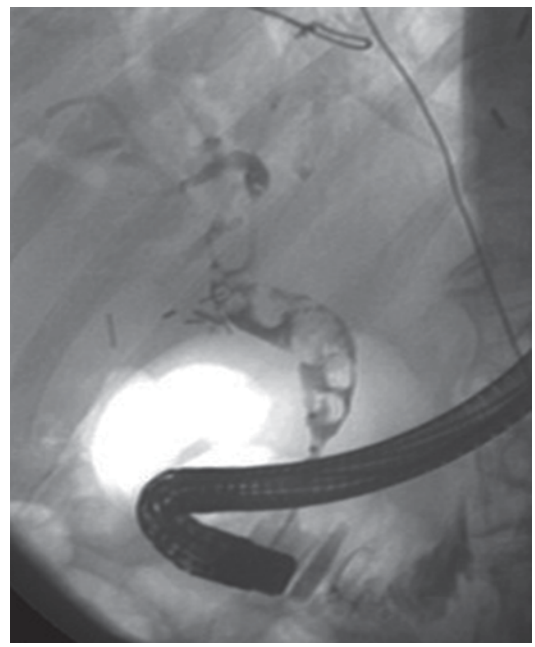

Fig. 5.3 ERCP cholangiogram with multiple CBD stones down to the distal CBD

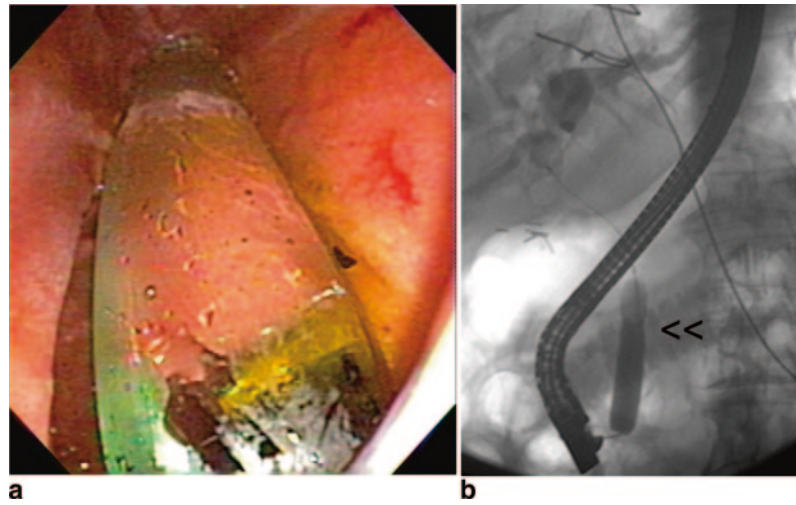

Fig. 5.4 **a**. Balloon inserted with minimal balloon *above* the major papilla. **b**. The radiographic view showing a waist in the balloon (*arrows*) at the papilla with minimal balloon upstream

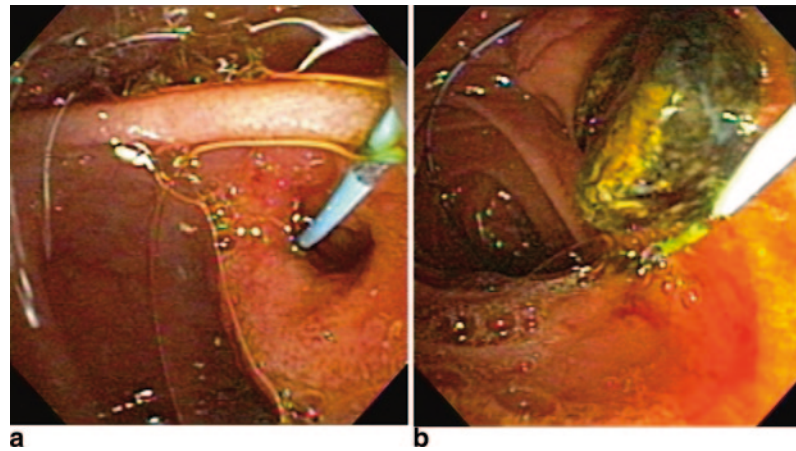

Fig. 5.5 **a**. Ampulla postdilation. **b**. Stone extracted postdilation

significantly higher technical success for stone extraction (80 vs 93%) and lower rate of pancreatitis (15 vs 5%) in the group that underwent 5 min dilation[27]. However, the control group (1 min dilation) had a much lower rate of technical success than generally expected (80%), which may have overinflated the difference in success between the two groups. We tend to sequentially dilate the papilla for 1 min at each level of the balloon thus totaling 3 min. Once the dilation is complete, the stone can be extracted with a balloon or basket (Fig. 5.5a, b). Thus, ESLBD combines the best of both worlds with lower rates of pancreatitis than EBD and decreased need for mechanical lithotripsy compared to EST in the extraction of large stones (up to 2 cm), provided the distal CBD is dilated enough to accommodate the large balloon.

During stone extraction using a basket, it is prudent to have a rescue lithotripter system available such as a Soehendra lithotripter (Cook Medical, Bloomington, IN) or an Olympus reusable emergency lithotripter (Olympus, Center Valley, PA) because stone/basket impaction is a potential complication with possible significant repercussions if not resolved (Fig. 5.6a). A technique for resolution is to cut the handle and remove the sheath from the basket and the endoscope from the patient. Next insert the metal sheath of the lithotripter over the broken wires of the basket, place the wires in the handle, advance the lithotripter under fluoroscopic guidance, and crush the

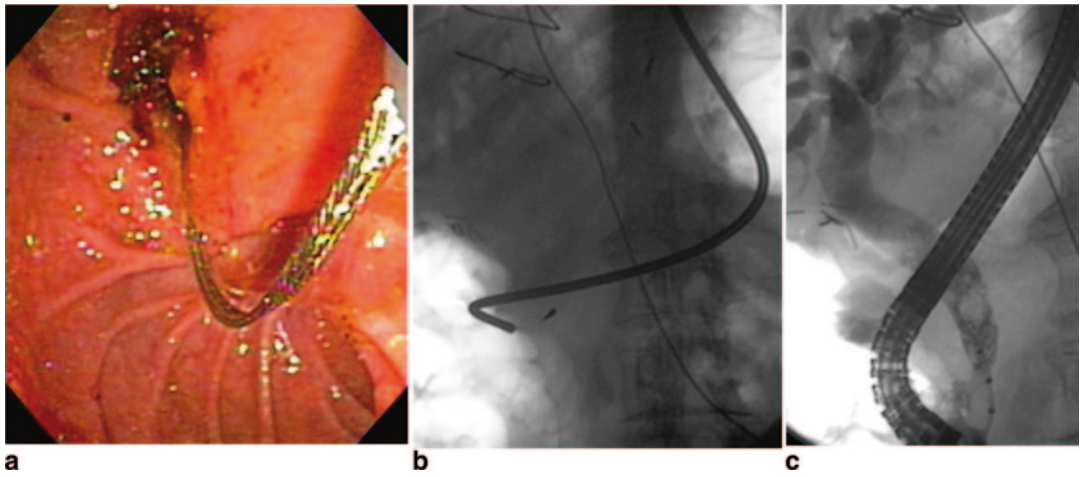

Fig. 5.6 **a**. Endoscopic view of basket wire with plastic sheath covering removed after failed stone extraction. **b**. The endoscope has been removed and the "rescue" lithotripter sheath inserted over the wire. **c**. Following stone fragmentation and basket removal, stone fragments are ready for extraction

impacted stone (Fig. 5.6b, c). Some rescue lithotripters operate through the scope channel while others require removal of the duodenoscope.

Lithotripsy

Mechanical lithotripsy was first described by Demling in 1983 as a safe and effective way of fragmenting large stone thus facilitating removal. Mechanical lithotripsy improves rate of bile duct clearance in difficult stone cases up to 90% with about 4–13% rate of complications including pancreatitis, bleeding, perforation, and basket impaction [28]. This technique involves using a nonemergency lithotripter composed of a basket, plastic sheath, and outer metal sheath to capture the stone within the basket and advance a metal sheath over it to fragment the stone. The device is introduced through the papilla using the "kissing technique" whereby close contact is maintained between the scope and papilla while cannulating the duct. Once confirmed fluoroscopically within the bile duct, we like to pass the closed basket above the stone and draw the open basket down to engage the stone with a shaking movement to try to ensure placement of the wires symmetrically around the stone. The basket is then closed and the metal sheath approximated against the basket to crush the stone. The fragments are disengaged from the basket. Contrast is then injected to see whether any large stone fragments remain that require additional lithotripsy. After the apparatus is withdrawn, the remaining stone fragments can then be extracted with a basket or a balloon. The distal fragments are first extracted to ensure that the fragments do not get impacted at the outlet, and work should progress from the distal to proximal bile duct until all fragments are removed. In about 10% of patients, mechanical lithotripsy will fail, necessitating other techniques such as electrohydraulic lithotripsy (EHL) or laser lithotripsy (LL) (28). These latter approaches are typically best suited for large impacted stones.

EHL involves creating an oscillating cavitation bubble in a liquid media by an electrical spark from an EHL probe which then forms a mechanical shockwave that fragments the stone. This technique was adapted from the mining industry. The EHL probe measuring 3Fr is introduced through the working channel of a Spyglass ® (Boston Scientific Inc, Marlborough, MA) cholangioscope via a therapeutic duodenoscope or a peroral cholangioscope and advanced under

direct visualization to the level of the stone with at least 5 mm of the probe protruding from the tip of the endoscope. Shots are fired in 1–2 s bursts at energy ranging from 50 to 100 W. Care is taken to maintain direct contact between the probe and the stone and to avoid the bile duct wall to minimize injury. Saline is intermittently injected into the bile duct to clear the field for better visualization of the stone fragmentation. EHL successfully fragments large stones and enables bile duct clearance in up to 98% of cases in various studies with overall complication rates of 3–15%, which include a risk of hemobilia, cholangitis, pancreatitis, bile leak, hemothorax, and perforation [29–33]. Advantages of EHL include its relatively low cost and lack of need for special protective equipment.

Laser lithotripsy involves creating an oscillating cavitation bubble in a liquid media using optical energy from lasers of specific wavelengths which then forms a mechanical shockwave that fragments the stone. Over the years, several different types of lasers have existed ranging from dye lasers to solid state lasers with different physical properties defined by specific wavelengths which determine the depth of penetration. The shorter the wavelength, the greater the depth of penetration. The dye lasers have shorter wavelengths and consequently a higher degree of penetration (>5 mm), thus making them very effective but also expensive and more prone to cause injury. The solid-state lasers have longer wavelengths and lower penetration (<5 mm) with lower cost and higher safety. A hybrid of these two technologies—Frequency Doubled Double Pulse neodymium (FREDDY)—uses coumarin dye in succession with neodymium:YAG and in studies effectively fragments stones and enables duct clearance in 88–92% of cases with a complication rate of 7–23% [34–36]. Holmium:YAG laser has a longer wavelength very close to the peak absorption of water thus minimizing any scatter which makes it theoretically precise and safe by minimizing duct injury. Holmium:YAG laser has been evaluated in studies showing effective bile duct clearance rates of 90–100% with complication rates of 4–14% [37–39]. We do not routinely administer antibiotics during lithotripsy unless there is incomplete stone removal.

ESWL is another modality for management of large stones with ductal clearance rates of ~80% [40]. However, the availability of ESWL equipment is limited to few centers as it is expensive. Two randomized trials comparing LL to ESWL demonstrated higher rate of ductal clearance with LL (83–97% vs 53–73%) [41, 42]. A randomized trial comparing EHL to ESWL showed comparable rates of ductal clearance (74 vs 79%) [43]. Given the widespread availability and comparable to superior efficacy of endoscopic lithotripter tools, most if not all large stones can be successfully removed using intraductal lithotripsy, obviating the need to use ESWL in biliary stones. There is however a role for ESWL in managing pancreatic duct stones which are hard and heavily calcified and not easy to fragment unlike biliary stones (Chap. 13).

Case Concluded

At the next ERCP, the stent was removed and the cholangiogram again showed a smooth narrowing in the distal CBD. At this point, given the persistent narrowing of the CBD, the decision was made to use intraductal ultrasound (IDUS) to evaluate the possible stricture. A guidewire was placed into the intrahepatics, and the Olympus 20 MHz over-the-wire ultrasound probe (Fig. 5.7a, b) revealed a long cystic duct which was parallel to the CHD, contained a large stone (Mirizzi's syndrome), and merged into the CBD just a few centimeters above the ampulla (Video 5.1). The stone was visualized with the Spyglass system (Boston Scientific, Marlborough, MA) and fragmented with EHL using the Nortech Autolith ® system (Northgate Technologies Inc., Elgin IL). The cystic duct, CHD, and CBD were swept free of stone fragments. Final cholangiogram showed no residual stricture or stone (Fig. 5.8).

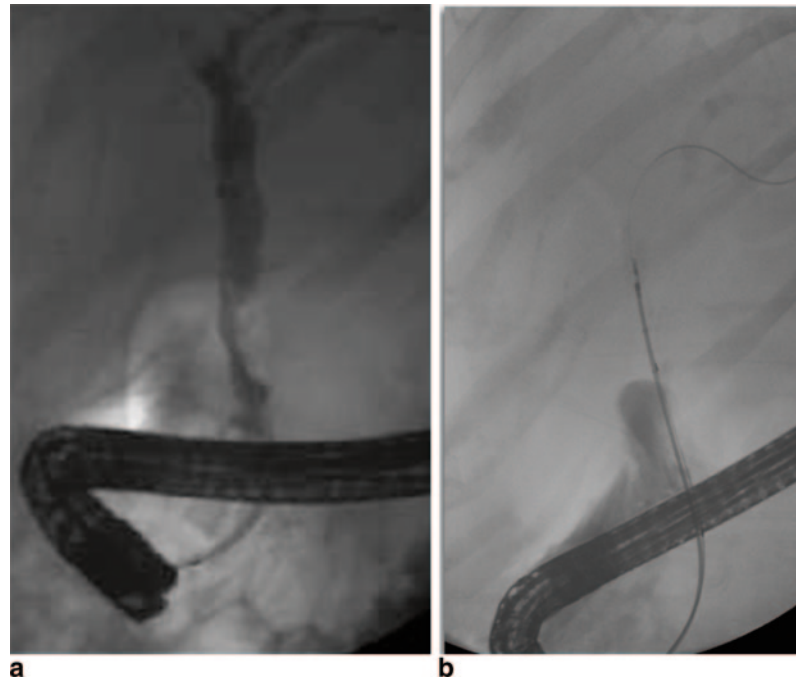

Fig. 5.7 **a**. Third ERCP with persistence of distal narrowing in bile duct. **b**. Over-the-wire 20 MHz ultrasound probe advanced deep into the biliary tree

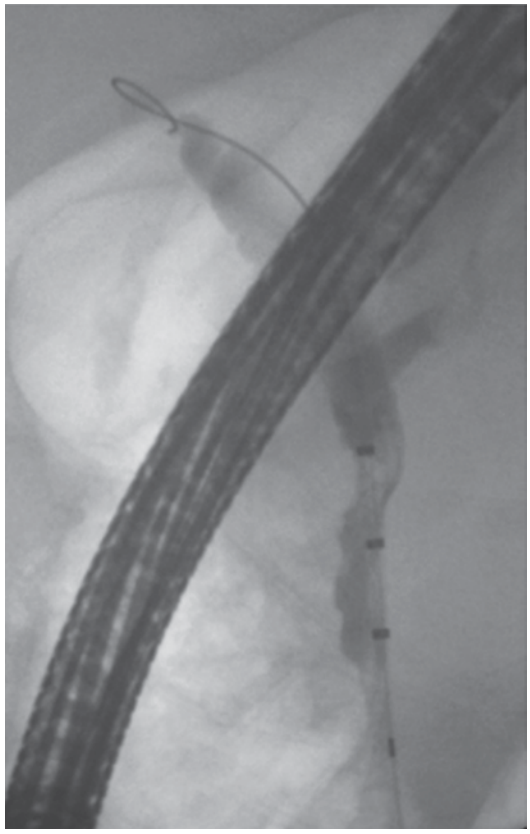

Fig. 5.8 Final cholangiogram with stone fragment removed and distal stricture resolved

Is There a Role for Intraductal Ultrasound (IDUS) in Clearing the Bile Duct?

A mini-ultrasound probe ranging from 12 to 30 MHz over a guidewire can be introduced into the bile duct to evaluate for choledocholithiasis. Several studies have evaluated the role of IDUS in detecting choledocholithiasis missed on cholangiography during ERCP [44, 45]. IDUS is particularly useful for visualizing small stones (<8 mm) in the setting of a dilated bile duct (>12 mm) when such stones may be missed on cholangiogram [46]. Residual choledocholithiasis after EST and basket/balloon extraction was detected by IDUS in 40% of patients [47]. IDUS is also useful for ensuring complete duct clearance after lithotripsy and stone extraction [48, 49]. The clinical significance of detecting these small (usually less than 4 mm) residual CBD stones by IDUS is unclear. Thus, when there is suspicion for CBD stones based on preprocedure imaging that cannot be visualized during a cholangiogram, especially in the setting of a dilated CBD, IDUS can be used to evaluate for small stones. Occasionally in situations as illustrated in the case when there is a linear narrowing of the CBD especially around

the cystic duct, an IDUS can be used to exclude Mirrizi's syndrome. We do not use IDUS to ensure complete duct clearance after lithotripsy as any small fragments should pass spontaneously through the wide open papilla.

When Should Biliary Stenting Be Considered?

Biliary stenting provides biliary drainage in situations where there is incomplete duct clearance due to difficult stones as a temporizing measure or as a more definitive solution in patients with limited life span when comorbidities and advanced age preclude aggressive techniques of duct clearance. When used as a temporizing solution in the elderly population prior to definitive endoscopic or surgical therapy, there is a complication rate of 10% compared to greater than 50% when used as a definitive treatment. Approximately one out of 5 patients died of infectious biliary complications when stents were used as definitive therapy, and thus this treatment option should only be used in very select patients with short life expectancy [50]. Temporizing stents have been placed for short duration (2–6 months) in patients with large stones (>2 cm) and multiple stones (>3 stones) to help fragment the stones. A decrease in stone burden by greater than 50% was observed following stent placement for 2–6 months [51, 52]. Single or multiple stents of the straight or pigtail variety may be used. Although most of the experience to date has been with plastic stents, fully covered self-expandable metal stents have also been used successfully in the management of complex biliary stones [53]. Due to the cost and risk of complications associated with metal stents, they cannot be advocated for the management of biliary stones at this time.

When Should Nonendoscopic Modalities Be Considered for Removal of CBD Stones?

Cholecystectomy is recommended for most patients with cholelithiasis after ductal clearance by ERCP given the low morbidity of laparoscopic cholecystectomy [54]. Laparoscopic cholecystectomy should be performed ideally within 2 weeks of ductal clearance by ERCP to minimize the risk of recurrent choledocholithiasis, biliary colic, gallstone pancreatitis, and cholecystitis [55–57]. A randomized clinical trial showed a higher risk of recurrent biliary events with some necessitating emergency surgery when laparoscopic cholecystectomy was delayed (6–8 weeks) compared to early surgery (within 72 h) following EST for CBD stones [58].

An alternative to preoperative ERCP is laparoscopic CBD exploration (LCBDE) for removal of CBD stones following cholecystectomy. It can be considered a one-step operation when IOC demonstrates CBD stones which can be removed in the same setting if technical expertise in this modality is available. Randomized clinical trials comparing LCBDE with ERCP (preoperative or postoperative) for stone removal have shown comparable technical success, morbidity, and mortality [59–62]. It can also be used in cases of prior failed ERCP, lack of local endoscopic expertise, or in the setting of altered anatomy like Roux-en Y reconstruction with long limbs when the success rate for ERCP is low. Given the high success rate of ERCP (unless precluded by altered anatomy), we prefer postoperative ERCP to CBD exploration for stone removal at our institution. Percutaneous removal of extrahepatic duct stones has been described via an indwelling T-tube or percutaneous transhepatic route with success rates of ~90% although with a risk of hemorrhagic complications (hemobilia) and death [63]. This is rarely ever employed to remove extrahepatic duct stones given the length of time it takes for the tract to mature (~4–6 weeks) and the potential hemorrhagic complications and death.

What is the Role of ERCP in Intrahepatic Duct Stones?

Hepatolithiasis or intrahepatic duct stones are more common in East Asia compared to the Western population. These stones are frequently multiple and associated with strictures. Etiologies typically include postoperative biliary strictures,

primary sclerosing cholangitis, and recurrent pyogenic cholangitis. They often present with recurrent cholangitis and sepsis. Long-standing hepatolithiasis may lead to secondary biliary cirrhosis, hepatic lobe atrophy, and intrahepatic cholangiocarcinoma. Patients with multiple stones confined to one lobe of the liver are often managed by surgical resection of the involved liver with or without a bilioenteric anastomosis. Greater rates of stone clearance were achieved with hepatectomy (83 %) compared to nonoperative modalities like percutaneous removal (64 %) or ERCP (43 %) [64]. In the same study, during median follow-up of 8 years, a nonsignificant trend of lower recurrence rates and cholangitis were seen with hepatectomy compared with nonoperative management [64].

Endoscopic therapy of hepatolithiasis is difficult due to the recurrent nature of the disease requiring multiple interventions and the presence of multiple stones, concomitant intrahepatic strictures, peripheral stone impactions, and duct angulations [30]. Peroral cholangioscopy with lithotripsy can be used for difficult stones that cannot be extracted using a balloon or basket [32]. The success rate for endoscopic removal of intrahepatic stones (64 %) is lower than for extrahepatic stones [65]. Care should be taken to avoid injection of an atrophied hepatic lobe during ERCP due to the high risk of infectious complications. Percutaneous cholangioscopy with lithotripsy is technically successful in up to 85 % of patients. Both endoscopic and percutaneous treatment carry a high rate of recurrence and/or cholangitis of 22–63 % [66]. Consequently, endoscopic or percutaneous methods of stone removal may be employed in patients with limited stone disease, bilateral liver involvement where surgery is not feasible, and recurrent stones after surgery.

Recurrent or Inoperable Stones

Up to 10 % of patients who have undergone EST and stone extraction will develop recurrent CBD stones, because either the gallbladder was not removed or new stones formed within the CBD in the absence of a gallbladder [67]. In these patients, 57 % had juxtapapillary diverticula, and most of these stones were pigmented stones that do not benefit from ursodiol or antibiotics for preventing recurrence. Other risk factors for recurrent choledocholithiasis include dilated CBD to greater than 15 mm, angulated bile duct, biliary stricture, and papillary stenosis, which all predispose to biliary stasis. A regular schedule of liver function tests or ERCP at defined intervals is indicated. Annual ERCP to clear the bile duct led to decreased rates of cholangitis in a small study of patients with at least two occurrences of choledocholithiasis [68]. Surgical bypass with choledochoduodenostomy for recurrent stones refractory to endoscopic therapy is not routinely recommended due to high morbidity (10–28 %) including cholangitis, sump syndrome, bile leak and up to 5 % mortality [69–72].

In patients who are unable to undergo cholecystectomy due to significant comorbidities, endoscopic transpapillary gallbladder stenting (ETGS) can be considered as an alternative to surgery. A prospective study of this patient population using double pigtail stents for ETGS in symptomatic gallbladder disease was technically successful in 23 of 29 patients (79 %) and provided long-term patency (median stent patency 760 days) without needing scheduled stent exchanges [73]. This is a technically demanding procedure, as negotiating the tortuous cystic duct is difficult and greatly influenced by the endoscopist's experience [74].

Conclusion

The majority of bile duct stones are cholesterol stones in the Western population. Due to the risk of complications including cholangitis, sepsis, and secondary biliary cirrhosis associated with choledocholithiasis, even stones in asymptomatic patients should be extracted if feasible. MRI and EUS have good accuracy in detecting choledocholithiasis, when there is an intermediate probability of harboring a bile duct stone. Most stones smaller than 10 mm can be removed with EST and balloon or basket extraction. Stones between 10 and 15 mm can be retrieved after EST with or without balloon dilation of the papilla and balloon

or basket extraction. During stone removal using a basket, it is prudent to have a rescue lithotripter system available due to the risk of stone or basket impaction, which can have significant repercussions if not resolved. Several endoscopic modalities are available for extraction of difficult stones including ESLBD, mechanical lithotripsy, electrohydraulic lithotripsy, and laser lithotripsy. Stones measuring 15–20 mm can be removed with ESLBD or lithotripsy. Stones greater than 20 mm in size generally require lithotripsy. In patients with significant comorbidities that preclude surgical or aggressive endoscopic therapy, biliary stenting with plastic stents can be used as a temporizing solution for biliary drainage. IDUS has a role in the detection of small stones, particularly in a dilated bile duct, where such stones may be missed on cholangiogram. Up to 10% of patients will have recurrent stones after endoscopic extraction and cholecystectomy, and these patients may benefit from a regular schedule of follow-up liver tests or ERCP at defined intervals.

Key Points

- Suspected choledocholithiasis should be further investigated and once confirmed, stones extracted to minimize the risk of complications. Management is determined by risk stratification for the likelihood of common bile duct (CBD) stones using clinical parameters, liver tests, and imaging.
- Patients with symptomatic cholelithiasis at intermediate risk of choledocholithiasis can undergo (a) preoperative confirmatory imaging (EUS/MRCP) followed by ERCP as indicated or (b) IOC followed by LCBDE or postoperative ERCP if needed, depending on local availability, expertise, patient characteristics, and preference.
- Uncomplicated stones can be successfully extracted with a balloon or basket after endoscopic sphincterotomy. Large stones (15–20 mm) can be removed with ESLBD or lithotripsy (ML/EHL/LL). Stones >20 mm generally require lithotripsy.
- Because stone or basket impaction is a potential complication with significant repercussions if not resolved, it is prudent to have a rescue lithotripter system available when performing stone extraction with a basket.
- IDUS is particularly useful for visualizing small stones (<8 mm) within a dilated bile duct (>12 mm) when such stones may be missed on cholangiogram.
- Biliary stenting acts as a temporizing measure in cases of incomplete stone extraction or severe acute cholangitis. Occasionally, it can provide a definitive solution in patients with limited life span when comorbidities and advanced age preclude aggressive techniques of duct clearance.
- LCBDE offers an alternative to ERCP when local expertise is available in cases where (a) IOC shows choledocholithiasis, (b) prior ERCP has failed or (c) Roux-en Y reconstructions with long limbs make the success rate for ERCP low.
- Hepatectomy should be considered for hepatolithiasis in surgically fit patients with heavy unilateral intrahepatic stone burden, especially with concomitant biliary strictures and/or lobar atrophy. Percutaneous or endoscopic therapy can be offered in select situations, but carries a higher risk of recurrence, incomplete stone removal, and cholangitis.
- In patients with recurrent choledocholithiasis, a regular schedule of liver function tests with ERCP at defined intervals is preferable to surgical bypass (choledochoduodenostomy) given the relatively high morbidity and mortality associated with the latter.

Video Caption

Video 5.1 ERCP with electrohydraulic lithotripsy and balloon extraction of stone fragments from the common hepatic duct, CBD, and cystic duct

References

1. Maple JT, Ben-Menachem T, Anderson MA, Appalaneni V, Banerjee S, Cash BD, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. Gastrointest Endosc. 2010;71(1):1–9. PubMed PMID: 20105473. Epub 2010/01/29. eng.
2. Frossard JL, Hadengue A, Amouyal G, Choury A, Marty O, Giostra E, et al. Choledocholithiasis: a prospective study of spontaneous common bile duct stone migration. Gastrointest Endosc. 2000;51(2):175–9. PubMed PMID: 10650260. Epub 2000/01/29. eng.
3. Yang MH, Chen TH, Wang SE, Tsai YF, Su CH, Wu CW, et al. Biochemical predictors for absence of common bile duct stones in patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2008;22(7):1620–4. PubMed PMID: 18000708. Epub 2007/11/15. eng.
4. Cronan JJ. US diagnosis of choledocholithiasis: a reappraisal. Radiology. 1986;161(1):133–4. PubMed PMID: 3532178. Epub 1986/10/01. eng.
5. Videhult P, Sandblom G, Rasmussen IC. How reliable is intraoperative cholangiography as a method for detecting common bile duct stones?: a prospective population-based study on 1171 patients. Surg Endosc. 2009;23(2):304–12. PubMed PMID: 18398646. Epub 2008/04/10. eng.
6. Petrov MS, Savides TJ. Systematic review of endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis. Br J Surg. 2009;96(9):967–74. PubMed PMID: 19644975. Epub 2009/08/01. eng.
7. Verma D, Kapadia A, Eisen GM, Adler DG. EUS vs MRCP for detection of choledocholithiasis. Gastrointest Endosc. 2006;64(2):248–54. PubMed PMID: 16860077. Epub 2006/07/25. eng.
8. Sugiyama M, Atomi Y, Hachiya J. Magnetic resonance cholangiography using half-Fourier acquisition for diagnosing choledocholithiasis. Am J Gastroenterol. 1998;93(10):1886–90. PubMed PMID: 9772049. Epub 1998/10/15. eng.
9. Lauri A, Horton RC, Davidson BR, Burroughs AK, Dooley JS. Endoscopic extraction of bile duct stones: management related to stone size. Gut. 1993;34(12):1718–21. PubMed PMID: 8282260. Pubmed Central PMCID: PMC1374470. Epub 1993/12/01. eng.
10. Vaira D, D'Anna L, Ainley C, Dowsett J, Williams S, Baillie J, et al. Endoscopic sphincterotomy in 1000 consecutive patients. Lancet. 1989;2(8660):431–4. PubMed PMID: 2569609. Epub 1989/08/19. eng.
11. Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med. 1996;335(13):909–18. PubMed PMID: 8782497. Epub 1996/09/26. eng.
12. Tanaka M, Takahata S, Konomi H, Matsunaga H, Yokohata K, Takeda T, et al. Long-term consequence of endoscopic sphincterotomy for bile duct stones. Gastrointest Endosc. 1998;48(5):465–9. PubMed PMID: 9831833. Epub 1998/12/01. eng.
13. Staritz M, Ewe K, Meyer zum Buschenfelde KH. Endoscopic papillary dilatation, a possible alternative to endoscopic papillotomy. Lancet. 1982;1(8284):1306–7. PubMed PMID: 6123047. Epub 1982/06/05. eng.
14. Weinberg BM, Shindy W, Lo S. Endoscopic balloon sphincter dilation (sphincteroplasty) versus sphincterotomy for common bile duct stones. Cochrane Database Syst Rev. 2006;4:CD004890. PubMed PMID: 17054222. Epub 2006/10/21. eng.
15. Disario JA, Freeman ML, Bjorkman DJ, Macmathuna P, Petersen BT, Jaffe PE, et al. Endoscopic balloon dilation compared with sphincterotomy for extraction of bile duct stones. Gastroenterology. 2004;127(5):1291–9. PubMed PMID: 15520997. Epub 2004/11/03. eng.
16. Bergman JJ, Rauws EA, Fockens P, van Berkel AM, Bossuyt PM, Tijssen JG, et al. Randomised trial of endoscopic balloon dilation versus endoscopic sphincterotomy for removal of bileduct stones. Lancet. 1997;349(9059):1124–9. PubMed PMID: 9113010. Epub 1997/04/19. eng.
17. Baron TH, Harewood GC. Endoscopic balloon dilation of the biliary sphincter compared to endoscopic biliary sphincterotomy for removal of common bile duct stones during ERCP: a metaanalysis of randomized, controlled trials. Am J Gastroenterol. 2004;99(8):1455–60. PubMed PMID: 15307859. Epub 2004/08/17. eng.
18. Ersoz G, Tekesin O, Ozutemiz AO, Gunsar F. Biliary sphincterotomy plus dilation with a large balloon for bile duct stones that are difficult to extract. Gastrointest Endosc. 2003;57(2):156–9. PubMed PMID: 12556775. Epub 2003/01/31. eng.
19. Draganov PV, Evans W, Fazel A, Forsmark CE. Large size balloon dilation of the ampulla after biliary sphincterotomy can facilitate endoscopic extraction of difficult bile duct stones. J Clin Gastroenterol. 2009;43(8):782–6. PubMed PMID: 19318979. Epub 2009/03/26. eng.
20. Maydeo A, Bhandari S. Balloon sphincteroplasty for removing difficult bile duct stones. Endoscopy. 2007;39(11):958–61. PubMed PMID: 17701853. Epub 2007/08/19. eng.
21. Attasaranya S, Cheon YK, Vittal H, Howell DA, Wakelin DE, Cunningham JT, et al. Large-diameter biliary orifice balloon dilation to aid in endoscopic bile duct stone removal: a multicenter series. Gastrointest Endosc. 2008;67(7):1046–52. PubMed PMID: 18178208. Epub 2008/01/08. eng.
22. Feng Y, Zhu H, Chen X, Xu S, Cheng W, Ni J, et al. Comparison of endoscopic papillary large balloon dilation and endoscopic sphincterotomy for retrieval of choledocholithiasis: a meta-analysis of randomized controlled trials. J Gastroenterol. 2012;47(6):655–63. PubMed PMID: 22361862. Epub 2012/03/01. eng.

23. Stefanidis G, Viazis N, Pleskow D, Manolakopoulos S, Theocharis L, Christodoulou C, et al. Large balloon dilation vs. mechanical lithotripsy for the management of large bile duct stones: a prospective randomized study. Am J Gastroenterol. 2011;106(2):278–85. PubMed PMID: 21045816. Epub 2010/11/04. eng.
24. Itoi T, Itokawa F, Sofuni A, Kurihara T, Tsuchiya T, Ishii K, 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(3):560–5. PubMed PMID: 19174779. Epub 2009/01/29. eng.
25. Teoh AY, Cheung FK, Hu B, Pan YM, Lai LH, Chiu PW, et al. Randomized trial of endoscopic sphincterotomy with balloon dilation versus endoscopic sphincterotomy alone for removal of bile duct stones. Gastroenterology. 2013;144(2):341–5.e1. PubMed PMID: 23085096. Epub 2012/10/23. eng.
26. Attam R, Freeman ML. Endoscopic papillary large balloon dilation for large common bile duct stones. J Hepatobiliary Pancreat Surg. 2009;16(5):618–23. PubMed PMID: 19551331. Epub 2009/06/25. eng.
27. Liao WC, Lee CT, Chang CY, Leung JW, Chen JH, Tsai MC, et al. Randomized trial of 1-minute versus 5-minute endoscopic balloon dilation for extraction of bile duct stones. Gastrointest Endosc. 2010;72(6):1154–62. PubMed PMID: 20869710. Epub 2010/09/28. eng.
28. Demling L, Seuberth K, Riemann JF. A mechanical lithotripter. Endoscopy. 1982;14(3):100–1. PubMed PMID: 7075559. Epub 1982/05/01. eng.
29. Bonnel DH, Liguory CE, Cornud FE, Lefebvre JF. Common bile duct and intrahepatic stones: results of transhepatic electrohydraulic lithotripsy in 50 patients. Radiology. 1991;180(2):345–8. PubMed PMID: 2068295. Epub 1991/08/01. eng.
30. Binmoeller KF, Bruckner M, Thonke F, Soehendra N. Treatment of difficult bile duct stones using mechanical, electrohydraulic and extracorporeal shock wave lithotripsy. Endoscopy. 1993;25(3):201–6. PubMed PMID: 8519238. Epub 1993/03/01. eng.
31. Arya N, Nelles SE, Haber GB, Kim YI, Kortan PK. Electrohydraulic lithotripsy in 111 patients: a safe and effective therapy for difficult bile duct stones. Am J Gastroenterol. 2004;99(12):2330–4. PubMed PMID: 15571578. Epub 2004/12/02. eng.
32. Piraka C, Shah RJ, Awadallah NS, Langer DA, Chen YK. Transpapillary cholangioscopy-directed lithotripsy in patients with difficult bile duct stones. Clin Gastroenterol Hepatol. 2007;5(11):1333–8. PubMed PMID: 17644045. Epub 2007/07/24. eng.
33. Siegel JH, Ben-Zvi JS, Pullano WE. Endoscopic electrohydraulic lithotripsy. Gastrointest Endosc. 1990;36(2):134–6. PubMed PMID: 2335279. Epub 1990/03/01. eng.
34. Kim TH, Oh HJ, Choi CS, Yeom DH, Choi SC. Clinical usefulness of transpapillary removal of common bile duct stones by frequency doubled double pulse Nd: YAG laser. World J Gastroenterol. 2008;14(18):2863–6. PubMed PMID: 18473411. Pubmed Central PMCID: PMC2710728. Epub 2008/05/14. eng.
35. Cho YD, Cheon YK, Moon JH, Jeong SW, Jang JY, Lee JS, et al. Clinical role of frequency-doubled double-pulsed yttrium aluminum garnet laser technology for removing difficult bile duct stones (with videos). Gastrointest Endosc. 2009;70(4):684–9. PubMed PMID: 19573867. Epub 2009/07/04. eng.
36. Liu F, Jin ZD, Zou DW, Li ZS. Efficacy and safety of endoscopic biliary lithotripsy using FREDDY laser with a radiopaque mark under fluoroscopic guidance. Endoscopy. 2011;43(10):918–21. PubMed PMID: 21833900. Epub 2011/08/13. eng.
37. Maydeo A, Kwek BE, Bhandari S, Bapat M, Dhir V. Single-operator cholangioscopy-guided laser lithotripsy in patients with difficult biliary and pancreatic ductal stones (with videos). Gastrointest Endosc. 2011;74(6):1308–14. PubMed PMID: 22136776. Epub 2011/12/06. eng.
38. Lee TY, Cheon YK, Choe WH, Shim CS. Direct cholangioscopy-based holmium laser lithotripsy of difficult bile duct stones by using an ultrathin upper endoscope without a separate biliary irrigating catheter. Photomed Laser Surg. 2012;30(1):31–6. PubMed PMID: 22043820. Epub 2011/11/03. eng.
39. Patel SN, Rosenkranz L, Hooks B, Tarnasky PR, Raijman I, Fishman DS, 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. PubMed PMID: 24268531. Epub 2013/11/26. Eng.
40. Meyenberger C, Meierhofer U, Michel-Harder C, Knuchel J, Wirth HP, Buhler H, et al. Long-term follow-up after treatment of common bile duct stones by extracorporeal shock-wave lithotripsy. Endoscopy. 1996;28(5):411–7. PubMed PMID: 8858228. Epub 1996/06/01. eng.
41. Jakobs R, Adamek HE, Maier M, Kromer M, Benz C, Martin WR, et al. Fluoroscopically guided laser lithotripsy versus extracorporeal shock wave lithotripsy for retained bile duct stones: a prospective randomised study. Gut. 1997;40(5):678–82. PubMed PMID: 9203950. Pubmed Central PMCID: PMC1027174. Epub 1997/05/01. eng.
42. Neuhaus H, Zillinger C, Born P, Ott R, Allescher H, Rosch T, et al. Randomized study of intracorporeal laser lithotripsy versus extracorporeal shock-wave lithotripsy for difficult bile duct stones. Gastrointest Endosc. 1998;47(5):327–34. PubMed PMID: 9609422. Epub 1998/06/03. eng.
43. Adamek HE, Maier M, Jakobs R, Wessbecher FR, Neuhauser T, Riemann JF. Management of retained bile duct stones: a prospective open trial comparing extracorporeal and intracorporeal lithotripsy. Gastrointest Endosc. 1996;44(1):40–7. PubMed PMID: 8836715. Epub 1996/07/01. eng.
44. Das A, Isenberg G, Wong RC, Sivak MV, Jr, Chak A. Wire-guided intraductal US: an adjunct to ERCP in the management of bile duct stones.

Gastrointest Endosc. 2001;54(1):31–6. PubMed PMID: 11427838. Epub 2001/06/28. eng.
45. Kubota Y, Takaoka M, Yamamoto S, Shibatani N, Shimatani M, Takamido S, et al. Diagnosis of common bile duct calculi with intraductal ultrasonography during endoscopic biliary cannulation. J Gastroenterol Hepatol. 2002;17(6):708–12. PubMed PMID: 12100618. Epub 2002/07/09. eng.
46. Endo T, Ito K, Fujita N, Noda Y, Kobayashi G, Obana T, et al. Intraductal ultrasonography in the diagnosis of bile duct stones: when and whom? Dig Endosc. 2011;23(2):173–5. PubMed PMID: 21429024. Epub 2011/03/25. eng.
47. Ang TL, Teo EK, Fock KM, Lyn Tan JY. Are there roles for intraductal US and saline solution irrigation in ensuring complete clearance of common bile duct stones? Gastrointest Endosc. 2009;69(7):1276–81. PubMed PMID: 19249039. Epub 2009/03/03. eng.
48. Ohashi A, Ueno N, Tamada K, Tomiyama T, Wada S, Miyata T, et al. Assessment of residual bile duct stones with use of intraductal US during endoscopic balloon sphincteroplasty: comparison with balloon cholangiography. Gastrointest Endosc. 1999;49(3 Pt 1):328–33. PubMed PMID: 10049416. Epub 1999/02/27. eng.
49. Tamada K, Ohashi A, Tomiyama T, Wada S, Satoh Y, Higashizawa 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(1):100–3. PubMed PMID: 11206304. Epub 2001/02/24. eng.
50. Bergman JJ, Rauws EA, Tijssen JG, Tytgat GN, Huibregtse K. Biliary endoprostheses in elderly patients with endoscopically irretrievable common bile duct stones: report on 117 patients. Gastrointest Endosc. 1995;42(3):195–201. PubMed PMID: 7498682. Epub 1995/09/01. eng.
51. Horiuchi A, Nakayama Y, Kajiyama M, Kato N, Kamijima T, Graham DY, et al. Biliary stenting in the management of large or multiple common bile duct stones. Gastrointest Endosc. 2010;71(7):1200–3.e2. PubMed PMID: 20400079. Epub 2010/04/20. eng.
52. Jain SK, Stein R, Bhuva M, Goldberg MJ. Pigtail stents: an alternative in the treatment of difficult bile duct stones. Gastrointest Endosc. 2000;52(4):490–3. PubMed PMID: 11023565. Epub 2000/10/07. eng.
53. Cerefice M, Sauer B, Javaid M, Smith LA, Gosain S, Argo CK, et al. Complex biliary stones: treatment with removable self-expandable metal stents: a new approach (with videos). Gastrointest Endosc. 2011;74(3):520–6. PubMed PMID: 21872710. Epub 2011/08/30. eng.
54. Maple JT, Ikenberry SO, Anderson MA, Appalaneni V, Decker GA, Early D, et al. The role of endoscopy in the management of choledocholithiasis. Gastrointest Endosc. 2011;74(4):731–44. PubMed PMID: 21951472. Epub 2011/09/29. eng.
55. Schiphorst AH, Besselink MG, Boerma D, Timmer R, Wiezer MJ, van Erpecum KJ, et al. Timing of cholecystectomy after endoscopic sphincterotomy for common bile duct stones. Surg Endosc. 2008;22(9):2046–50. PubMed PMID: 18270768. Epub 2008/02/14. eng.
56. Ito K, Ito H, Whang EE. Timing of cholecystectomy for biliary pancreatitis: do the data support current guidelines? J Gastrointest Surg. 2008;12(12):2164–70. PubMed PMID: 18636298. Epub 2008/07/19. eng.
57. Chiang DT, Thompson G. Management of acute gallstone pancreatitis: so the story continues. ANZ J Surg. 2008;78(1–2):52–4. PubMed PMID: 18199206. Epub 2008/01/18. eng.
58. Reinders JS, Goud A, Timmer R, Kruyt PM, Witteman BJ, Smakman N, et al. Early laparoscopic cholecystectomy improves outcomes after endoscopic sphincterotomy for choledochocystolithiasis. Gastroenterology. 2010;138(7):2315–20. PubMed PMID: 20206179. Epub 2010/03/09. eng.
59. Sgourakis G, Karaliotas K. Laparoscopic common bile duct exploration and cholecystectomy versus endoscopic stone extraction and laparoscopic cholecystectomy for choledocholithiasis. A prospective randomized study. Minerva Chir. 2002;57(4):467–74. PubMed PMID: 12145577. Epub 2002/07/30. eng.
60. Noble H, Tranter S, Chesworth T, Norton S, Thompson M. A randomized, clinical trial to compare endoscopic sphincterotomy and subsequent laparoscopic cholecystectomy with primary laparoscopic bile duct exploration during cholecystectomy in higher risk patients with choledocholithiasis. J Laparoendosc Adv Surg Tech A. 2009;19(6):713–20. PubMed PMID: 19792866. Epub 2009/10/02. eng.
61. Nathanson LK, O'Rourke NA, Martin IJ, Fielding GA, Cowen AE, Roberts RK, et al. Postoperative ERCP versus laparoscopic choledochotomy for clearance of selected bile duct calculi: a randomized trial. Ann Surg. 2005;242(2):188–92. PubMed PMID: 16041208. Pubmed Central PMCID: PMC1357723. Epub 2005/07/26. eng.
62. Rhodes M, Sussman L, Cohen L, Lewis MP. Randomised trial of laparoscopic exploration of common bile duct versus postoperative endoscopic retrograde cholangiography for common bile duct stones. Lancet. 1998;351(9097):159–61. PubMed PMID: 9449869. Epub 1998/02/05. eng.
63. Garcia-Garcia L, Lanciego C. Percutaneous treatment of biliary stones: sphincteroplasty and occlusion balloon for the clearance of bile duct calculi. Am J Roentgenol. 2004;182(3):663–70. PubMed PMID: 14975967. Epub 2004/02/21. eng.
64. Cheon YK, Cho YD, Moon JH, Lee JS, Shim CS. Evaluation of long-term results and recurrent factors after operative and nonoperative treatment for hepatolithiasis. Surgery. 2009;146(5):843–53. PubMed PMID: 19744434. Epub 2009/09/12. eng.
65. Shah RJ, Adler DG, Conway JD, Diehl DL, Farraye FA, Kantsevoy SV, et al. Cholangiopancreatoscopy. Gastrointest Endosc. 2008;68(3):411–21. PubMed

PMID: 18538326. Epub 2008/06/10. eng.
66. Huang MH, Chen CH, Yang JC, Yang CC, Yeh YH, Chou DA, et al. Long-term outcome of percutaneous transhepatic cholangioscopic lithotomy for hepatolithiasis. Am J Gastroenterol. 2003;98(12):2655–62. PubMed PMID: 14687812. Epub 2003/12/23. eng.
67. Lai KH, Lo GH, Lin CK, Hsu PI, Chan HH, Cheng JS, et al. Do patients with recurrent choledocholithiasis after endoscopic sphincterotomy benefit from regular follow-up? Gastrointest Endosc. 2002;55(4):523–6. PubMed PMID: 11923765. Epub 2002/03/30. eng.
68. Geenen DJ, Geenen JE, Jafri FM, Hogan WJ, Catalano MF, Johnson GK, et al. The role of surveillance endoscopic retrograde cholangiopancreatography in preventing episodic cholangitis in patients with recurrent common bile duct stones. Endoscopy. 1998;30(1):18–20. PubMed PMID: 9548038. Epub 1998/04/21. eng.
69. Baker AR, Neoptolemos JP, Leese T, James DC, Fossard DP. Long term follow-up of patients with side to side choledochoduodenostomy and transduodenal sphincteroplasty. Ann R Coll Surg Engl. 1987;69(6):253–7. PubMed PMID: 2892457. Pubmed Central PMCID: PMC2498515. Epub 1987/11/01. eng.
70. Uchiyama K, Onishi H, Tani M, Kinoshita H, Kawai M, Ueno M, et al. Long-term prognosis after treatment of patients with choledocholithiasis. Ann Surg. 2003;238(1):97–102. PubMed PMID: 12832971. Pubmed Central PMCID: PMC1422666. Epub 2003/07/02. eng.
71. Escudero-Fabre A, Escallon A, Jr, Sack J, Halpern NB, Aldrete JS. Choledochoduodenostomy. Analysis of 71 cases followed for 5 to 15 years. Ann Surg. 1991;213(6):635–42; discussion 43–4. PubMed PMID: 2039295. Pubmed Central PMCID: PMC1358593. Epub 1991/06/01. eng.
72. Parrilla P, Ramirez P, Sanchez Bueno F, Perez JM, Candel MF, Muelas MS, et al. Long-term results of choledochoduodenostomy in the treatment of choledocholithiasis: assessment of 225 cases. Br J Surg. 1991;78(4):470–2. PubMed PMID: 2032108. Epub 1991/04/01. eng.
73. Lee TH, Park DH, Lee SS, Seo DW, Park SH, Lee SK, et al. Outcomes of endoscopic transpapillary gallbladder stenting for symptomatic gallbladder diseases: a multicenter prospective follow-up study. Endoscopy. 2011;43(8):702–8. PubMed PMID: 21425042. Epub 2011/03/23. eng.
74. Itoi T, Coelho-Prabhu N, Baron TH. Endoscopic gallbladder drainage for management of acute cholecystitis. Gastrointest Endosc. 2010;71(6):1038–45. PubMed PMID: 20438890. Epub 2010/05/05. eng.

Biliary Infections

6

Sundeep Lakhtakia and Shyam Varadarajulu

Introduction

Biliary infection or acute cholangitis is defined as bacterial infection of the bile ducts. In approximately a quarter to two-thirds of cases, it is characterized clinically by Charcot's triad (right upper quadrant abdominal pain, fever, and jaundice) [1–3]. Although cholangitis is usually associated with obstruction of the biliary system, this alone is insufficient as infection of the biliary tract is a requisite to precipitate cholangitis.

Bile flowing from the liver into the duodenum is usually sterile and washes down any debris or bacterial contamination in the biliary tract. The Sphincter of Oddi acts as a natural barrier to biliary contamination, by preventing duodeno-biliary reflux. In addition, hepatic Kupffer cells secrete IgA and bile salts which sterilize the bile. Therefore, any obstruction to the flow of bile causes loss of these natural protective mechanisms and can potentially lead to biliary infection or cholangitis [4].

Mechanisms proposed for the pathogenesis of cholangitis include bacterial ascent from the small bowel into the bile duct (ascending cholangitis), and less commonly bacterial translocation through the bowel wall followed by bacterial contamination of portal blood and hematogenous seeding of the biliary tree [5].

Patients with acute cholangitis are at risk for developing severe infection that can be fatal in up to 10 % unless timely and appropriate medical care is provided [5]. Advances in antibiotic therapy and acute care, as well as expertise in biliary endoscopy, have resulted in reduced morbidity and mortality from acute cholangitis. However, this still remains a life-threatening disease and early determination of disease severity is essential to select appropriate therapy, particularly the timing of biliary decompression [6].

Case Study

A 35-year-old Indian male presented with right upper quadrant pain of 2 weeks duration, which gradually increased in intensity and was associated with fever and chills of five days duration. On physical examination, he was febrile with tachycardia and hypotension. He had icterus with tenderness in the right hypochondrium. His laboratory investigations revealed a serum total bilirubin of 7.1 mg/dl (normal < 2.0 mg/dl), alkaline phosphatase 476 U/L (normal < 120 U/L), aspartate transaminase 86 U/L (normal < 40 U/L), alanine transaminase 62 U/L (normal < 40 U/L),

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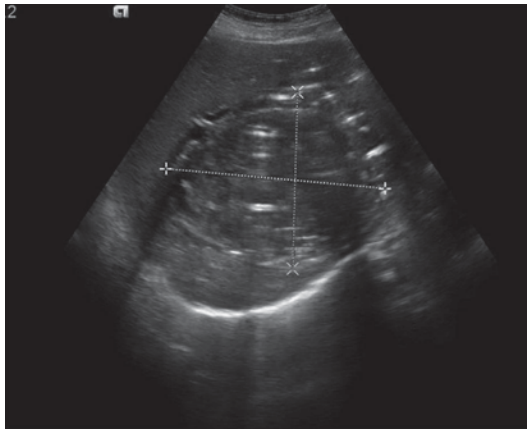

Fig. 6.1 Transabdominal ultrasound revealing a large (128×103 mm) cystic lesion in right lobe of liver with internal echoes

serum albumin 2.9 gm/dl (normal 3.5–5.5 gm/dl), and white blood cell count of 18,700 with 90% neutrophils. A transabdominal ultrasound revealed a large (128×103 mm) cystic lesion in the right lobe of the liver with internal echoes and bilateral intrahepatic ductal dilation (Fig. 6.1).

How Is Cholangitis Diagnosed?

Etiologies of Cholangitis

Biliary stones are the commonest cause of cholangitis. Other causes include benign and malignant bile duct strictures, primary sclerosing cholangitis (PSC), hepato-biliary infection by parasites, recurrent pyogenic cholangitis, acquired immune deficiency syndrome cholangiopathy, and also following ineffective biliary tract instrumentation.

Clinical Presentation

Cholangitis can be characterized by Charcot's triad, which is defined by fever (seen in about 90% of patients with cholangitis), abdominal pain (70%), and jaundice (60%) [7]. The presence of all three features is considered diagnostic of acute cholangitis [6]. Very sick patients may have additional features of altered mentation (in 10–20%) and hypotension (in 30%) resulting in Reynolds' pentad [8]. Laboratory abnormalities include leukocytosis, hyperbilirubinemia, mild-to-moderate elevations of transaminases and alkaline phosphatase. Severe liver dysfunction with coagulopathy can occur as a result of prolonged or severe cholangitis, often associated with high morbidity and mortality.

Diagnostic Criteria

Some physicians base their diagnosis on clinical features, whereas others rely more on imaging studies or endoscopic confirmation of biliary obstruction and pus in the biliary tree. Diagnostic criteria for cholangitis called the Tokyo Guidelines were recently updated (Table 6.1) [5, 6]. These criteria combine clinical features, laboratory data, and imaging studies in an attempt to establish the diagnosis and severity of acute cholangitis with greater accuracy [6]. The sensitivity of the Tokyo guidelines is significantly

Table 6.1 Updated Tokyo guidelines: diagnostic criteria for acute cholangitis systemic inflammation. (Adapted from [6])

A1	Fever (>38 °C) and/or shaking chills
A2	Laboratory data: evidence of inflammation (white blood cells<4 or>10 thousand per uL, CRP>1 mg/L2
A	Cholestasis
B1	Jaundice (total bilirubin>2 mg/dL)
B2	Laboratory data: ALP, GGT, AST, ALT>1.5 X upper limit of normal
B	Imaging
C1	Biliary dilation
C2	Evidence of cause on imaging (stricture, stone, stent, and so forth.)

Definite diagnosis: 1 item each in A, B, and C
Suspected diagnosis: 1 item in A plus 1 item in either B or C

Table 6.2 Updated Tokyo guidelines: severity assessment for acute cholangitis. (Adapted from [6])

Grade III (Severe) acute cholangitis	
"Grade III" acute cholangitis is defined as acute cholangitis that is associated with the onset of dysfunction in at least one of any of the following organ/systems:	
1. Cardiovascular dysfunction	Hypotension requiring dopamine ≥5 μg/kg per min. or any dose of norepinephrine
2. Neurological dysfunction	Disturbance of consciousness
3. Respiratory dysfunction	PaO_2/FiO_2 ratio <300
4. Renal dysfunction	Oliguria, serum creatinine >2.0 mg/dl
5. Hepatic dysfunction	PT-INR >1.5
6. Hematological dysfunction	Platelet count <1,000,000/mm^3
Grade II (moderate) acute cholangitis	
"Grade II" acute cholangitis is associated with any two of the following conditions:	
1. Abnormal WBC count (>12,000/mm^3, <4,000/mm^3)	
2. High fever (≥39°C)	
3. Age (≥75 years old)	
4. Hyperbilirubinemia (total bilirubin ≥ 5mg/dL)	
5. Hypoalbuminemia (<STD x 0.7	
Grade I (mild) acute cholangitis	
"Grade I" acute cholangitis does not meet the criteria of "Grade III (severe)" or "Grade II (moderate)" acute cholangitis at initial diagnosis.	

higher than Charcot's triad (92 versus 26%) at the expense of decrease in specificity (78 versus 96%) [6]. Table 6.2 summarizes the criteria for determining severity of cholangitis. Severe cholangitis requires organ dysfunction while moderate cholangitis necessitates a couple of clinical and laboratory findings. Assessing severity is important to determining appropriate timing of biliary drainage. The severity of acute cholangitis can vary from a mild, self-limiting form to life-threatening disease with hemodynamic instability and septic shock. Accurate diagnosis and early severity assessment are imperative to guide the type and timing of therapy.

Imaging

Several imaging modalities can be considered in patients with acute cholangitis to determine the cause and site of biliary obstruction. These include transabdominal ultrasound (US), abdominal CT scan, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC).

The selection of imaging modality depends on the ease of availability and clinical condition of the patient. Although ERCP is the most sensitive diagnostic test for cholangitis and also offers therapeutic option at the same session, the procedure itself and need for sedation carry significant risks in critically ill patients; therefore, non-invasive imaging studies (US, CT, MRCP) or lower-risk endoscopic tests (EUS) are often required. The choice of imaging modality and the order in which they are performed depends primarily on the clinical stability of the patient and the cause of obstruction.

Ultrasound is usually the initial imaging modality of choice. It is highly sensitive and specific for confirming the presence of gallstones and detecting biliary dilatation; however, its ability to detect bile duct stones is low, with a sensitivity ranging from 20 to 50% [9]. A CT scan is useful when differential diagnoses include malignancy, chronic pancreatitis, or common bile duct (CBD) stone [10, 11]. MRCP is superior to US and CT for imaging the biliary tree and detecting bile duct stones [10, 11]. The sensitivities of EUS and MRCP for detecting bile duct stones are comparable [12, 13]. However, the accuracy of MRCP for small lesions and stones smaller than 6 mm is limited [14]. EUS is highly sensitive and specific for imaging the biliary

tree and the pancreas to evaluate for obstructing lesions, with the additional option of fine-needle aspiration (FNA) in the same session. An EUS evaluation before ERCP is being accepted as a preferred management strategy for patients with low or intermediate probability for bile duct stones or tumor. EUS helps select patients for therapeutic ERCP, which can occur in the same session.

The non-invasive and less invasive tests (US, CT, MRCP, EUS) may be performed in a clinically stable patient with low or moderate likelihood of cholangitis; however, in a severely ill patient with high probability of cholangitis, it is prudent to proceed directly to ERCP or EUS followed by ERCP. ERCP is the gold standard test for diagnosing biliary obstruction and also serves as a therapeutic modality by facilitating initial biliary drainage. Because it is the most invasive of modalities with highest potential morbidity, ERCP is preferred when a therapeutic intervention is planned and not as a purely diagnostic modality for evaluation of cholangitis [15, 23].

Organisms

The typical organisms cultured in the blood and bile are the usual bacteria found in the gastrointestinal tract, namely, E. coli, Enterobacter, Enterococcus, and Klebsiella. However, instrumentation may allow Pseudomonas, skin, and oral flora to be introduced into the biliary system [16]. Escherichia and Klebsiella are the most common microorganisms identified in the biliary system with the rate of extended spectrum beta lactamase (ESBL) producers being greater than 20% [17]. This high rate of ESBL producers in these organisms implies the necessity for broad-spectrum antibiotic coverage when traditional antibiotics are insufficient to control infection [18].

How Is Cholangitis Managed?

Initial Medical Management

Initial management includes intravenous fluids, broad-spectrum antibiotics, and correction of any underlying coagulopathy. The choice of antibiotic should be based on severity of the illness, setting of infection (community acquired or hospital acquired), presence of underlying hepato-biliary disease, history of biliary instrumentation or surgery such as bilio-enteric anastomosis, age and immune status of the patient, and local susceptibility patterns [4, 6, 19]. For mild-to-moderate cholangitis, 2–3 days of a first or second-generation cephalosporin such as cefoxitin, a penicillin with a β-lactamase inhibitor such as ampicillin and sulbactam, or a fluoroquinolone is recommended. Severe cholangitis can be treated with piperacillin and tazobactam, a third- or fourth-generation cephalosporin such as ceftriaxone with or without metronidazole for 5–7 days. The final antibiotic choice should be tailored to the final blood and bile culture results.

ERCP: When and How?

After initial clinical stabilization, biliary decompression should be performed to resolve cholangitis. Non-surgical methods are the procedures of choice, with ERCP preferred over percutaneous drainage. In special circumstances, EUS may be used to assist in drainage either in a rendezvous procedure or in antegrade stent placement.

While patients with mild cholangitis may be treated with antibiotics and elective ERCP, patients with moderate cholangitis should undergo biliary drainage within 24–48 h, and severe cholangitis requires urgent biliary drainage within 24 h. ERCP should not be delayed longer than 72 h as this is associated with worse outcome including death, persistent organ failure, and/or intensive care unit stay and increased length of hospital stay [20].

During ERCP in a patient with cholangitis after wire-guided cannulation, bile and/or pus should be aspirated first to decompress the biliary system and sent for culture. In addition, it may be better to perform a sphincterotomy and allow the infected bile and pus to drain out before injecting contrast to delineate the anatomy. Excessive injection of contrast in the obstructed biliary system should be avoided to prevent systemic spread via cholangio-venous reflux. Contrast should be injected gently and less than the amount of bile

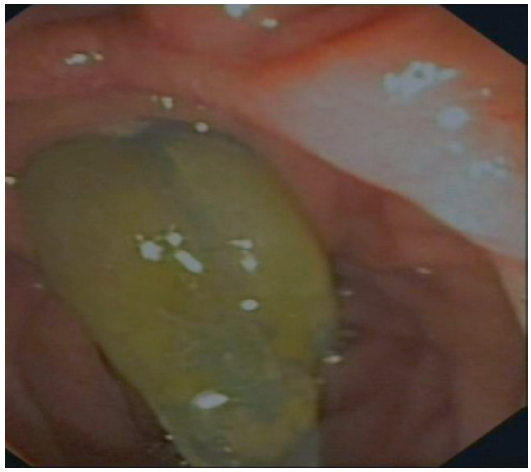

Fig. 6.2 Thick hydatid membranes are seen protruding out of the ampulla at duodenoscopy

aspirated. Even if no definite stones are identified during ERCP, performing biliary sphincterotomy for drainage is reasonable in patients with clinical suspicion of acute cholangitis from choledocholithiasis. In a very sick patient, it is advisable to rapidly establish drainage of the obstructed biliary system by placing a stent or nasobiliary drainage catheter, and later perform an elective ERCP for bile duct clearance. One should remember that patients with obstructed bile ducts are at highest risk of developing septic complications following ERCP, especially when biliary drainage is incomplete [19, 21]. Therefore, if ERCP is unsuccessful especially with retained contrast, urgent biliary drainage percutaneously or with another endoscopist should be performed.

Case Continued

After fluid resuscitation and administration of parenteral broad-spectrum antibiotics, the patient underwent an ERCP which revealed a large amount of thick membranes that were impacted at the papillary orifice (Video 6.1, Fig. 6.2). He underwent a wire-guided biliary sphincterotomy but without any contrast injection in the bile duct. Copious amounts of frank pus and a few membranes spontaneously ejected out of the papilla. Subsequent gentle contrast injection showed a dilated CBD with multiple floating irregular filling defects and a large ovoid filling defect (Fig. 6.3a). There was also a large intrahepatic cavity communicating with the biliary ductal system at the intrahepatic ductal confluence (Fig. 6.3b). Multiple balloon sweeps were performed to clear the CBD resulting in the extraction of multiple membrane-like structures (Video 6.2). A naso-biliary catheter was then inserted to irrigate the cystic cavity with normal saline for 96 h. A contrast-enhanced computed tomography (CECT) of the abdomen revealed pneumobilia and a large intrahepatic thin-walled cystic lesion with air pockets communicating with the biliary ductal system (Fig. 6.4).

How Should Parasitic Biliary Infections Be Managed?

Parasitic infestations of the biliary tract are a common cause of biliary obstruction in tropical countries, which can lead to complications of

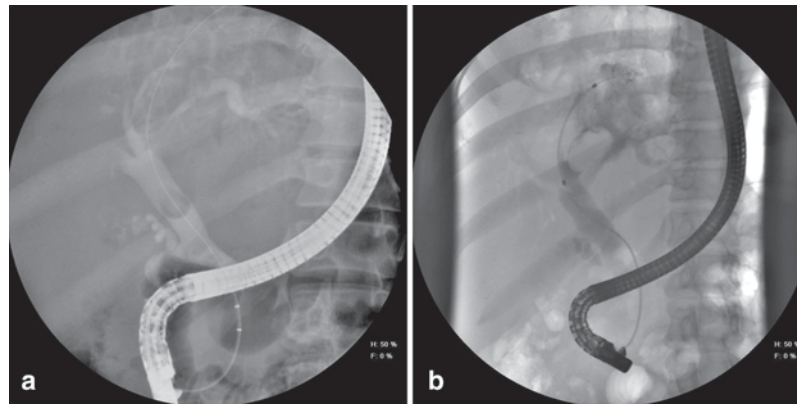

Fig. 6.3 **a** Cholangiogram revealing multiple filling defects (membranes) in the CBD with a large ovoid filling defect near the confluence (daughter cyst). **b** Cholangiogram reveals a large intrahepatic cavity communicating with the intrahepatic ductal system at the level of the ductal confluence

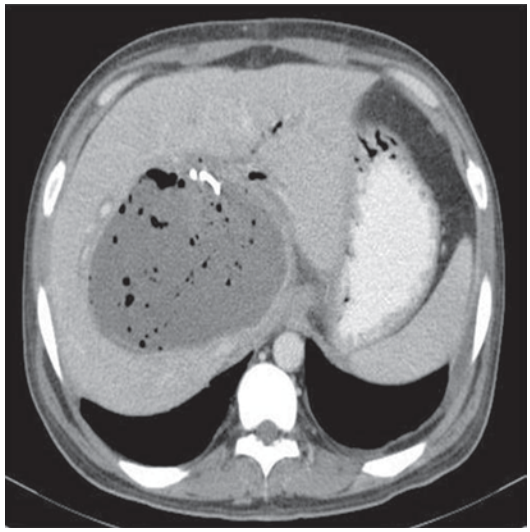

Fig. 6.4 Contrast-enhanced computed tomography revealing a large intrahepatic thin-walled cystic lesion with air pockets that is communicating with the biliary ductal system

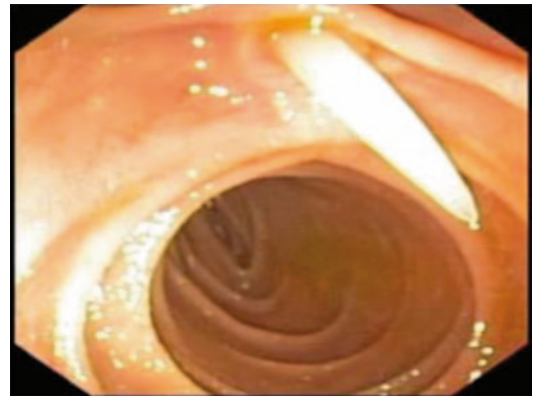

Fig. 6.5 Ascaris worm protruding out of the ampulla in a patient with cholangitis

cholangitis and cholangiocarcinoma. Widespread international travel and immigration have led clinicians in non-endemic countries to encounter these conditions. Ascariasis, hydatidosis, clonorchiasis, opisthorchiasis, and fascioliasis are the common hepato-biliary parasites, which may present with cholestasis, obstructive jaundice, biliary colic, acute cholangitis, and occasionally as pancreatitis. In patients with biliary ascariasis and hydatid disease, radiological assessment usually assists in diagnosis. However, the diagnosis of other biliary parasites (clonorchiasis, opisthorchiasis and fascioliasis) in non-endemic areas always remains a clinical challenge. Medical therapy remains the mainstay of treatment. Endoscopic therapy with biliary sphincterotomy and bile duct clearance is useful in the management of biliary complications caused by these parasites.

Ascariasis

Ascaris lumbricoides or round worm is an actively motile parasite which resides in the proximal small bowel of an infected person. It can invade the papilla and migrate inside the bile duct causing biliary obstruction, cholecystitis, or cholangitis [22]. This migration is enhanced by prior biliary sphincterotomy or bilio-enteric anastomosis [23]. Ascariasis-related biliary disease is common in areas where the rate of Ascaris infection is high. In India, the Kashmir valley is a highly endemic region for ascariasis, exceeding gallstones as a cause of biliary tract disease (37 versus 35%) [24]. Similarly, in Ecuador, which is also endemic for ascariasis, more than 11% of patients with gallbladder or biliary tract complications have ascaris worms in their biliary tract [25]. Biliary ascariasis has been reported to account for 10–19% of ascaris related hospital admissions [24]. Although hepato-biliary ascariasis is common in endemic areas, due to increased and widespread travel and population migration, ascariasis is now a worldwide problem with biliary ascariasis also being reported from non-endemic areas [26, 27].

Diagnosis of biliary ascaris is confirmed by abdominal US or ERCP. Ultrasonographic features suggestive of biliary ascariasis include the presence of long, linear, parallel echogenic structures without acoustic shadowing and the "four lines sign" of non-shadowing echogenic strips with a central anechoic tube representing the digestive tract of the parasite [28].

During endoscopy, the worm can be seen in the duodenum or protruding from the papilla (Fig. 6.5). At ERCP, cholangiographic features of Ascaris worm include the presence of long,

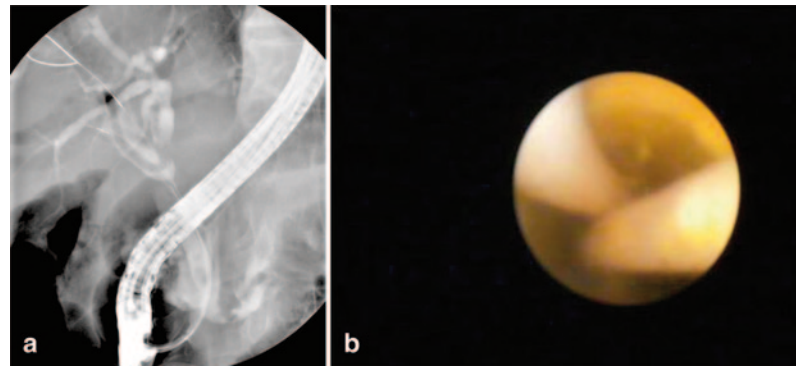

Fig. 6.6 **a** ERCP in a patient with ascariasis reveals a long smooth linear filling defect with a tapered end, located above the mid CBD stricture. **b** Cholangioscopy in the same patient reveals an ascaris worm with folded appearance in the CBD

smooth, linear filling defects with tapering ends (Fig. 6.6a); smooth, parallel filling defects; curves and loops crossing the hepatic ducts transversely; and dilatation of the CBD [29]. With cholangioscopy, the worm can be visualized directly within the bile duct (Fig. 6.6b).

Treatment

Endoscopy is the mainstay of treatment for biliary ascariasis [30–33]. An intact worm is relatively easy to extract when it protrudes out of the papilla. The projecting part of the worm in the duodenum is grasped with a rat tooth or alligator type forceps, and then the endoscope is gradually withdrawn as one unit out of the patient's mouth. A basket can also be used with the outer end of the worm maneuvered into the strings of the basket and gently held before extraction [33]. It is better to avoid the use of a snare for ascaris worm removal, as it often tends to cut the protruding part on tight closure. Remnants of worm inside the CBD can then lead to stone formation, and hence efforts should be made to ensure complete biliary clearance [31].

Extraction of the culprit biliary worm is usually associated with rapid symptom relief and is successful in more than 80% of patients [33, 34]. However, internal biliary migration of the worm may be associated with biliary calculi or strictures, which can be managed during ERCP [32]. Following endoscopic therapy, all patients should receive anti-helminthic medication to eradicate the remaining worms. A single oral dose of albendazole (400 mg) is highly effective against ascariasis [34]. For residents of endemic areas, periodic "de-worming" may have a useful role in preventing recurrence.

Echinococcus Granulosus

The "domestic strain" of Echinococcus granulosus or dog tapeworm is the main cause of human hydatid disease. Infections are found worldwide and remain endemic in sheep raising areas. The life cycle involves two hosts: the adult tapeworm is usually found in dogs (definitive host) while the sheep (intermediate host) are the usual host for larval stages. Human exposure is via oral fecal route. Contaminated food or water having embryonated eggs from the feces of dogs, when accidentally ingested by humans, lead to the infection [35]. The embryonated eggs hatch in the small intestine of humans and liberate oncospheres that migrate through the portal circulation to distant sites. The right lobe of the liver is the most common site for hydatid cyst formation. After infection, the vast majority of humans are usually asymptomatic for a long period of time, since cyst growth in the liver is usually slow with growth rate ranging from 1 to 5 mm in diameter per year [36]. In suspected patients, abdominal imaging with ultrasound or CECT combined with serologic studies usually establishes the diagnosis.

In about 25% of hepatic hydatid patients, the cyst ruptures into the biliary tree causing obstructive jaundice [37, 38]. Contents of the cyst (scolices and daughter cysts) which rupture into biliary tract may cause partial or complete obstruction of bile duct resulting in obstructive jaundice, cholangitis, and sometimes cholangiolytic abscesses.

Rarely, acute pancreatitis complicates intra-biliary rupture of hydatid cyst [39].

Cysto-biliary communication is reported in 10–42 % of patients [40, 41]. Cysto-biliary communications are often recognized at surgery when cysts are stained with bile. Unrecognized cysto-biliary communications may present in the post-operative period as a persistent biliary fistula leading to prolonged hospitalization and increased morbidity.

Treatment

Treatment of hydatid disease involves anti-helminthic therapy (Albendazole) combined with surgical resection of the cyst. Endoscopic intervention plays an important role when intra-biliary rupture of the hydatid cyst occurs [42, 43] or in the management of biliary complications following surgery [30, 44–47].

Intra-biliary rupture is a common but serious complication of hepatic hydatid cyst. This usually occurs because of higher pressure in the cyst of up to 80 cm H_2O [48]. ERCP is indicated when intra-biliary rupture is suspected clinically (because of jaundice), biochemically (because of cholestasis) or sonographically (dilated biliary ductal system in association with hydatid cysts in the liver) [36, 46, 49]. Duodenoscopy occasionally reveals whitish yellow, glistening membranes lying in the duodenum, or protruding from the papilla as observed in the patient presented in this chapter (Video 6.1, Fig. 6.2). On cholangiography, the hydatid cyst remnants may appear as (i) filiform, linear wavy material in the CBD representing the laminated hydatid membranes, (ii) round or oval lucent filling defects representing daughter cysts floating in the common bile duct, or (iii) brown, thick, amorphous debris [47, 50]. Cholangiography often reveals minor communications, particularly with peripheral ducts, which are of unclear clinical significance.

In patients presenting with obstructive jaundice or cholangitis, endoscopic biliary sphincterotomy facilitates extraction of the cysts and membranes using a basket or a biliary stone extraction balloon [51, 52]. Saline irrigation of the bile duct is necessary to flush out the hydatid sand and small daughter cysts. Life-threatening episodes of acute cholangitis can be managed by initial nasobiliary drainage as a temporizing method, followed later by extraction of hydatid cysts and membranes after sphincterotomy. The nasobiliary drain fluid can be examined for hydatid hooklets or membranes. Endoscopic management of acute biliary complications enables definitive surgery to be performed electively. Rarely, rupture of the hydatid cyst can be treated effectively by endoscopy alone [53].

If a hydatid cyst is freely communicating with the biliary ductal system, a hydrophilic guide wire can be negotiated into the cyst; a nasobiliary catheter can then be inserted to facilitate emptying of the cyst contents. Irrigating the cyst using hypertonic saline solution through the nasobiliary catheter ensures sterilization of the germinal layers and also the remaining daughter cysts [54]. However, in extensive disease with multiple communications between the bile duct and cyst, hypertonic saline irrigation should be avoided for fear of causing biliary strictures by seepage of the hypertonic saline solution into the bile duct [55, 56]. There have been only a handful of case reports of successful non-surgical management of complicated hydatid disease using only ERCP and medical therapy [57].

Biliary complications following hydatid liver disease surgery can occur in up to 14–16 % of patients [43, 58]. Early post-operative complications include persistent biliary fistula and obstructive jaundice. Sclerosing cholangitis and sphincter of Oddi stenosis are late post-operative complications. Persistent biliary fistula is a common post-operative complication occurring in 50–63 % of patients following surgery [44, 61]. Unrecognized cysto-biliary communications manifest as persistent biliary drainage through the T-tube or an external biliary fistula in the post-operative period. Low-output fistula (less than 300 ml/day) close spontaneously after a mean duration of 4 weeks. Patient with high-output fistulae require endoscopic intervention [43]. Endoscopic biliary sphincterotomy and ductal clearance followed by biliary stent placement for approximately 4–8 weeks is usually sufficient to achieve fistula closure. Biliary sphincterotomy alone may also be effective [52].

Obstructive jaundice occurs in up to 2% of patients following surgical resection of hydatid cyst. This typically presents within 2–4 weeks of surgery [36, 47, 52, 54]. Obstructive jaundice results from CBD obstruction by echinococcal remnants in the presence of cysto-biliary communication. In such cases, endoscopic biliary sphincterotomy and ductal clearance followed by internal stenting is required for approximately 4–8 weeks to achieve fistula closure.

Sclerosing cholangitis and sphincter of Oddi stenosis are seen in patients in whom formalin is used to sterilize the cysts during surgery. Seepage of formalin into bile ducts through minor communications results in inflammatory changes and stricture formation in the long term. Most scolicidal agents are associated clinically or experimentally with this complication. Among the various scolicidal agents available, hypertonic saline (20%) is most preferred [59, 60]. These complications can be treated endoscopically by biliary sphincterotomy and bile duct stenting with or without dilatation of the stricture using biliary balloons.

Clonorchis Sinensis

Clonorchis sinensis (Opisthorchis sinensis), or Chinese liver fluke, is a trematode (flat worm), commonly found in South East and Far East Asian countries, mainly China, Japan, Korea, Taiwan, and Vietnam. It is estimated that about 35 million people are infected globally, of which about 40% are in China [61]. It harbors in the biliary tract of humans and other fish-eating animals. Liver flukes have a long life span of 10–30 years; which may lead to East Asian immigrants developing clinical features of this infection years or decades after leaving the endemic area [62]. Opisthorchis felineus and Opisthorchis viverrini are other trematodes, which cause similar clinical manifestations.

Clonorchiasis is acquired in humans from eating infested raw fresh water fish (carp and salmon family). The infective metacercariae adhere to the common bile duct and migrate along the epithelial lining of the duct into the intrahepatic ducts, where they mature into flat, elongated, 10–23-mm-long adult worms. The smaller branches of the left lobe of liver are more commonly involved where the adult worm attains maturity in about 1 month and starts laying eggs. The migration of the immature flukes causes trauma, ulceration, and desquamation of the bile duct epithelium. Adenomatous hyperplasia and goblet cell metaplasia develop as a result of epithelial injury and may lead to encapsulating fibrosis of the bile duct. While a single exposure to the parasite is of little significance, repeated exposures provoke diffuse involvement of the biliary tree, including the large bile ducts and gallbladder. The average infection leads to harboring of about 20–200 adult flukes, which can increase up to 20,000 flukes during a heavy infection. Dilated sub-capsular bile ducts, adenomatous ductal hyperplasia with or without periductal fibrosis, and eosinophilic infiltration are seen in early infections. Cirrhosis may develop in patients with repeated infections in later phases. The endemic areas of Clonorchiasis and Opisthorchiasis coincide with the geographical distribution of liver tumors in Southeast Asia, notably that of cholangiocarcinoma [63].

Biliary clonorchiasis has a protean clinical presentation. The majority of patients with low parasite loads remain asymptomatic. Patients with high parasite load present with cholangitis, cholangiohepatitis or intrahepatic calculi. The liver fluke causes mechanical obstruction of bile flow; subsequent bile stasis predisposes to cholangitis which leads to the death of the fluke within the biliary tract. Paroxysms of colicky upper abdominal pain and cholangitis are often confused with gallstone disease. Biliary calculi may coexist as the eggs of parasite acts as a nidus for stone formation. Chronic infection is associated with the development of cholangiocarcinoma.

Clonorchiasis should be suspected in any patient who has lived in or has traveled to an endemic region, consumed raw fresh water fish, and subsequently developed clinical signs consistent with a biliary or hepatic disease.

Treatment

In patients presenting with acute cholangitis, ERCP with biliary sphincterotomy and ductal

decompression is the treatment of choice [64]. Aspirated bile may show adult worms and ova. Cholangiographic features of clonorchiasis include mulberry-like appearance due to multiple saccular or cystic dilatations of the intra-hepatic bile ducts; the "arrow head sign" due to rapid tapering of the intrahepatic bile ducts towards the periphery; and decrease in the number of intrahepatic radicles due to portal and peri-portal fibrosis. Ductal irregularities are due to adenomatous hyperplasia, which vary from small indentations to hemispherical filling defects. A scalloped appearance is seen as filamentous, wavy, and elliptical shaped filling defects. Endoscopic biopsy or brush cytology is indicated whenever cholangiocarcinoma is suspected. Surgical intervention is indicated in patients with hepatolithiasis complicated by multiple biliary strictures.

All patients with biliary clonorchiasis should receive Praziquantel (75 mg/kg per day in three divided doses for 2 days) to eradicate the infection. Biliary ductal abnormalities usually persist even after successful drug therapy [65].

Fasciola Hepatica

Fascioliasis is caused by the trematode Fasciola hepatica, the sheep liver fluke. The adult worm is flat, leaf-shaped, measuring 30 × 13 mm, and resides in the intrahepatic biliary tract. The definitive host is sheep, making this an important veterinary disease. A wide variety of mammalian ruminants (goats, cattle, horses, camels, hogs, rabbits, and deer) are also commonly infested. Intermediate hosts include numerous species of snail, both amphibious and aquatic forms. Due to the wide range of definitive and intermediate hosts, the disease is geographically widespread and occurs worldwide. Physicians should therefore be aware of the possibility of infection in all geographical areas. Peru and Bolivia have reportedly the highest endemicity [66].

Fascioliasis occurs where watercress (plant that grows in water and has leaves that are eaten in salads and sandwiches) is common and hence is epidemiologically linked to the distribution of the intermediate snail host populations in freshwater areas. Human infection occurs following ingestion of watercress that is infested with metacercariae, the infective form of the fluke. These larvae pass through the duodenal wall into the peritoneal cavity and migrate toward the liver.

Fascioliasis occurs in two stages. First, the "acute or hepatic" phase of illness occurs when the organism (metacercariae) penetrates the liver capsule and migrates through the numerous tracts in the liver parenchyma to finally lodge in the biliary tract where they mature into adult flukes. In the acute phase patients usually present with dyspepsia followed by an acute onset of fever and abdominal pain, particularly in the right upper quadrant. Urticaria and eosinophilia may be present. These symptoms are due to the inflammatory response caused by the migrating larvae. In about half of acute phase cases, the infection remains subclinical. This acute phase usually lasts for 3 months following ingestion of the metacercariae.

The second is the "chronic or biliary" phase which occurs when the parasite enters the biliary tract about 3–4 months after ingestion of the contaminated meal. Patients typically present with jaundice, fever, and right upper quadrant pain. Rare manifestations are acalculous cholecystitis, severe hemobilia, and acute pancreatitis [67, 68]. In the chronic stage, motile flukes may be visualized in the gallbladder. Liver function tests reflect a cholestatic picture. Serological tests (FAST-enzyme linked immunosorbent assay [ELISA]/Falcon assay screening test or dot blot ELISA) are highly sensitive (95–100%) and specific (97%) for diagnosis.

Inflammation due to toxic metabolites and mechanical effects of the larvae in the bile ducts leads to epithelial necrosis and adenomatous changes, eventually leading to biliary fibrosis. These changes further evolve into cystic dilatation, total or partial obstruction of bile ducts, periportal fibrosis and cirrhosis. Although the fibrotic changes are likely to persist despite successful therapy, some of the ductal changes are reversible. The adult form has a life span of approximately 9–13 years. Eggs or dead parasites can form a nidus for calculus formation, potentially leading to intra or extrahepatic biliary calculi.

Treatment

Oral drug therapy is the standard treatment for hepatic fascioliasis. Triclabendazole (10 mg/kg as a single dose) is the drug of choice. In severe or persistent infections, two doses of 10 mg/kg administered orally 12–24 h apart is recommended [69]. An alternative drug is Bithionol (30–50 mg/kg on alternate days for 10–15 doses). Patients should be advised about biliary colic during therapy caused by expulsion of parasites or parasite fragments, which usually occur 2–7 days after starting the medications.

Endoscopic therapy is required when biliary complications occur or medical therapy fails and in management of severe infection with multiple worms. During ERCP, Fasciola appear as small, radiolucent linear, or crescent-like shadows with jagged, irregular margins in the gallbladder or in dilated bile ducts [70]. Biliary fascioliasis has also been diagnosed on EUS, which shows a dilated common bile duct containing a floating, linear structure [71]. The worms can be extracted by using a balloon catheter or basket following biliary sphincterotomy. Patients usually harbor a single Fasciola worm in the bile duct with an occasional one in the gallbladder. When worms are present in the gallbladder or in the intrahepatic biliary radicles where they are not amenable to mechanical extraction, irrigating the biliary system with 20 ml of 2.5% povidone iodine solution (5 ml of 10% povidone iodine plus 15 ml of contrast material) during ERCP is helpful [72]. Bile aspirated may be examined for parasite eggs. It is essential to achieve adequate drainage particularly in patients with acute cholangitis.

The successful management of "massive forms" of biliary fascioliasis, where dozens or hundreds of mature parasites reside in the intrahepatic and extrahepatic ducts, has been described [73]. The initial step is extraction of parasites in the CBD with a basket or balloon catheter, followed by 10-minute instillation of 20 ml of 2.5% povidone iodine solution (5 ml of 10% povidone iodine plus 15 ml of contrast material) with balloon occlusion of the common hepatic duct. The ducts are then washed with saline solution, and the dead parasites are removed with a basket or balloon. Repeat treatment may be required for complete parasite clearance. In cases with cholangitis and liver abscesses, nasobiliary drain with povidone iodine flushing repeated three times under direct fluoroscopic control may be beneficial.

Recurrent Pyogenic Cholangitis

Recurrent Pyogenic Cholangitis, also known as "intrahepatic stone disease" and "Oriental cholangiohepatitis," was originally described in the natives of Hong Kong in the 1930s. This disease is a recognized common problem in East and Southeast Asia, especially Taiwan, Japan, Korea, Vietnam, Malaysia, Singapore, and the Philippines [74]. It has also been reported in India, Mexico, and Central and South America and among Caucasians [75]. Recent trends in Asian immigration have led to increases in the prevalence and recognition of this condition in the United States [76]. Recurrent pyogenic cholangitis affects both sexes equally and occurs in all ages.

The cause of recurrent pyogenic cholangitis is unknown, although the disease originates in the intrahepatic bile ducts. Bacterial infection of the biliary tree by way of the portal vein is postulated to be the crucial, if not the inciting event. The enteric bacteria that enter the biliary tract possess beta glucuronidase activity and cause the deconjugation of bilirubin glucuronide. The deconjugated bilirubin precipitates with calcium in the bile and forms insoluble calcium bilirubinate or bilirubin-pigment stones, which are characteristically soft, brown, and friable [77]. Intrahepatic stone formation is then thought to initiate a cycle of recurrent cholangitis and the formation of additional stones.

The predisposing factors to biliary tract infection in recurrent pyogenic cholangitis are not well understood. The high rate of infestation with biliary parasites such as Clonorchis sinensis and Ascaris lumbricoides found in some series suggests that these parasites induce ductal injury and stricture formation by evoking an exuberant inflammatory response and that secondary pyogenic infection leads to stone formation and recurrent

cholangitis [78, 79]. However, parasites are recovered from stool specimens in only 5–25 % of patients with recurrent pyogenic cholangitis [80].

With this disease, there is intense periductal inflammation, fibrosis, portal tract edema, strictures, and biliary ductal dilatation. In advanced stages, the intrahepatic ducts may become cysts filled with stones or sludge, resembling the cysts seen in Caroli's disease. Intrahepatic pyogenic abscesses, sometimes accompanied by aerobilia, may develop. The abscesses may be monomicrobial or polymicrobial. Cultures may yield either aerobic or anaerobic enteric bacteria or both. Often, the abscesses do not obviously communicate with the biliary tree because of superimposed obstruction.

The clinical presentation of recurrent pyogenic cholangitis is often an initial episode of cholangitis in 15–33 % of cases [81]. Fever or sepsis may result from cholangitis, abscess formation, or pylephlebitis. The disease may be mistaken for acute cholecystitis, and many patients (60 % in one series) have a history of cholecystectomy without a finding of gallstones [82]. Cholangiographic examination reveals stones in the intrahepatic bile ducts in nearly all patients and in the extrahepatic ducts in many. For unknown reasons, the intrahepatic stones occur more often in the left ductal system. The CBD is thickened and may also be dilated.

Since obstruction and infection hasten the progression of recurrent pyogenic cholangitis, therapeutic goals include the complete clearance of biliary calculi and debris and adequate drainage of the affected segments of the biliary tree. Although ERCP is useful in the assessment of anatomical discontinuity and in the management of disease confined to the CBD, its role in the treatment of intrahepatic calculi has been limited, which typically requires surgical management [82].

Case Follow-Up

In the patient presented earlier, the presence of a daughter cyst (ovoid filling defect) and membranes in the common bile duct along with an intrahepatic cystic lesion communicating with the biliary ductal system was highly suggestive of hydatid disease. The diagnosis was confirmed by ELISA and indirect hemagglutination. The patient was stabilized with biliary decompression and treated with albendazole 400 mg twice a day. He underwent elective surgical resection of the intrahepatic cyst and was doing well at 6-month follow-up.

Key Points

- Acute cholangitis is a medical emergency that requires urgent ERCP for biliary decompression.
- While gram-negative organisms are the most common cause of cholangitis, in endemic areas parasitic infections must be considered in the differential diagnosis.
- It is important to have basic knowledge of common parasites that can cause biliary obstruction, recognize clinical manifestations, and know how to initiate appropriate diagnostic work-up.
- In addition to endoscopic biliary decompression, correct anti-parasitic medication regimen must be administered to eradicate the organism.

Video Captions

Video 6.1 Thick hydatid membranes are seen protruding from the ampulla at duodenoscopy

Video 6.2 Extraction of hydatid worm membranes at ERCP

References

1. O'Connor MJ, Schwartz ML, McQuarrie DG, Sumer HW. Acute bacterial cholangitis: an analysis of clinical manifestation. Arch Surg. 1982;117:437–41.
2. Boey JH, Way LW. Acute cholangitis. Ann Surg. 1980;191:264–70.
3. Kinney TP. Management of ascending cholangitis. Gastrointest Endosc Clin N Am. 2007;17(2):289–306.
4. Hanau LH, Steigbigel NH. Acute (ascending) cholangitis. Infect Dis Clin North Am. 2000;14:521–46.
5. Kochar R, Banerjee S. Infections of the biliary tract. Gastrointest Endosc Clin N Am. 2013;23:199–218.

6. Kiriyama S, Takada T, Strasberg SM, et al. Tokyo guidelines revision committee. New diagnostic criteria and severity assessment of acute cholangitis in revis Tokyo guidelines. J Hepatobiliary Pancreat Sci. 2012;19:548–56.
7. Charcot M. De la fievre hepatique symptomatique. Comparison avec la fievre uroseptique. Lecons sur les maladies du foie des voies biliares et des reins. [Of symptomatic hepatic fever. Comparison with uroseptic fever. Lessons on diseases of the liver, biliary tract and kidneys]. Paris: Bourneville et Sevestre; 1877.pp. 176–85
8. Reynolds BM, Dargan EL. Acute obstructive cholangitis: a distinct clinical syndrome. Ann Surg. 1987;205:389–92.
9. Varghese JC, Liddell RP, Farrell MA, et al. Diagnostic accuracy of magnetic resonance cholangio pancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. Clin Radiol. 2000;55:25.
10. Soto JA, Alvarez O, Munera F, et al. Diagnosing bile duct stones: comparison of unenhanced helical CT, oral contrast-enhanced CT cholangiography, and MR cholangiography. Am J Roentgenol. 2000;175:1127.
11. Tseng CW, Chen CC, Chen TS, et al. Can computed tomography with coronal reconstruction improve the diagnosis of choledocholithiasis. J Gastroenterol Hepatol. 2008;23:1586.
12. Verma D, Kapadia A, Eisen GM, et al. EUS vs MRCP for detection of choledocholithiasis. Gastrointest Endosc. 2006;64:248.
13. Ledro-Cano D. Suspected choledocholithiasis: endoscopic ultrasound or magnetic resonance cholangio-pancreatography? A systematic review. Eur J Gastroenterol Hepatol.2007;19:1007.
14. Zidi SH, Prat F, LeGuen O, et al. Use of magnetic resonance cholangiography in the diagnosis of choledocholithiasis: prospective comparison with a reference imaging method. Gut. 1999;44:118.
15. Qureshi WA. Approach to the patient who has suspected acute bacterial cholangitis. Gastroenterol Clin North Am. 2006;35:409–23.
16. Chen MF, Jan YY, Lee TY. Percutaneous transhepatic biliary drainage for acute cholangitis. Int Surg. 1987;72:131–3.
17. Melzer M, Toner R, Lacey S, Bettany E, Rait G. Biliary tract infection and bacteraemia: presentation, structural abnormalities, causative organisms and clinical outcomes. Postgrad Med J. 2007;83:773–6.
18. Englesbe MJ, Dawes LG. Resistant pathogens in biliary obstruction: importance of cultures to guide antibiotic therapy. HPB (Oxford). 2005;7:144–8.
19. Mosler P. Diagnosis and management of acute cholangitis. Curr Gastroenterol Rep. 2011;13:166–72.
20. Khashab MA, Tariq A, Tariq U, et al. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. Clin Gastroenterol Hepatol. 2012;10:1157–61.
21. Deviere J, Motte S, Dumonceau JM, Serruys E, Thys JP, Cremer M. Septicemia after endoscopic retrograde cholangiopancreatography. Endoscopy. 1990;22:72–5
22. Khuroo MS. Ascariasis. Gastroenterol Clin N Am. 1996;25:553–77.
23. Khuroo MS, Mahajan R, Zargar SA, et al. Biliary and pancreatic ascariasis: a long term follow up. Natl Med J India. 1989;2:4–8.
24. Khuroo MS, Zargar SA. Biliary ascariasis: a common cause of biliary and pancreatic disease in endemic area. Gastroenterology. 1985;88:418–23.
25. Kamiya T, Morishita T, Peredo R, et al. Duodenoscopic management in biliary ascariasis. Dig Endosc. 1993;5:179–82.
26. Misra SP, Dwivedi M. Clinical features and management of biliary ascariasis in a non-endemic area. Postgrad Med J. 2000;76:29–32.
27. Valentine CC, Hoffner RJ, Henderson SO. Three common presentations of ascariasis infection in an urban emegency department. J Emerg Med. 2001;20:135–9.
28. Khuroo MS, Zargar SA, Mahajan R, Bhat RL, Javid G. Sonogaphic appearances in biliary ascariasis. Gastoenterology. 1987;93:276–72.
29. Reddy DN, Rao GV, Ong WC, Banerjee R. Parasitic disease: endoscopic diagnosis and management of tropical parasitic infestations. In: Baron T, Kozarek R, Carr-Locke DL, editors. ERCP. (Ed 1). Philadelphia: Elsevier. p. 393–8.
30. Al Karawi M Sanai FM Yasawy MI Mohammed AE. Biliary strictures and cholangitis secondary to ascariasis: endoscopic management. Gastrointest Endosc. 1999;50:695–7.
31. Beckingham IJ, Cullis SN, Krige JE, Bornman PC, Terblanche J. Management of hepatobiliary and pancreatic ascarisis infestation in adults after failed medical treatment. Br J Surg. 1998;85:907–10.
32. Misra SP, Dwivedi M. Endoscopy—assisted emergency treatment of gastroduodenal and pancreatobiliary ascariasis. Endoscopy. 1996:28:629–32.
33. Sandouk F, Haffar S, Zada MM, Graham DY, Anand BS. Pancreatic-biliary ascariasis: experience of 300 cases. Am J Gastroenterol. 1997;92:2264–7.
34. Albonico M, Smith PG, Hall A, Chwaya HM, Alawi KS, Savioli L. A randomized controlled trial comparing mebendazole and albendazole against Ascaris, Trichuris and hookworm infections. Trans R Soc Trop Med Hyg. 1994;88:585–9.
35. Reather W, Hanel H. Epidemiology, clinical manifestations and diagnosis of zoonotic cestode infections: an update. Parasitol Res. 2003;91:412–38.
36. Gruttadauria S. Hepatic echinococcosis: clinical and therapeutic aspects. World J Gastroenterol 2012; 18: 1448–58.
37. Dadoukis J, Gamvros O, Aletras H. Intrabiliary rupture of the hydatid cyst of the liver. World J Surg. 1984;8:786–90.
38. Erzurumlu K, Dervisoglu A, Polat C, et al. Intrabiliary rupture: an algorithm in the treatment of contro-

versial complication if hepatic hydatidosis. World J Gastroenterol. 2005;11:2472–6.
39. Toma AA, Vermeijden RJ, Van De WA. Acute pancreatitis complicating intrabiliary rupture of liver hydatid cyst. Eur J Intern Med. 2004;15:65–7.
40. Agarwal S, Sikora SS, Kumar A, Saxena R, Kapoor VK. Bile leaks following surgery for hepatic hydatid disease. Indian J Gastreenterol. 2005;24:55–8.
41. Simsek H, OZaslan E, Sayek I, Savas C, Abbasoglu O, Soylu AR, et al. Diagnostic and therapeutic ERCP in hepatic hypatic hydatid disease. Gastrointest Endosc. 2003;58:384–9.
42. Karawi MA, Mohamed AR, Yasawy I, Haleem A. Non-surgical endoscopic trans-papillary treatment of ruptured echinococcus liver cyst obstructing the biliary tree. Endoscopy. 1987;19:81–3
43. Karawi MA, Yasawy MI, Shiek Mohamed AR. Endoscopic management of biliary hydatid disease: report on six cases. Endoscopy. 1991;23:278–81.
44. Zargar SA, Khuroo MS, Khan BA, Dar MY, Alai MS, Koul P. Intrabiliary rupture of hepatic hydatid cyst: sonographic and cholangiographic appearances. Gastrointest Radiol. 1992;17:41–5.
45. Spiliadis C, Georgopoulos S, Dailianas A, Konstantinidis A, Rimikis M, Skandalis N. The use of ERCP in the study of patients with hepatic echinococcosis before and after surgical intervention. Gastrointest Endosc. 1996;43:575–9
46. Rodriguez AN, Sanchez del Rio AL, Alguacil LV, Dios Vega JF, Fugarolas GM. Effectiveness of endoscopic sphincterotomy in complicated hepatic hydatid disease. Gastrointest Endosc. 1998;48:593–7.
47. Saritas U, Parlak E, Akoglu M, Sahin B. Effectiveness of endoscopic treatment modalities in complicated hepatic hydatid disease after surgical intervention. Endoscopy. 2001;33:858–63.
37. Dadoukis J, Gamvros O, Aletras H. Intrabiliary rupture of the hydatid cyst of the liver. World J Surg. 1984;8:786–90.
49. Iscan M, Duren M. Endoscopic sphincterotomy in the management of postoperative complications of hepatic hydatid disease. Endoscopy. 1991;23:282–3.
50. Busic Z, Amic E, Servis D, Predrijevac M, Stipancic I, Busic D. Common bile duct obstruction caused by the hydatid daughter cysts. Coll Antropol. 2004;28:325–9.
51. Tekant Y, Bile O, Acarli K, Alper A, Emre A, Ariogul O. Endoscopic sphincterotomy in the treatment of postoperative biliary fistulas of hepatic hydatid disease. Surg Endosc. 1996;10:909–11.
46. Rodriguez AN, Sanchez del Rio AL, Alguacil LV, Dios Vega JF, Fugarolas GM. Effectiveness of endoscopic sphincterotomy in complicated hepatic hydatid disease. Gastrointest Endosc. 1998;48:593–7.
53. Hilmioglu F, Karincaoglu M, Yilmaz S, Yildirim B, Kirimlioglu V, Aladag M, et al. Complete treatment of ruptured hepatic cyst into biliary tree by ERCP. Dig Dis Sci. 2001;46:463–7.
54. Al Karawi MA, Yasawy MI, Shiek Mohamed AR. Endoscopic management of biliary hydatid disease: report on six cases. Endoscopy. 1991;23:278–81.
55. Belghiti J, Benhamou JP, Houry S, Grenieer P, Huguier M, Fekete F. Caustic sclerosing cholangitis. A complication of the surgical treatment of hydatid disease of the liver. Arch Surg. 1986;121:1162–5.
56. Belghiti J, Perniceni T, Kabbej M, Fekete F. Complication of preoperative sterilization of hydatid cysts of the liver. Apropos of 6 cases. Chirurgie. 1991;117:343–6.
57. Khoshbaten M, Farhang S, Hajavi N. Endoscopic retrograde cholangiography for intrabiliary rupture of hydatid cyst. Digestive Endoscopy. 2009;21:277.
58. Bilse Y, Bulut T, Yamaner S, Buyukuncu Y, Buyukuncu Y, Bugra D, Akyuz A, et al. ERCP in the diagnosis and management of complications after surgery for hepatic echinococcosis. Gastrointest Endosc. 2003;57:210–3.
59. Sahin M, Eryilmaz R, Bulbuloglu E. The effect of scolicidal agents on liver and biliary tree (experimental study). J Invest Surg. 2004;17:323–6
60. Tozar E, Topeu O, Karayalcin K, Akbay SI, Hengirmen S. The effects of cetrimide-chlorhexidine combination on the hepato-pancreatico-biliary system. World J Surg. 2005;29:754–8.
61. Lun ZR, Gasser RB, Lai DH, Li AX, Zhu XQ, Yu ZB, et al. Clonorchiasis: a key foodborne zoonosis in China. Lancet Infect Dis. 2005;5:31–41.
62. Stauffer WM, Sellman JS, Walker PR. Biliary liver flukes (Opisthorchiasis and Clonorchiasis) in immigrants in the United States: often subtle and diagnosed years after arrival. J Travel Med. 2004;11:157–9
63. Srivatanakul P, Sriplung H, Deerasamee S. Epidemiology of liver cancer: an overview. Asian Pac J Cancer Prev. 2004;5:118–25.
64. Navab F, Diner WC, Westbrook KC, Kumpuris DD, Uthman EO. Endoscopic biliary lavage in a case of Clonorchis sinensis. Gastrointest Endosc. 1984;30:292–4
65. Leung JW, Sung JY, Banez VP, Wu ZM, Agas FV Jr, Ling TK, et al. Endoscopic cholangiopancreatography in hepatic clonorchiasis—a follow-up study. Gastrointest Endosc. 1990;36:360–3.
66. Mas-Coma MS, Esteban JG, Bargues MD. Epidemiology of human fascioliasis: a review and proposed new classification. Bull World Health Organ. 1999;77:340–6.
67. Badalov N, Anklesaria A, Tenner S. Fasciola hepatica causing acute pancreatitis complicated by biliary sepsis. Gastroint Endosc. 2009;70 386.
68. Dias LM, Silva R, Viana HL, Palhinhas M, Viana L. Biliary fascioliasis: diagnosis, treatment and follow-up by ERCP. Gastrointest Endosc. 1996;43:616–20.
69. Saba R, Korkmaz M. Human fascioliasis. Clin Microbiol Newslett. 2005;27:27–34.
70. Hauser SC, Bynum TE. Abnormalities on ERCP in a case of human fascioliasis. Gastrointest Endosc. 1984, 30:80–2.

71. Gandhi V, Jain P, Rathod V, Nagral S. Endoscopic ultrasound in biliary fasciolosis. Indian J Gastroenterol. 2010;29:128.
72. Dowidar B, EI Sayad M, Osman M, Salem A. Endoscopic therapy of fascioliasis resistant to oral therapy. Gastrointest Endosc. 1999;50(3):345–51.
73. Roig GV. Hepatic fascioliasis in the Americas: a new challenge for therapeutic endoscopy. Gastrointest Endosc. 2002;56(2):315–7.
74. Nakayama F, Koga A. Hepatolithiasis: present status. World J Surg. 1984;8:9–14.
75. Turner WW Jr, Cramer CR. Recurrent oriental cholangiohepatitis. Surgery. 1983;93:397–401.
76. Carmona RH, Crass RA, Lim RC Jr, Trunkey DD. Oriental cholangitis. Am J Surg. 1984;148:117–24
77. Tabata M, Nakayama F. Bacteria and gallstones: etiological significance. Dig Dis Sci. 1981;26:218–24.
78. Fung J. Liver fluke infestation and cholangio-hepatitis. Br J Surg. 1961;48:404–15.
79. Seel DJ, Park YK. Oriental infestational cholangitis. Am J Surg. 1983;146:366–70.
80. Ong GB. A study of recurrent pyogenic cholangitis. Arch Surg. 1962;84:199–225.
81. Harris HW, Kumwenda ZL, Sheen-Chen SM, Shah A, Schecter WP. Recurrent pyogenic cholangitis. Am J Surg. 1998;176:34–7.
82. Lam SK. A study of endoscopic sphincterotomy in recurrent pyogenic cholangitis. Br J Surg. 1984;71:262–6.

Diagnosing Biliary Strictures and Indeterminate Biliary Strictures

7

Mansour A. Parsi and John J. Vargo

Case Presentation

A 54-year-old man with known primary sclerosing cholangitis (PSC) presented to his hepatologist with jaundice. He was diagnosed with ulcerative colitis and PSC 13 years ago. Since his initial diagnosis, he had undergone several endoscopic retrograde cholangiopancreatography (ERCP) procedures. The most recent ERCP was approximately a year ago during which intrahepatic ductal changes of beading and strictures consistent with PSC were seen on the cholangiogram. The ERCP also showed small stones in the biliary tree that were successfully removed by sweeping the ducts. At that time there were no dominant strictures that required endoscopic treatment.

His current episode of jaundice started rather abruptly a few days prior to his presentation. At presentation, his major complaint was diffuse itching of the skin. His weight had been stable. Serum bilirubin was elevated at 8.6 with alkaline phosphatase 432. Serum CA 19-9 was also increased at 236. What should be the next step?

Non-invasive Investigation of Biliary Strictures

What Clues from the History and Laboratory Data Aid in Diagnosing Biliary Strictures?

History

The differential diagnosis of biliary strictures is broad (Table 7.1) In some cases clues in a patient's history such as advanced age, significant weight loss or rapid onset of jaundice especially when painless, makes presence of malignancy more likely. On the other hand, a stricture after a complicated gallbladder surgery or history of liver transplantation with duct-to-duct anastomosis is suggestive of a benign post-surgical etiology, history of inflammatory bowel disease may indicate presence of PSC, history of alcohol abuse may suggest chronic pancreatitis and existence of other autoimmune disorders may suggest presence of autoimmune cholangitis or pancreatitis. Although historical clues by themselves cannot establish a diagnosis, they affect the pretest probability of the disease and influence choice of further diagnostic tests (Table 7.2) Historical and clinical data such as presence of other comorbid conditions may also affect the degree of aggressiveness for pursuing a final diagnosis. For instance, in a debilitated elderly patient who is not a surgical candidate, establishing the benign or malignant nature of a biliary

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Table 7.1 Differential diagnosis of biliary strictures

Benign	Malignant
Inflammatory	*Primary Cancer*
Primary sclerosing cholangitis	Pancreatic
Chronic pancreatitis	Biliary
Acute pancreatitis	Hepatocellular
Recurrent cholangitis	Ampullary
Gallstone induced	Gallbladder
Autoimmune (cholangitis or pancreatitis)	
Iatrogenic	*Metastatic Cancer*
Post cholecystectomy	Intrahepatic
Liver transplantation	Hilar lymph nodes
Other	*Systemic Cancer*
Papillary stenosis	Lymphoma
Ischemia	
Radiation therapy	
Pancreatic cysts	
Mirizzi syndrome	

Table 7.2 Historic and demographic clues and increased pretest probability of underlying conditions

Historic/demographic clue	Increased likelihood of underlying pathology
Age (>60)	Cholangiocarcinoma
IBD (Ulcerative colitis or Crohn's disease)	Primary sclerosing cholangitis
Complicated gallbladder surgery (bile leak, conversion to open surgery, excessive use of clips)	Iatrogenic biliary stricture
Liver transplant recipient	Benign anastomotic or ischemic stricture
Young female with autoimmune disorders	Autoimmune cholangitis or pancreatitis
Recurrent cholangitis	Benign stricture due to chronic inflammation
Radiation treatment in the right upper quadrant of the abdomen	Radiation induced stricture

IBD inflammatory bowel disease

stricture may not affect the treatment strategy and thus may be of little or no value.

Laboratory Work Up

Among the serum tumour markers used for differentiating benign from malignant biliary strictures, carbohydrate antigen 19-9 (CA19-9) is the most widely used and studied. CA19-9 has been reported to have wide variation in sensitivity (50–90%) and specificity (54–98%) for distinguishing between benign and malignant strictures [1–3]. This wide variation likely results from differences in patient populations and the cut-off levels utilized for determining the outcome measures across studies. Although there is no agreement on the best threshold for diagnosing malignancy, higher cut-off levels offer increased specificity (lower false positive results) at the cost of lower sensitivity (higher false negative results).

In a review article published in 1990, Steinberg identified 24 studies that compared serum CA 19-9 levels in patients with pancreatic cancer and controls. Combining data from the 24 studies, at a cut-off point of 37 U/mL, CA 19-9 was found to have an overall sensitivity of approximately 80% and specificity of 90% [4]. Increasing the cut-off point to 100 U/mL increased the specificity to 98% but reduced the sensitivity of the test to 68%. At a cut-off point of 1000 U/mL, specificity approached 100% but sensitivity was further reduced to only 41% [4].

A similar article published in 2007 reviewed studies published from 1990 (the time of Steinberg's review) to 2005 that had compared CA 19-9 levels in pancreatic cancer patients versus controls [5]. Combining data from 22 studies including 2283 patients showed a median sensitivity of 79% (range 70–90%) and a median specificity

of 82% (range 68–91%) for diagnosing pancreatic cancer using CA 19-9 as a tumour marker.

The authors noticed that presence of jaundice increased the number of false positive results and thus led to a fall in specificity of the test. Other studies have shown that CA 19-9 may be falsely elevated in benign biliary disease or cholangitis, with levels falling after relief of biliary obstruction or sepsis [6–10]. It has therefore been suggested that elevated CA 19-9 levels should be reassessed after biliary stenting and relief of biliary obstruction or cholangitis [5, 11].

Serum CA 19-9 levels may be increased in non-pancreaticobiliary malignancies such as ovarian cancer, colon cancer and gastric cancer [12, 13]. In addition, elevated serum CA 19-9 levels have been reported in various benign conditions such a thyroiditis, lung disease, diabetes mellitus and ovarian cysts [14–20]. There are even reports that smoking status may influence serum CA 19-9 levels [21]. Furthermore, in approximately 5–10% of the population who are negative for the Lewis antigen, CA19-9 is virtually undetectable [4, 5, 22]. Although CA 19-9 is not a reliable marker for diagnosing malignant strictures, the test performs better when the levels are high in the absence of jaundice.

Several other potential tumour markers in the serum, bile and urine have been suggested to be more sensitive and specific than CA 19-9; however, the studies indicating their accuracy have not been replicated and their role in clinical practice remains uncertain [23–25].

Utility of Radiology Imaging in Differentiating Benign from Malignant Biliary Strictures

Cross-Sectional Imaging

Transabdominal ultrasound is frequently the initial diagnostic modality for investigation of suspected biliary pathology because of its non-invasiveness, widespread availability and relatively low cost. Dilated ducts on ultrasound are highly suggestive of biliary obstruction. Hilar lesions usually cause intrahepatic ductal dilatation with normal caliber extrahepatic ducts, while more distal lesions cause both intrahepatic and extrahepatic ductal dilatation. Although transabdominal ultrasound is a relatively accurate test for evaluation of ductal dilatation, it cannot accurately determine the etiology of an obstruction or reliably examine the distal part of the common bile duct, which is often obscured by air in the bowel [26, 27].

Abdominal CT is probably the most commonly used imaging modality for investigation of hepatobiliary pathology. Although CT is excellent for differentiating between resectable and unresectable tumours by demonstrating the location of the tumour and abdominal vessels on different imaging planes with high spatial resolution, it has suboptimal sensitivity for the detection of early tumours and for differentiating benign from malignant strictures in the absence of a focal mass [27].

Since its first description in 1991, magnetic resonance cholangiopancreatography (MRCP) has evolved as a non-invasive alternative to ERCP for diagnosis of biliary disorders [28, 29]. MRCP takes advantage of the difference in T2-weighted signal intensity between bile and surrounding structures. While bile has a high signal intensity on T2-weighted images, the surrounding structures do not enhance and can be suppressed during image analysis [30]. MRCP can demonstrate the site and extent of biliary strictures with a reported sensitivity of 91–100% (Fig. 7.1) [29]. In patients with PSC, MRCP is not as sensitive as ERCP in the detection of early changes, but is useful for follow-up of established cases [29]. On MRCP, a typical benign stricture involves a short segment with a regular margin and symmetric narrowing, while malignancy is suggested by long (>10 mm), asymmetric and irregular strictures [29, 31]. However, these criteria are neither sensitive nor specific to reliably distinguish malignant from benign strictures [27, 32, 33].

The “double duct sign” refers to simultaneous dilatation of the common bile and pancreatic ducts. Although this sign was initially described by ERCP, nowadays it is more commonly detected by other imaging modalities such as MRCP, CT or ultrasound [34]. The classic double-duct sign was thought to be pathognomonic of a

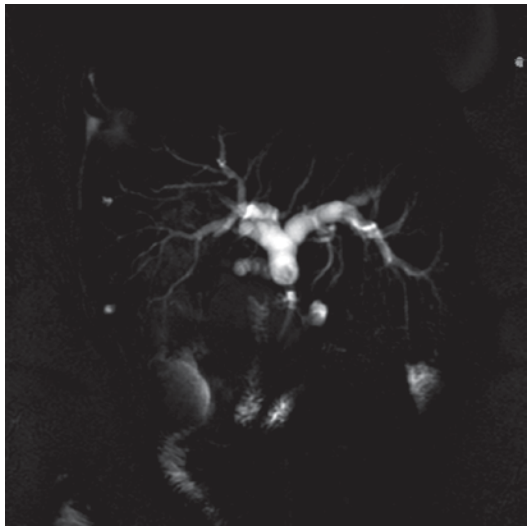

Fig. 7.1 MRCP image showing a near-occlusive stricture in the distal common hepatic duct with dilatation of the ducts proximal to the stricture

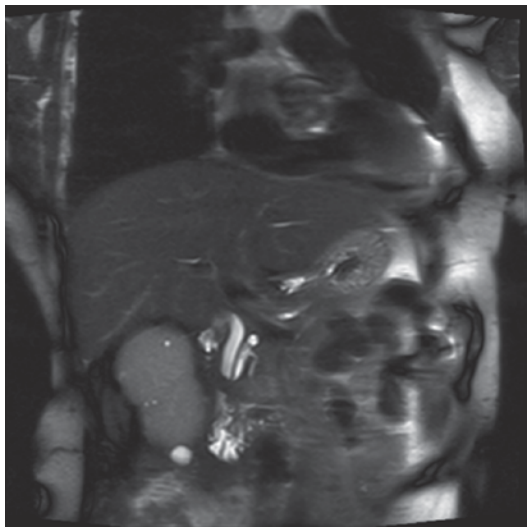

Fig. 7.2 MRI coronal image of dilated bile and pancreatic ducts (*double duct sign*) due to a benign obstruction at the level of the ampulla

malignant process involving the distal bile duct or pancreatic duct [35]. However, we know now that many patients with a double duct sign have benign disease (Fig. 7.2) [35, 36].

Case Continued

Radiologic imaging was indicated. Dual phase computed tomography (CT) of the abdomen was obtained and revealed no focal mass. Diffuse moderate intrahepatic biliary dilation was visualized. Now what?

Invasive Investigation of Biliary Strictures

What Cholangiographic Features Help Differentiate Benign From Malignant Biliary Strictures?

Endoscopic Retrograde Cholangiopancreatography

ERCP was first reported by McCune et al. in 1968 [37]. Since that time, ERCP has transformed from a mere diagnostic test to a predominantly therapeutic procedure. In the USA alone, approximately half a million ERCP procedures are performed annually. Currently, ERCP is the most widely used endoscopic procedure for evaluation of bile duct strictures [38].

On ERCP, certain cholangiographic features are suggestive of malignancy. Reported features associated with malignancy include longer length of the stricture, an abrupt transition point, irregular margins, shelf-like appearance and asymmetric narrowing of the stricture (Figs. 7.3 and 7.4) [39, 40]. Two studies have suggested that in patients with biliary stricture, intrahepatic ductal dilatation is more likely to be seen in the setting of malignancy [39, 41]. Concentric appearance and smooth transition of a stricture, on the other hand, are suggestive of a benign underlying process (Figs. 7.5 and 7.6) [31, 32]. Cholangiographic appearance of a stricture alone (without historical or clinical data) has been reported to have a sensitivity ranging from 11 to 74% and a specificity ranging from 63 to 100% for differentiation of benign from malignant strictures [40, 42–44].

Other studies have suggested that the sensitivity, specificity, positive predictive value (PPV),

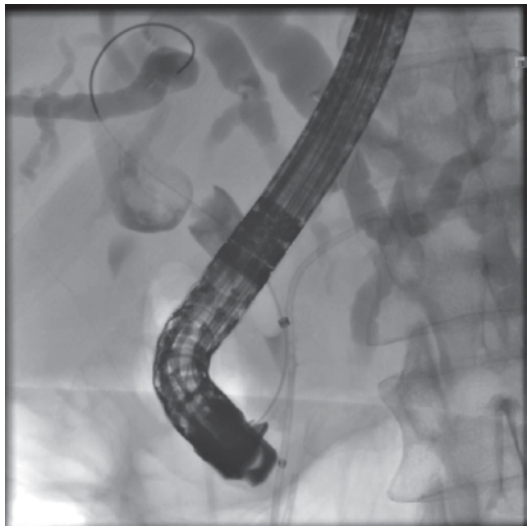

Fig. 7.3 Biliary stricture with an abrupt transition point and shelf-like appearance in a patient with cholangiocarcinoma

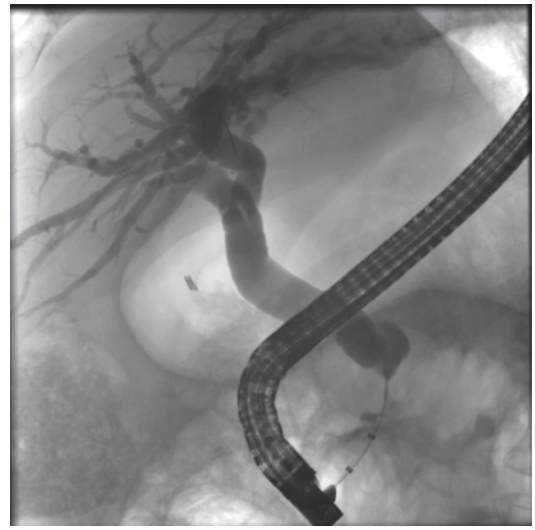

Fig. 7.5 Example of a benign ampullary stenosis with smooth concentric narrowing and dilatation of the biliary tree proximal to the ampulla. Note the low insertion of the cystic duct remnant

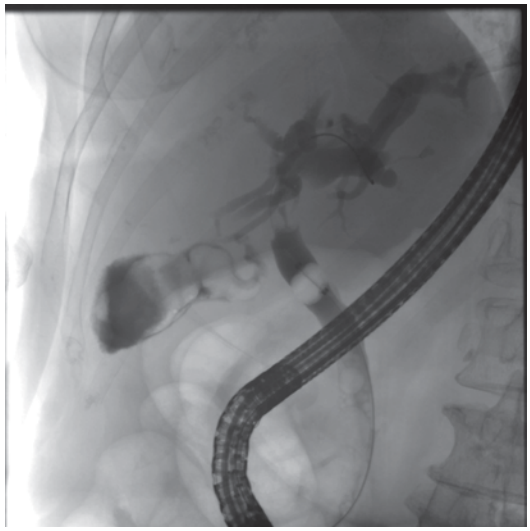

Fig. 7.4 Appearance of a malignant stricture affecting the common hepatic duct on occlusion cholangiogram. Note abrupt transition point and "apple core" appearance

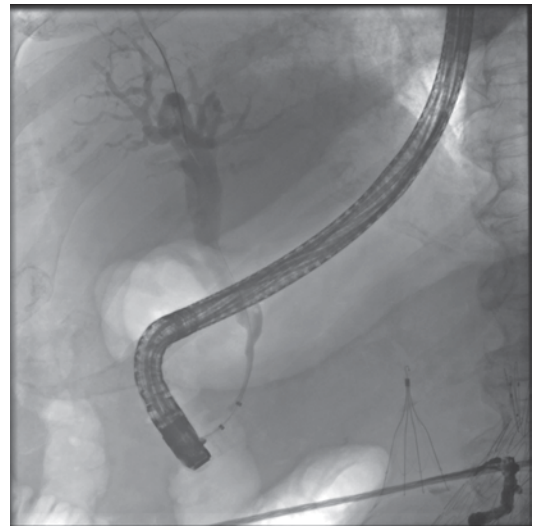

Fig. 7.6 Benign distal common bile duct stricture with smooth, concentric narrowing

negative predictive value (NPV) and accuracy of cholangiography (ERCP or percutaneous) in diagnosing malignancy are about 74–85, 70–75, 74–79, 70–82 and 72–80% respectively [38]. The low accuracy rates of cholangiography in diagnosing malignancy have stimulated research in tissue acquisition and advanced imaging techniques [38].

What Are the Pros and Cons of Tissue Sampling Techniques During ERCP?

Although tissue diagnosis may not be necessary in a subset of patients with biliary stricture, such as those who are surgical candidates and have a surgically resectable mass on cross-sectional imaging, it is often required for patients with undiagnosed biliary stricture without a mass or those who are candidates for chemo- or radiation therapy. During ERCP, tissue can be obtained by bile aspirated for cytology, cytologic examination of removed plastic stents, brush cytology or fluoroscopy guided forceps biopsy. As expected, diagnostic yield of both bile cytology and stent cytology are low at 11.5 and 13.5 %. The reported technique of bile collection for cytology involves aspirating 20 cc of bile from above the biliary stricture after brush cytology is performed while any and all tissue from the proximal end of the retrieved stent is smeared onto a glass slide and washed into cytology solution [45]. Alternatively, the entire stent may be sent to cytology in the solution.

Brush Cytology

Endoscopic retrograde brush cytology was first described by Osnes et al. at the University of Oslo in 1975 [46, 47]. Nowadays in patients with a biliary stricture, brush cytology is often performed during therapeutic ERCP. Endoscopic brush cytology during ERCP is safe, does not require special expertise and adds little to the cost of ERCP. It has therefore become the preferred initial method of pursuing a diagnosis in many patients with a biliary stricture.

The technique for endoscopic retrograde brush cytology in many institutions, including ours, is standardized. Under fluoroscopic guidance, the brush and its sheath are inserted into the duct of interest over a guidewire and positioned just distal to the stricture. The brush is then advanced from the sheath to a point proximal to the stricture and moved across the stricture in a to-and-fro manner approximately 10 times (Fig. 7.7) [48, 49]. The brush is then withdrawn into the sheath, and both are subsequently withdrawn from the endoscope as a single unit [48, 49]. The brush segment of the brushing device is cut from the supporting wire, placed in a preservative solution and transported to cytology laboratory.

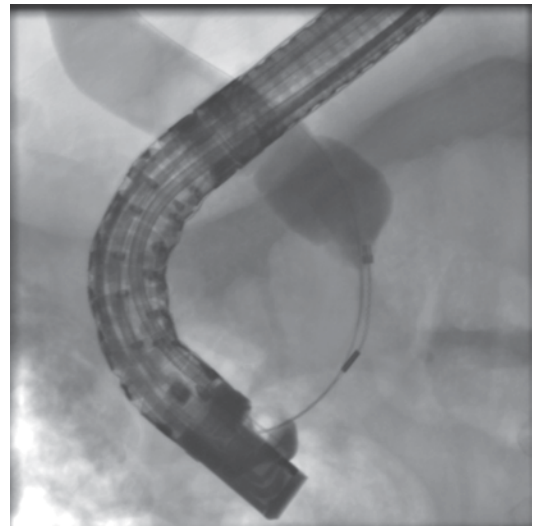

Fig. 7.7 Fluoroscopic image of brush cytology during ERCP

Brush cytology allows easy and convenient sampling and has a low complication rate [50–52]. The diagnostic specificity of biliary brush cytology is very high and few false-positive diagnoses have been reported [50, 53]. The major limitation of this technique has been the relatively modest diagnostic sensitivity, ranging from 10 to 50 % in most series [50, 53].

The variation in reported sensitivity of brush cytology across studies is in part because of differences in patient populations. For example, brush cytology has higher sensitivity in patients with evidence of a mass on cross-sectional imaging studies [48, 54]. Another factor affecting the variation in reported sensitivity is inconsistent categorization of cytology diagnoses as positive versus negative test results. In most institutions, including ours, the brush cytology results are grouped in four categories: benign, atypical, suspicious for malignancy or malignant. Some investigators have classified equivocal (e.g. atypical or suspicious for malignancy) diagnoses as positive for the presence of malignancy, whereas others have considered equivocal diagnoses as negative for malignancy. Regardless of classification or patient population, the sensitiv-

ity of brush cytology for detection of malignancy remains disappointingly low, while specificity is excellent. In other words, a positive result on brush cytology can be trusted, while a negative test is not trustworthy.

There have been attempts to improve the sensitivity of brush cytology obtained during ERCP. Physical changes to the brushing device itself such as use of longer and stiffer brushes have not improved sensitivity [55]. Balloon dilatation of strictures, to expose underlying tissue, prior to obtaining brush samples has been tried but also not shown to be beneficial [56]. Mutation analysis of the cells obtained by brushing does not seem to improve diagnostic accuracy [57], and DNA methylation analysis of brush specimens has shown only small benefit [50].

Recently fluorescent in situ hybridization (FISH) studies on brush cytology specimens have gained interest. FISH is a technique that uses fluorescently labeled DNA probes to detect chromosomal alterations in cells [58]. FISH looks for changes in the number of chromosomes (aneuploidy), the structure of chromosomes and for losses (deletions) and gains (duplications) of genetic material [58]. Polysomy (extra chromosomes) of chromosomes 3, 7 and 17 has been associated with malignancy [53, 59]. However, only 80% of pancreaticobiliary malignancies express these cellular alterations, thus inherently limiting the sensitivity of FISH [53, 60, 61]. In addition, some patients with benign bile duct strictures such as those with PSC, also exhibit chromosomal abnormalities. As a result, the specificity of FISH is lower than routine cytology, ranging from 67 to 88% [60, 62]. Although FISH is not recommended as a routine screening tool for malignancy because of its low PPV, in select cases with high pre-test probability for malignancy it may improve sensitivity of brush cytology [60, 63].

Fluoroscopy-Guided Forceps Biopsy

Tissue samples for histological investigation can be obtained from biliary strictures by using a biopsy forceps that is directed to the site of the stricture using fluoroscopy. Fluoroscopy-guided forceps biopsy of biliary strictures is technically more difficult and time consuming than brushing and has a higher risk profile with rare reports of bleeding and biliary perforation. It is therefore less widely used. However, forceps biopsy can provide a sample of subepithelial stroma that is usually not sampled by brush cytology. As a result, at least theoretically, it can diagnose a subset of cholangiocarcinomas that do not project into the biliary lumen and only affect the subepithelial bile duct wall.

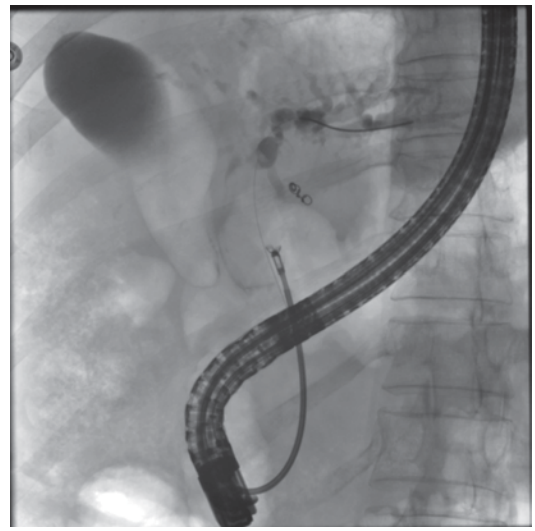

Fig. 7.8 Fluoroscopic image of forceps biopsy of a biliary mass. The guidewire delineates the course of the bile duct on fluoroscopy

Forceps biopsy of biliary strictures is usually carried out after placement of a guidewire in the bile duct [64]. The guidewire keeps the biliary sphincter open, thereby allowing easier passage of the forceps through the sphincter. It also delineates the course of the bile duct on fluoroscopy, which is of help in navigating the biopsy forceps in the appropriate direction through the bile duct (Fig. 7.8). Although in most cases the biopsy forceps can be passed through the biliary sphincter even without a sphincterotomy, a prior sphincterotomy will ease the passage of the forceps and facilitate the process. Higher number of biopsies will likely increase the yield at the cost of higher complication rates. Specialized wire-guided biliary forceps are available and easier to use [65, 66].

In older literature, the overall cancer detection rate of forceps biopsy is higher than brush cytology, ranging from 43 to 81% [67–69]. More recent studies, have continued to confirm higher sensitivity for forceps biopsy with comparable specificity to brush cytology [70]. It has been suggested that three or more biopsy samples are required to maximize sensitivity [71].

Multimodality Tissue Sampling

It seems that the sensitivity of tissue sampling techniques for detection of malignancy improves when different modalities are combined. For example, in a study of 58 patients, the sensitivity of transpapillary brush cytology was 41.4% and the sensitivity of forceps biopsy was 53.4%. When combined, the diagnostic sensitivity increased to 60.3% [70]. In another study involving 133 patients with a biliary stricture the sensitivity of brushing alone, FNA alone and biopsy alone were 30, 30 and 43% respectively. The combination of brushing and biopsy increased the sensitivity to 55% and when all three modalities were combined the sensitivity further increased to 62% [72].

Multiple other studies have confirmed that sampling of a biliary stricture with two or more techniques is the most effective method for diagnosis of malignant strictures [73, 74]. Consequently, some endoscopists prefer multimodality tissue sampling during ERCP in patients with biliary strictures when malignancy is highly suspected. In our practice, when there is suspicion of malignancy, brushing and biopsy of the strictures are often obtained during initial ERCP and if negative, with repeated ERCP procedures.

Case Continued

Given presence of jaundice and symptomatic itching in a patient with PSC, the patient was referred for an ERCP, which identified a high grade hilar stricture with moderately diffusely dilated intrahepatic ducts (Fig. 7.9) Brush cytology of the stricture demonstrated “atypical cells”. Fluoroscopy-guided biopsy forceps could not reach the stricture. The stricture was dilated and stented with a plastic biliary stent. What should be done next?

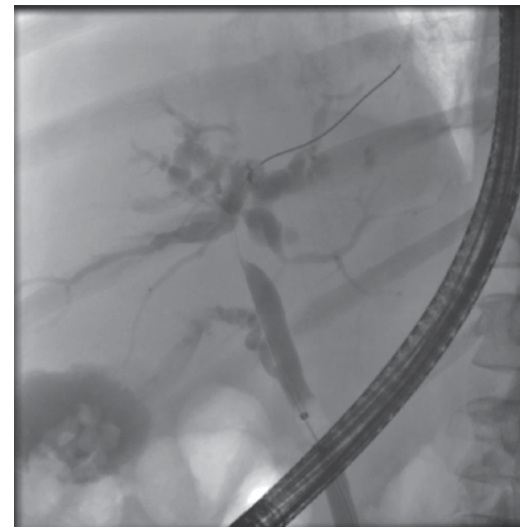

Fig. 7.9 ERCP image of a hilar stricture in a patient with PSC who presented with obstructive jaundice

What Does Cholangioscopy Add in the Diagnosis of Biliary Strictures?

Technique of Cholangioscopy

As opposed to the two-dimensional image offered by cholangiography, cholangioscopy offers a three-dimensional image of the bile duct lumen. In recent years, cholangioscopy has gained significant interest as a complementary procedure to ERCP for diagnosis and treatment of various biliary disorders, particularly indeterminate biliary strictures.

Available dedicated cholangioscopes in the USA are typically fiberoptic and reusable or semidisposable. Video cholangioscopes have limited availability and typically offer higher quality imaging. Cholangioscopy can be performed in one of three ways: two operator, single operator or direct peroral. In both the single and dual operator systems, the cholangioscope is advanced down the working channel of the therapeutic duodenoscope, while the newer direct peroral cholangioscopy (DPOC) technique involves passing an ultralsim upper endoscope through the

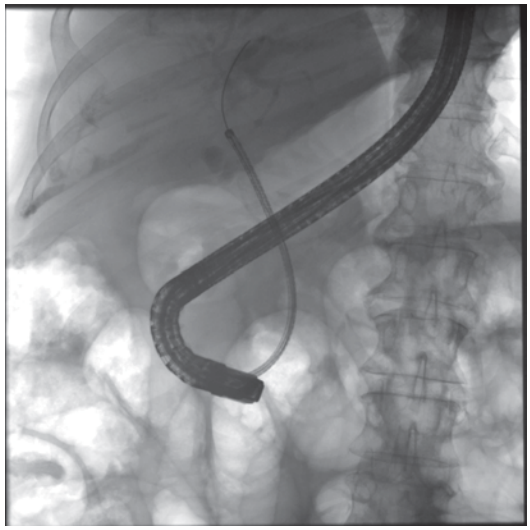

Fig. 7.10 Fluoroscopic image of a video cholangioscope inserted inside the bile duct over a guidewire to visualize biliary mucosa during ERCP

mouth and directly into the bile duct. DPOC will be discussed further, later in this chapter.

The two operator system uses a reusable cholangioscope with single plane tip deflection (up-down), a working channel for accessories, air/water and suction buttons. Biliary sphincterotomy and stricture dilatation are performed as needed to facilitate passage of the cholangioscope. Although biliary cannulation can be achieved directly with the tip of the cholangioscope, most endoscopists prefer cannulation over a guidewire (Fig. 7.10). The guidewire is advanced down the cholangioscope and used to cannulate the duct, or if backloading the wire, a catheter should be advanced down the working channel of the cholangioscope to capture the wire and avoid damaging the channel. Care must be taken to keep the elevator maximally open to avoid damaging the cholangioscope. The duodenoscope tip is usually positioned close to and underneath the ampulla as the cholangioscope is advanced into the duct. Back tension on the guidewire may help. Once in position, the guidewire is removed to allow use of the working channel. The bile duct is irrigated with sterile saline solution through this channel to enable adequate visualization, followed by slow withdrawal of the cholangioscope, allowing systematic inspection of the biliary mucosa. The cholangioscope position can be adjusted by moving it or the duodenoscope with the assistant operating the up-down knob on the cholangioscope. When advancing accessories down the channel, the elevator should be open with the angle of the duodenoscope and cholangioscope reduced, or the accessories may need to be preloaded into the cholangioscope. A specially designed breastplate to which the cholangioscope is attached can allow single operator use [75].

The single operator reusable system (Spyglass, Boston Scientific, Marlborough, MA) consists of several parts: reusable optical fiber; disposable 10Fr catheter with 4-way tip deflection and three ports (optical probe port, accessory channel, and irrigation port) that is attached to the duodenoscope with a silastic band; and disposable 3Fr biopsy forceps. There is no suction port on the catheter, and a syringe can be attached to the working channel to provide manual suction. The optical fiber is preloaded into the catheter and the system is advanced through the working channel of the duodenoscope in a similar fashion as the reusable cholangioscopes. Once positioned inside the bile duct, the optical fiber is gently advanced beyond the tip of the catheter to enable visualization; the two dials can be adjusted and locked to adjust the tip of the catheter. In the near future, introduction of a new digital system with a chip at the tip of the catheter to provide images will obviate the need for an optical fiber.

In one study, ERCP with cholangioscopy was associated with higher rates of cholangitis thought to result from saline infusion during cholangioscopy [76]. In our centre we avoid cholangioscopy procedures in the setting of acute ascending cholangitis. Saline infusion should be limited to the lowest rate that allows adequate quality of the image. An adequate sphincterotomy, allowing the excess saline to exit through the sphincter, likely decreases the risk of cholangitis. Saline can also be suctioned through the working channel of the cholangioscope. Prophylactic antibiotics should be used.

Visualizing the Mucosa at the Stricture

It is well-known that the presence of irregularly dilated and tortuous blood vessels (so-called tu-

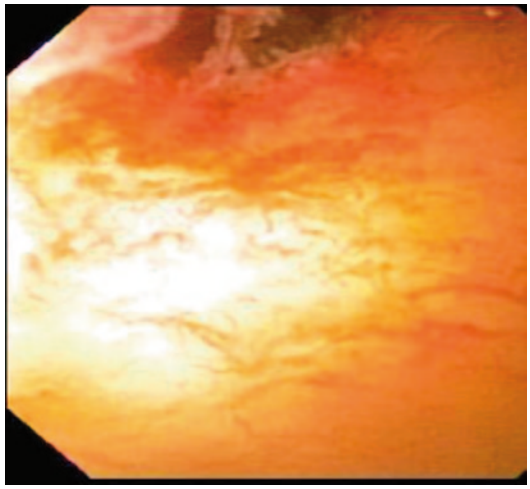

Fig. 7.11 Neovascularization at the site of a biliary stricture visualized by a video cholangioscope

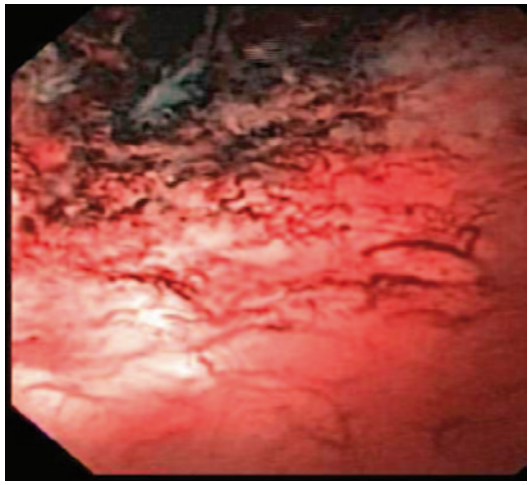

Fig. 7.12 Neovascularization at the site of a biliary stricture visualized by a video cholangioscope using NBI (same lesion as in Fig. 7.11). Note improved visualization of abnormal blood vessels

mour vessels) due to neovascularization at the site of pancreatic or biliary strictures is indicative of malignancy [79–81]. Tumour vessels can be detected by direct visualization using a cholangioscope (Fig. 7.11, Video 7.1) [77, 79]. Narrow band imaging (NBI) is an imaging technique especially suited for visualization and characterization of mucosal vascular pattern. Use of cholangioscopes with NBI capability facilitates detection of neovascularization at the site of

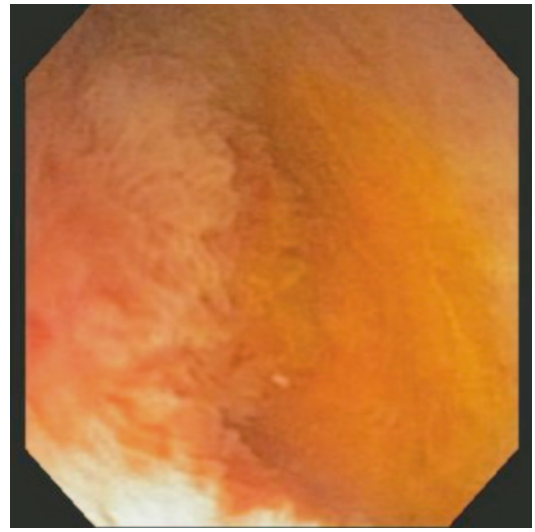

Fig. 7.13 Bile duct lesion with short finger-like projections on video cholangioscopy

biliary strictures and thereby diagnosis of malignancy (Fig. 7.12) [77, 82]. Intraductal nodules or masses can also be indicative of malignancy and be easily detected by cholangioscopy (Fig. 7.13) [80]. Intense vascularization is associated with the nodular type of cholangiocarcinoma and less so with the infiltrative type. The infiltrative type may involve only the subepithelial layers of the bile duct wall and cannot be detected by cholangioscopy, which visualizes the superficial layers. An infiltrative mass may only be visible as tapering of the lumen causing a stricture. The papillary type of cholangiocarcinoma is characterized by numerous papillary projections [72]. Biliary strictures caused by extraluminal compression, such as those associated with pancreatic cancer, cannot be detected by cholangioscopy, unless at later stages when the tumour has infiltrated and penetrated the bile duct wall [78].

In theory, peroral cholangioscopy can improve diagnosis of indeterminate biliary strictures by directly visualizing the mucosa at the stricture, and allowing targeted biopsy [78]. Studies to assess the value of stricture visualization by cholangioscopy have reported high sensitivity for detection of malignant lesions. In one of the largest cholangioscopic studies to date, diagnostic fiberoptic cholangioscopy using the Spyglass system was performed in 226 patients with various bili-

ary disorders. In patients with a biliary stricture, the ssensitivity for the diagnosis of malignancy was 51% for ERCP impression, 78% for cholangioscopic impression and 49% for targeted biopsy [83]. Smaller studies using video cholangioscopes with better imaging capability have reported even higher sensitivity for detection of malignancy by visualization of the stricture site alone [82, 84, 85]. Overall, the findings of these studies suggest that addition of cholangioscopy enhances the diagnostic performance of ERCP, especially its capability to diagnose indeterminate biliary strictures [77].

Cholangioscopy-Guided Targeted Biopsy

Cholangioscopy-guided targeted biopsy is defined as biopsy of the sites that are affected by disease under direct cholangioscopic visualization (Fig. 7.14) [78]. On a practical note, when using the Spyglass system, there may be resistance to the passage of the biopsy forceps through the cholangioscope. The site of resistance is usually at the bend of the cholangioscope where it exits the tip of the duodenoscope and enters the bile duct. Moving the cholangioscope back and forth while continuously advancing the biopsy forceps usually allows passage of the forceps. A larger accessory channel in the new digital Spyglass system is expected to solve this problem.

Theoretically, targeted biopsy should improve cancer detection rate in malignant biliary strictures by allowing sampling of the sites that appear suspicious. In a large multicentre study, the sensitivity of fiberoptic cholangioscopy-guided targeted biopsy for diagnosis of indeterminate biliary strictures was only 49%, far below the sensitivity of cholangioscopic visualization (78%) [83]. However, the specificity of targeted biopsy was higher than visualization alone (98 vs. 82%) [83]. Another study compared the diagnostic accuracy of peroral video cholangioscopic visual findings with that of video cholangioscopy-guided forceps biopsy for diagnosis of indeterminate biliary lesions. The sensitivity and specificity for visual findings were 100 and 91.7% and for biopsy were 38.1 and 100%, respectively [86].

A study of 89 patients aimed to compare the diagnostic performance of fluoroscopy-guided and cholangioscopy-guided biopsies for diagnosis of indeterminate biliary strictures [87]. While 100% specificity was achieved with both methods, fluoroscopy-guided biopsy had a higher sensitivity (76%) than cholangioscopy-guided biopsy (57%). The authors suggested that the most likely reason for this finding related to the larger cup size of the fluoroscopic-guided biopsy forceps along with the greater ease of passing these devices through the working channel of a duodenoscope compared with the smaller forceps in cholangioscopy-guided sampling [87]. A positive association between the size of biopsy specimens and their sensitivity for detection of malignancy in biliary strictures has been previously described [88]. It should be pointed out, however, that bigger biopsy samples might be associated with higher rates of perforation.

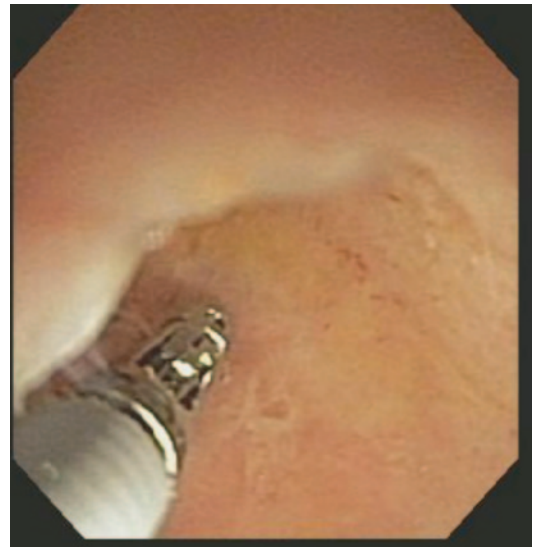

Fig. 7.14 Targeted biopsy of a biliary lesion

Direct Peroral Cholangioscopy

Peroral cholangioscopy using a dedicated cholangioscope requires expensive and fragile equipment. Therefore, use of ultraslim upper endoscopes for access to the bile duct and visualization of the biliary mucosa (DPOC) has gained interest. Aside from lower cost, DPOC offers additional advantages over cholangioscopy using dedicated cholangioscopes. The ultraslim endoscope uses a single operator platform, provides

high-definition digital image quality, allows simultaneous irrigation and therapy, is not fragile and has a larger working channel enabling enhanced diagnostic sampling and therapeutic interventions [89–91]. Despite its many advantages, DPOC is rarely performed in non-academic settings. The biggest disadvantage of DPOC has been the difficult and time-consuming task of bile duct cannulation with an upper endoscope, often ending in failure. There are several published reports with innovative suggestions on how to achieve this task. Introduction of the endoscope over a guidewire, through a regular overtube, or with the help of a double-balloon overtube are some of the suggestions [92–94]. However, despite use of these accessories, failure rate remains high [95]. Different variations of inflatable balloons used as an anchor within the biliary tree have been introduced and shown to facilitate access [89, 96].

Another disadvantage of DPOC is its inability to visualize the ducts proximal to the common hepatic duct [89]. Even with the use of anchoring balloons, DPOC can rarely visualize the ducts proximal to the confluence of the right and left hepatic ducts [89].

Studies using DPOC for evaluation of biliary strictures are small. Nonetheless, they all suggest a high sensitivity for detection of malignancy [89, 96]. Given excellent image quality and the ability to obtain larger biopsy specimens, one would expect a higher sensitivity for detection of malignancy in biliary strictures by DPOC compared to a dedicated cholangioscope for biliary strictures distal to the confluence of the hepatic ducts. The true value of DPOC for investigation of indeterminate biliary strictures remains uncertain given lack of large studies.

What is the Role of Endoscopic Ultrasound in the Diagnosis of Biliary Strictures?

Endoscopic ultrasound (EUS) takes advantage of the proximity of the stomach and duodenum to the extrahepatic biliary system. EUS has emerged as a sensitive tool for evaluation of various pancreaticobiliary disorders. Introduction of fine needle aspiration (FNA) has expanded the diagnostic potential of EUS, allowing tissue sampling for pathologic verification.

The role of EUS in the evaluation of indeterminate biliary strictures has been investigated in multiple studies, only two of which are fairly large and include 40 or more patients [97–99]. Lee et al. retrospectively evaluated 40 patients with unexplained bile duct strictures after a work up including CT/MRI without explanation for the stricture and ERCP with brushings (with or without biopsies). The finding of a pancreatic head mass or an irregular bile duct wall was 88 % sensitive and 100 % specific for malignancy. Bile duct wall thickness ≥ 3 mm had a sensitivity and specificity of 79 % for diagnosis of malignancy. Sensitivity of EUS-FNA for malignancy was 47 % with specificity of 100 %. The authors concluded that EUS-FNA cytology is specific but insensitive for diagnosis of unexplained biliary strictures [97]. In a prospective study of 50 patients, Rosch and colleagues compared ERCP tissue acquisition (brush cytology and forceps biopsy) to EUS-FNA for biliary strictures. The sensitivity of EUS-FNA was inferior to ERCP in patients with proximal and hilar biliary tumours (EUS 25 vs. ERCP 75 %) and superior to ERCP in patients with distal biliary stricture in the setting of pancreatic mass (EUS 60 vs. ERCP 38 %) [98]. Compared to ERCP alone, the addition of EUS-FNA significantly increased diagnostic accuracy from 70 to 86 %. Therefore, for biliary strictures, if initial ERCP for suspected biliary malignancy is non-diagnostic, EUS should be performed, while for distal biliary strictures possibly resulting from an unidentified pancreatic mass combined EUS and ERCP may be most efficient for achieving a diagnosis.

What Novel Tools May Help Diagnose Biliary Strictures?

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy is an imaging technique that allows microscopic visualization of the epithelial and subepithelial layers of the

mucosa in vivo [100]. It is performed after intravenous injection of a contrast agent such as fluorescein (2.5–5 cc of 10% sodium fluorescein) that diffuses through the capillaries and stains the extracellular matrix of the surface epithelium [100, 101]. Confocal laser endomicroscopy in the bile duct is carried out by using specialized probes that can be introduced through the working channel of a cholangioscope or through the lumen of various ERCP catheters [102]. The radio-opaque tip of the probe assists with localization of the probe within the bile duct by fluoroscopy. Practically, the probe is positioned in direct contact with and as perpendicular as possible to the mucosa at the site of the stricture. Various catheters such as the Swing-tip cannula (Olympus, Center Valley, PA) and sphincterotomes may be used to enable this orientation. Differences in contrast uptake, blood flow and contrast leakage through the capillaries may allow differentiation of normal surface mucosa from neoplastic tissue. Although initial studies have reported encouraging results, there is lack of validated criteria for diagnosing malignancy especially in the presence of inflammation [103]. A recent multicenter trial examined the added value of probe confocal endomicroscopy to standard of care using ERCP imaging and tissue sampling results in diagnosing indeterminate biliary strictures with final diagnoses determined by malignant pathology or negative pathology with at least 6 month benign follow-up. There was a trend towards improved diagnostic accuracy with the addition of probe confocal endomicroscopy (88% versus 79% standard of care alone) although these results missed statistical significance (p=0.06) [121]. Ongoing studies are expected to shed more light on the role of this technology in evaluation of indeterminate biliary strictures.

Cholangiocarcinoma in PSC

PSC is a chronic, cholestatic liver disease characterized by inflammation and fibrosis of the bile ducts leading to the formation of multifocal bile duct strictures [104]. PSC is a progressive disorder that in the majority of patients eventually leads to portal hypertension, cirrhosis and hepatic decompensation [104, 105]. A diagnosis of PSC is made in patients with a cholestatic biochemical profile, when cholangiography (e.g. MRCP, ERCP or percutaneous transhepatic cholangiography) shows characteristic bile duct changes with multifocal strictures and dilatations (Fig. 7.15) [104]. Dominant strictures defined by some as stenoses with a diameter ≤ 1.5 mm in the common bile duct or ≤ 1 mm in the hepatic ducts are common findings in PSC patients [104, 106, 107]. Such strictures have been associated with significantly higher risk of cholangiocarcinoma and thus a poor prognosis. In a study of 128 patients with PSC who were followed for a mean of 9.8 years, 21 patients developed cholangiocarcinoma [108]. All cholangiocarcinomas occurred in patients with dominant strictures [108]. Although the risk of cholangiocarcinoma in PSC patients is high, dominant strictures are far more often benign than malignant [44, 104].

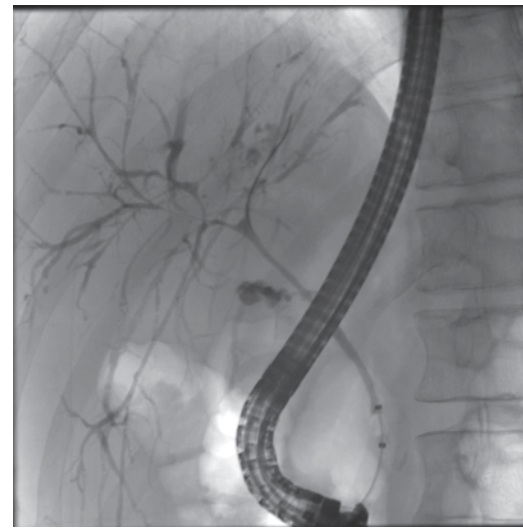

Fig. 7.15 ERCP image showing typical intrahepatic ductal changes of PSC

Dominant strictures have been reported in 45–58% of patients with PSC during follow up [105, 106, 109], while cholangiocarcinoma in PSC patients has a 10-year cumulative incidence of 7–9% and a lifetime risk of 20% [110–112].

The distinction between a dominant stricture and cholangiocarcinoma is often very difficult as sensitivity and specificity of various tissue

acquisition techniques is inconsistent, and mass lesions are uncommon in early cholangiocarcinoma [104]. In 2010, the American Association for Study of Liver Diseases (AASLD) published practice guidelines for diagnosis and management of PSC, including a section on diagnosis of cholangiocarcinoma in patients with PSC [104]. Although the section is somewhat vague, it recommends that PSC patients with a dominant stricture undergo MRI of the liver, ERCP with brush cytology for conventional as well as FISH analysis and measurement of serum CA 19-9 levels. In a study of 50 patients, of whom 21 had PSC, combining FISH with standard cytology from dominant strictures increased both sensitivity (89%) and specificity (97%) for diagnosing malignancy [113]. Evaluation for FISH polysomy in addition to both homozygous and heterozygous 9p21 deletions was performed in this study, as allelic loss of this gene locus has been implicated in the development of cholangiocarcinoma [114]. However, a recent meta-analysis, involving eight studies and 828 patients, suggested that FISH polysomy is specific but not sensitive for detecting cholangiocarcinoma in PSC patients, necessitating development of better markers for early diagnosis of cholangiocarcinoma in these patients [115].

According to the guidelines, with a negative MRI scan, CA 19-9 value < 130 U/mL, and negative cytology, a dominant stricture can be assumed to be benign. If the MRI scan is negative but there is concern for cholangiocarcinoma, it is recommended that the MRI, serum CA 19-9, and ERCP with brushings for cytology and FISH be repeated over time [104]. In our centre the timing for repeat tests is individualized depending on the clinical scenario and the degree of suspicion for malignancy.

The guidelines do not comment on the role of cholangioscopy or confocal laser endomicroscopy for evaluating dominant strictures. New studies have suggested that these imaging modalities may be valuable for identifying cholangiocarcinoma in PSC patients [84, 116–118]. A prospective study of 53 PSC patients with a dominant stricture demonstrated superior efficacy for detecting malignancy with cholangioscopy compared to ERCP alone [119]. Greater sensitivity (92 vs. 66%), specificity (93 vs. 51%), accuracy (93 vs. 55%) and both positive (79 vs. 29%) and NPVs (97 vs. 84%) were observed in the cholangioscopy group. Cholangioscopy may thus have a role in PSC patients with dominant strictures. Some experts have advocated routine use of cholangioscopy for evaluating suspicious biliary strictures in PSC and non-PSC patients [60]. For accurate diagnosis of biliary strictures, the quality of the cholangioscopic image is of utmost importance. Among currently available dedicated cholangioscopes, only high-definition video cholangioscopes offer sufficient image quality for a reliable diagnosis [120]. These are currently produced as prototypes and thus not available for commercial use. In large academic centres, including ours, the use of cholangioscopy for evaluating dominant strictures in PSC patients has been limited by the lack of availability of high-definition video cholangioscopes with NBI capability. The discovery of new biomarkers for cholangiocarcinoma from biliary brush specimens may aid in the identification of cholangiocarcinoma in PSC. Recently a panel of four DNA methylation biomarkers were found to improve sensitivity for cholangioarcinoma from 61% for brush cytology alone to 85% for the biomarker panel and 94% for both combined [122].

Case Continued

Following stenting, the patient's itching improved, bilirubin normalized and repeat serum CA 19-9 was 105. Given the high clinical suspicion of cancer in this patient with PSC and a new dominant stricture, the patient underwent repeat ERCP with cholangioscopy and repeat brushing for conventional cytology and FISH. Although FISH did not reveal polysomy, cholangioscopy revealed neovascularization at the site of the stricture. The patient was referred for transplantation. Pathology of the explanted liver confirmed diagnosis of cholangiocarcinoma.

Conclusion

In clinical practice, diagnosis of biliary strictures is based on a combination of history, clinical presentation, laboratory tests, imaging studies and various tissue-sampling techniques. The decision on what diagnostic procedure to perform depends on the patient's clinical status and comorbidities, presence or absence of tumour on imaging studies, available expertise and resources and the clinical setting.

ERCP is an invaluable tool for palliation of symptoms and for an initial attempt at diagnosis. Combination of various tissue sampling techniques during ERCP increases the diagnostic sensitivity. EUS-FNA is the procedure of choice for diagnosis of biliary strictures in the presence of a mass lesion. Cholangioscopes with high definition digital image quality can play a significant role in the diagnosis of indeterminate biliary strictures. Unfortunately, these cholangioscopes are costly, not readily available and break easily. It will be interesting to see whether new technology such as confocal laser endomicroscopy or single operator cholangioscopes with enhanced image quality can further facilitate diagnosis of these strictures.

Key Points

- A multifaceted approach to indeterminate biliary strictures is important.
- During ERCP, performing both brushing and biopsy of the biliary stricture increases diagnostic yield.
- Although currently available cholangioscopes have limited image quality, direct visualization and targeted biopsy during cholangioscopy may improve ability to identify malignant strictures.
- The addition of EUS and EUS-FNA to ERCP increases diagnostic accuracy for especially malignant distal biliary strictures.
- Dominant strictures in PSC must be thoroughly evaluated with serum CA 19-9, MRI and ERCP cytology at a minimum. FISH and cholangioscopy may improve diagnostic yield.

Video Caption

Video 7.1 Cholangioscopy demonstrating biliary stricture with neovascularization around the distal end of the stricture

References

1. Chalasani N, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, McCashland TM, Reddy KR, Zervos X, Anbari MA, Hoen H. Cholangiocarcinoma in patients with primary sclerosing cholangitis: a multicenter case-control study. Hepatology. 2000;31:7–11.
2. Patel AH, Harnois DM, Klee GG, LaRusso NF, Gores GJ. The utility of CA 19-9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. Am J Gastroenterol. 2000;95:204–7.
3. Levy C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD. The value of serum CA 19 – 9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Dig Dis Sci. 2005;50:1734–40.
4. Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. Am J Gastroenterol. 1990;85:350–5.
5. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol. 2007;33:266–70.
6. Kim HJ, Kim MH, Myung SJ, Lim BC, Park ET, Yoo KS, Seo DW, Lee SK, Min YI. A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve. Am J Gastroenterol. 1999;94:1941–6.
7. Mann DV, Edwards R, Ho S, Lau WY, Glazer G. Elevated tumour marker CA19-9: clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol. 2000;26:474–9.
8. Marrelli D, Caruso S, Pedrazzani C, Neri A, Fernandes E, Marini M, Pinto E, Roviello F. CA19-9 serum levels in obstructive jaundice: clinical value in benign and malignant conditions. Am J Surg. 2009;198:333–9.
9. Sinakos E, Saenger AK, Keach J, Kim WR, Lindor KD. Many patients with primary sclerosing cholangitis and increased serum levels of carbohydrate antigen 19-9 do not have cholangiocarcinoma. Clin Gastroenterol Hepatol. 2011;9:434–9e1.
10. Bonney GK, Craven RA, Prasad R, Melcher AF, Selby PJ, Banks RE. Circulating markers of biliary malignancy: opportunities in proteomics? Lancet Oncol. 2008;9:149–58.
11. Morris-Stiff G, Taylor MA. Ca19-9 and pancreatic cancer: Is it really that good? J Gastrointest Oncol. 2012;3:88–9.
12. Locker GY, Hamilton S, Harris J, Jessup JM, Kemeny

N, Macdonald JS, Somerfield MR, Hayes DF, Bast RC Jr. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol. 2006;24:5313–27.
13. Uygur-Bayramicli O, Dabak R, Orbay E, Dolapcioglu C, Sargin M, Kilicoglu G, Guleryuzlu Y, Mayadagli A. Type 2 diabetes mellitus and CA 19-9 levels. World J Gastroenterol. 2007;13:5357–9.
14. Parra JL, Kaplan S, Barkin JS. Elevated CA 19-9 caused by Hashimoto's thyroiditis: review of the benign causes of increased CA 19-9 level. Dig Dis Sci. 2005;50:694–5.
15. Murai J, Soga S, Saito H, Otsuki M, Kitada T, Saisho Y, Nakamura H, Kasayama S, Koga M. Study on the mechanism causing elevation of serum CA19-9 levels in diabetic patients. Endocr J. 2013;60:885–91.
16. Yu H, Li R, Zhang L, Chen H, Bao Y, Jia W. Serum CA19-9 level associated with metabolic control and pancreatic beta cell function in diabetic patients. Exp Diabetes Res. 2012;2012:745189.
17. Brain O, Brown LH, Suvarna S, Chapman R. Markedly elevated CA19-9 associated with benign ovarian cyst and ascites. BMJ Case Rep. 2009;doi: 10.1136/bcr.11.2008.
18. Kodama T, Satoh H, Ishikawa H, Ohtsuka M. Serum levels of CA19-9 in patients with nonmalignant respiratory diseases. J Clin Lab Anal. 2007;21:103–6.
19. Kim HR, Lee CH, Kim YW, Han SK, Shim YS, Yim JJ. Increased CA 19-9 level in patients without malignant disease. Clin Chem Lab Med. 2009;47:750–4.
20. Coskun A, Kiran G, Ozdemir O. CA 19-9 can be a useful tumor marker in ovarian dermoid cysts. Clin Exp Obstet Gynecol. 2008;35:137–9.
21. Kawai S, Suzuki K, Nishio K, Ishida Y, Okada R, Goto Y, Naito M, Wakai K, Ito Y, Hamajima N. Smoking and serum CA19-9 levels according to Lewis and secretor genotypes. Int J Cancer. 2008;123:2880–4.
22. Tempero MA, Uchida E, Takasaki H, Burnett DA, Steplewski Z, Pour PM. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. Cancer Res. 1987;47:5501–3.
23. Metzger J, Negm AA, Plentz RR, Weismuller TJ, Wedemeyer J, Karlsen TH, Dakna M, Mullen W, Mischak H, Manns MP, Lankisch TO. Urine proteomic analysis differentiates cholangiocarcinoma from primary sclerosing cholangitis and other benign biliary disorders. Gut. 2013;62:122–30.
24. Alvaro D. Serum and bile biomarkers for cholangiocarcinoma. Curr Opin Gastroenterol. 2009;25:279–84.
25. Zabron AA, Horneffer-van der Sluis VM, Wadsworth CA, Laird F, Gierula M, Thillainayagam AV, Vlavianos P, Westaby D, Taylor-Robinson SD, Edwards RJ, Khan SA. Elevated levels of neutrophil gelatinase-associated lipocalin in bile from patients with malignant pancreatobiliary disease. Am J Gastroenterol. 2011;106:1711–7.
26. Songur Y, Temucin G, Sahin B. Endoscopic ultrasonography in the evaluation of dilated common bile duct. J Clin Gastroenterol. 2001;33:302–5.
27. Victor DW, Sherman S, Karakan T, Khashab MA. Current endoscopic approach to indeterminate biliary strictures. World J Gastroenterol. 2012;18:6197–205.
28. Wallner BK, Schumacher KA, Weidenmaier W, Friedrich JM. Dilated biliary tract: evaluation with MR cholangiography with a T2-weighted contrast-enhanced fast sequence. Radiology. 1991;181:805–8.
29. Griffin N, Charles-Edwards G, Grant LA. Magnetic resonance cholangiopancreatography: the ABC of MRCP. Insights Imaging. 2012;3:11–21.
30. Nandalur KR, Hussain HK, Weadock WJ, Wamsteker EJ, Johnson TD, Khan AS, D'Amico AR, Ford MK, Nandalur SR, Chenevert TL. Possible biliary disease: diagnostic performance of high-spatial-resolution isotropic 3D T2-weighted MRCP. Radiology. 2008;249:883–90.
31. Park MS, Kim TK, Kim KW, Park SW, Lee JK, Kim JS, Lee JH, Kim KA, Kim AY, Kim PN, Lee MG, Ha HK. Differentiation of extrahepatic bile duct cholangiocarcinoma from benign stricture: findings at MRCP versus ERCP. Radiology. 2004;233:234–40.
32. Rosch T, Meining A, Fruhmorgen S, Zillinger C, Schusdziarra V, Hellerhoff K, Classen M, Helmberger H. A prospective comparison of the diagnostic accuracy of ERCP, MRCP, CT, and EUS in biliary strictures. Gastrointest Endosc. 2002;55:870–6.
33. Sai JK, Suyama M, Kubokawa Y, Watanabe S, Maehara T. Early detection of extrahepatic bile-duct carcinomas in the nonicteric stage by using MRCP followed by EUS. Gastrointest Endosc. 2009;70:29–36.
34. Ahualli J. The double duct sign. Radiology. 2007;244:314–5.
35. Baillie J, Paulson EK, Vitellas KM. Biliary imaging: a review. Gastroenterology. 2003;124:1686–99.
36. Menges M, Lerch MM, Zeitz M. The double duct sign in patients with malignant and benign pancreatic lesions. Gastrointest Endosc. 2000;52:74–7.
37. McCune WS, Shorb PE, Moscovitz H. Endoscopic cannulation of the ampulla of vater: a preliminary report. Ann Surg. 1968;167:752–6.
38. Yoon WJ, Brugge WR. Endoscopic evaluation of bile duct strictures. Gastrointest Endosc Clin N Am. 2013;23:277–93.
39. Bain VG, Abraham N, Jhangri GS, Alexander TW, Henning RC, Hoskinson ME, Maguire CG, Lalor EA, Sadowski DC. Prospective study of biliary strictures to determine the predictors of malignancy. Can J Gastroenterol. 2000;14:397–402.
40. Levy MJ, Baron TH, Clayton AC, Enders FB, Gostout CJ, Halling KC, Kipp BR, Petersen BT, Roberts LR, Rumalla A, Sebo TJ, Topazian MD, Wiersema MJ, Gores GJ. Prospective evaluation of advanced molecular markers and imaging techniques in patients with indeterminate bile duct strictures. Am J Gastroenterol. 2008;103:1263–73.
41. Al-Mofleh IA, Aljebreen AM, Al-Amri SM, Al-Rashed RS, Al-Faleh FZ, Al-Freihi HM, Abdo AA, Isnani AC. Biochemical and radiological predictors of malignant biliary strictures. World J Gastroenterol. 2004;10:1504–7.

42. Witt BL, Kristen Hilden RN, Scaife C, Chadwick B, Layfield L, Cory Johnston W, Safaee M, Siddiqui A, Adler DG. Identification of factors predictive of malignancy in patients with atypical biliary brushing results obtained via ERCP. Diagn Cytopathol. 2012. doi: 10.1002/dc.22924. [Epub ahead of print].
43. 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.
44. Lindberg B, Arnelo U, Bergquist A, Thorne A, Hjerpe A, Granqvist S, Hansson LO, Tribukait B, Persson B, Broome U. Diagnosis of biliary strictures in conjunction with endoscopic retrograde cholangiopancreaticography, with special reference to patients with primary sclerosing cholangitis. Endoscopy. 2002;34:909–16.
45. Mansfield JC, Griffin SM, Wadehra V, Matthewson K. A prospective evaluation of cytology from biliary strictures. Gut. 1997;40:671–7.
46. Osnes M, Serck-Hanssen A, Myren J. Endoskopisk børstecytologi av cancer i pancreas og galleveier. Tidsskr Nor Laegeforen. 1975;95:1729–31.
47. Osnes M, Serck-Hanssen A, Myren J. Endoscopic retrograde brush cytology (ERBC) of the biliary and pancreatic ducts. Scand J Gastroenterol. 1975;10:829–31.
48. Parsi MA, Deepinder F, Lopez R, Stevens T, Dodig M, Zuccaro G. Factors affecting the yield of brush cytology for the diagnosis of pancreatic and biliary cancers. Pancreas. 2011;40:52–4.
49. Papachristou GI, Smyrk TC, Baron TH. Endoscopic retrograde cholangiopancreatography tissue sampling: when and how? Clin Gastroenterol Hepatol. 2007;5:783–90.
50. Parsi MA, Li A, Li CP, Goggins M. DNA methylation alterations in endoscopic retrograde cholangiopancreatography brush samples of patients with suspected pancreaticobiliary disease. Clin Gastroenterol Hepatol. 2008;6:1270–8.
51. Govil H, Reddy V, Kluskens L, Treaba D, Massarani-Wafai R, Selvaggi S, Gattuso P. Brush cytology of the biliary tract: retrospective study of 278 cases with histopathologic correlation. Diagn Cytopathol. 2002;26:273–7.
52. Selvaggi SM. Biliary brushing cytology. Cytopathology. 2004;15:74–9.
53. Moreno Luna LE Kipp B Halling KC Sebo TJ Kremers WK Roberts LR Barr Fritcher EG Levy MJ Gores GJ. Advanced cytologic techniques for the detection of malignant pancreatobiliary strictures. Gastroenterology. 2006;131:1064–72.
54. Mahmoudi N, Enns R, Amar J, AlAli J, Lam E, Telford J. Biliary brush cytology: factors associated with positive yields on biliary brush cytology. World J Gastroenterol. 2008;14:569–73.
55. Fogel EL, deBellis M, McHenry L, Watkins JL, Chappo J, Cramer H, Schmidt S, Lazzell-Pannell L, Sherman S, Lehman GA. Effectiveness of a new long cytology brush in the evaluation of malignant biliary obstruction: a prospective study. Gastrointest Endosc. 2006;63:71–7.
56. Ornellas LC, Santos Gda C, Nakao FS, Ferrari AP. Comparison between endoscopic brush cytology performed before and after biliary stricture dilation for cancer detection. Arq Gastroenterol. 2006;43:20–3.
57. Stewart CJ, Burke GM. Value of p53 immunostaining in pancreatico-biliary brush cytology specimens. Diagn Cytopathol. 2000;23:308–13.
58. Halling KC, Kipp BR. Fluorescence in situ hybridization in diagnostic cytology. Hum Pathol. 2007;38:1137–44.
59. Fritcher EG, Kipp BR, Halling KC, Oberg TN, Bryant SC, Tarrell RF, Gores GJ, Levy MJ, Clayton AC, Sebo TJ, Roberts LR. A multivariable model using advanced cytologic methods for the evaluation of indeterminate pancreatobiliary strictures. Gastroenterology. 2009;136:2180–6.
60. Cote GA, Sherman S. Biliary stricture and negative cytology: what next? Clin Gastroenterol Hepatol. 2011;9:739–43.
61. Bergquist A, Tribukait B, Glaumann H, Broome U. Can DNA cytometry be used for evaluation of malignancy and premalignancy in bile duct strictures in primary sclerosing cholangitis? J Hepatol. 2000;33:873–7.
62. Bangarulingam SY, Bjornsson E, Enders F, Barr Fritcher EG, Gores G, Halling KC, Lindor KD. Long-term outcomes of positive fluorescence in situ hybridization tests in primary sclerosing cholangitis. Hepatology. 2010;51:174–80.
63. Chapman WC. Fluorescent in situ hybridization testing in primary sclerosing cholangitis: useful testing or a random chance result? Hepatology. 2010;51:16–9.
64. Higashizawa T, Tamada K, Tomiyama T, Wada S, Ohashi A, Satoh Y, Gotoh Y, Miyata T, Ido K, Sugano K. Biliary guidewire facilitates bile duct biopsy and endoscopic drainage. J Gastroenterol Hepatol. 2002;17:332–6.
65. Asada M, Yazumi S, Yoshimoto T, Tamaki H, Matsuura M, Hasegawa K, Uenoyama Y, Hisatsune H, Nishio A, Chiba T. Transpapillary biliary biopsy for early stage cholangiocarcinoma of the distal common bile duct. Gastrointest Endosc. 2006;64:125–6; discussion 126.
66. Tamada K, Higashizawa T, Tomiyama T, Wada S, Ohashi A, Satoh Y, Ido K, Sugano K. Ropeway-type bile duct biopsy forceps with a side slit for a guidewire. Gastrointest Endosc. 2001;53:89–92.
67. Ponchon T, Gagnon P, Berger F, Labadie M, Liaras A, Chavaillon A, Bory R. 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.
68. Sugiyama M, Atomi Y, Wada N, Kuroda A, Muto T. Endoscopic transpapillary bile duct biopsy without sphincterotomy for diagnosing biliary strictures: a prospective comparative study with bile and brush cytology. Am J Gastroenterol. 1996;91:465–7.

69. Schoefl R, Haefner M, Wrba F, Pfeffel F, Stain C, Poetzi R, Gangl A. Forceps biopsy and brush cytology during endoscopic retrograde cholangiopancreatography for the diagnosis of biliary stenoses. Scand J Gastroenterol. 1997;32:363–8.
70. Weber A, von Weyhern C, Fend F, Schneider J, Neu B, Meining A, Weidenbach H, Schmid RM, Prinz C. Endoscopic transpapillary brush cytology and forceps biopsy in patients with hilar cholangiocarcinoma. World J Gastroenterol. 2008;14:1097–101.
71. Kawashima H, Itoh A, Ohno E, Goto H, Hirooka Y. Transpapillary biliary forceps biopsy to distinguish benign biliary stricture from malignancy: how many tissue samples should be obtained? Dig Endosc. 2012;24 Suppl 1:22–7.
72. Jailwala J, Fogel EL, Sherman S, Gottlieb K, Flueckiger J, Bucksot LG, Lehman GA. Triple-tissue sampling at ERCP in malignant biliary obstruction. Gastrointest Endosc. 2000;51:383–90.
73. Kitajima Y, Ohara H, Nakazawa T, Ando T, Hayashi K, Takada H, Tanaka H, Ogawa K, Sano H, Togawa S, Naito I, Hirai M, Ueno K, Ban T, Miyabe K, Yamashita H, Yoshimura N, Akita S, Gotoh K, Joh T. Usefulness of transpapillary bile duct brushing cytology and forceps biopsy for improved diagnosis in patients with biliary strictures. J Gastroenterol Hepatol. 2007;22:1615–20.
74. de Bellis M, Sherman S, Fogel EL, Cramer H, Chappo J, McHenry L Jr, Watkins JL, Lehman GA. Tissue sampling at ERCP in suspected malignant biliary strictures (Part 2). Gastrointest Endosc. 2002;56:720–30.
75. Farrell JJ, Bounds BC, Al-Shalabi S, Jacobson BC, Brugge WR, Schapiro RH, Kelsey PB. Single-operator duodenoscope-assisted cholangioscopy is an effective alternative in the management of choledocholithiasis not removed by conventional methods, including mechanical lithotripsy. Endoscopy. 2005;37:542–7.
76. Sethi A, Chen YK, Austin GL, Brown WR, Brauer BC, Fukami NN, Khan AH, Shah RJ. ERCP with cholangiopancreatoscopy may be associat with higher rates of complications than ERCP alone: a single-center experience. Gastrointest Endosc. 2011;73:251–6.
77. Parsi MA. High-definition endoscopy and narrow-band imaging of the bile ducts: new possibilities for diagnosis of indeterminate strictures. Gastroenterology. 2014;146:343–4.
78. Parsi MA. Peroral cholangioscopy in the new millennium. World J Gastroenterol. 2011;17:1–6.
79. Kim HJ, Kim MH, Lee SK, Yoo KS, Seo DW, Min YI. Tumor vessel: a valuable cholangioscopic clue of malignant biliary stricture. Gastrointest Endosc. 2000;52:635–8.
80. Seo DW, Lee SK, Yoo KS, Kang GH, Kim MH, Suh DJ, Min YI. Cholangioscopic findings in bile duct tumors. Gastrointest Endosc. 2000;52:630–4.
81. Tang D, Nagano H, Yamamoto H, Wada H, Nakamura M, Kondo M, Ota H, Yoshioka S, Kato H, Damdinsuren B, Marubashi S, Miyamoto A, Takeda Y, Umeshita K, Dono K, Wakasa K, Monden M. Angiogenesis in cholangiocellular carcinoma: expression of vascular endothelial growth factor, angiopoietin-1/2, thrombospondin-1 and clinicopathological significance. Oncol Rep. 2006;15:525–32.
82. Itoi T, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, Ishii K, Tsuji S, Moriyasu F, Gotoda T. Peroral cholangioscopic diagnosis of biliary-tract diseases by using narrow-band imaging (with videos). Gastrointest Endosc. 2007;66:730–6.
83. Chen YK, Parsi MA, Binmoeller KF, Hawes RH, Pleskow DK, Slivka A, Haluszka O, Petersen BT, Sherman S, Deviere J, Meisner S, Stevens PD, Costamagna G, Ponchon T, Peetermans JA, Neuhaus H. Single-operator cholangioscopy in patients requiring evaluation of bile duct disease or therapy of biliary stones (with videos). Gastrointest Endosc. 2011;74:805–14.
84. Parsi MA, Stevens T, Collins J, Vargo JJ. Utility of a prototype peroral video cholangioscopy system with narrow-band imaging for evaluation of biliary disorders (with videos). Gastrointest Endosc. 2011;74:1148–51.
85. Parsi MA, Jang S, Sanaka M, Stevens T, Vargo JJ. Diagnostic and therapeutic cholangiopancreatoscopy: performance of a new digital cholangioscope. Gastrointest Endosc. 2014;79:936–42.
86. Nishikawa T, Tsuyuguchi T, Sakai Y, Sugiyama H, Miyazaki M, Yokosuka O. 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.
87. Hartman DJ, Slivka A, Giusto DA, Krasinskas AM. Tissue yield and diagnostic efficacy of fluoroscopic and cholangioscopic techniques to assess indeterminate biliary strictures. Clin Gastroenterol Hepatol. 2012;10:1042–6.
88. Ikeda M, Maetani I, Terada K, Ukita T, Tada T, Shigoka H, Omuta S, Takahashi K. Usefulness of endoscopic retrograde biliary biopsy using large-capacity forceps for extrahepatic biliary strictures: a prospective randomized study. Endoscopy. 2010;42:837–41.
89. Parsi MA, Stevens T, Vargo JJ. Diagnostic and therapeutic direct peroral cholangioscopy using an intraductal anchoring balloon. World J Gastroenterol. 2012;18:3992–6.
90. Waxman I, Dillon T, Chmura K, Wardrip C, Chennat J, Konda V. Feasibility of a novel system for intraductal balloon-anchored direct peroral cholangioscopy and endotherapy with an ultraslim endoscope (with videos). Gastrointest Endosc. 2010;72:1052–6.
91. Pohl J, Meves VC, Mayer G, Behrens A, Frimberger E, Ell C. Prospective randomized comparison of short-access mother-baby cholangioscopy versus direct cholangioscopy with ultraslim gastroscopes. Gastrointest Endosc. 2013. pii: S0016-5107(13)01838–5. doi: 10.1016/j.gie.2013.04.177. [Epub ahead of print].

92. Larghi A, Waxman I. Endoscopic direct cholangioscopy by using an ultra-slim upper endoscope: a feasibility study. Gastrointest Endosc. 2006;63:853–7.
93. Bohle W. A simple and rapid technique of direct cholangioscopy. Gastrointest Endosc. 2007;65:559.
94. Choi HJ, Moon JH, Ko BM, Hong SJ, Koo HC, Cheon YK, Cho YD, Lee JS, Lee MS, Shim CS. Overtube-balloon-assisted direct peroral cholangioscopy by using an ultra-slim upper endoscope (with videos). Gastrointest Endosc. 2009;69:935–40.
95. Terheggen G, Neuhaus H New options of cholangioscopy. Gastroenterol Clin North Am. 2010;39:827–44.
96. Moon JH, Ko BM, Choi HJ, Hong SJ, Cheon YK, Cho YD, Lee JS, Lee MS, Shim CS. Intraductal balloon-guided direct peroral cholangioscopy with an ultraslim upper endoscope (with videos). Gastrointest Endosc. 2009;70:297–302.
97. Lee JH, Salem R, Aslanian H, Chacho M, Topazian M. Endoscopic ultrasound and fine-needle aspiration of unexplained bile duct strictures. Am J Gastroenterol. 2004;99:1069–73.
98. Rosch T, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, Allescher HD, Classen M, Barbur M, Schenck U, Werner M. ERCP or EUS for tissue diagnosis of biliary strictures? a prospective comparative study. Gastrointest Endosc. 2004;60:390–6.
99. Gabbert C, Warndorf M, Easler J, Chennat J. Advanced techniques for endoscopic biliary imaging: cholangioscopy, endoscopic ultrasonography, confocal, and beyond. Gastrointest Endosc Clin N Am. 2013;23:625–46.
100. Kiesslich R, Goetz M, Neurath MF. Confocal laser endomicroscopy for gastrointestinal diseases. Gastrointest Endosc Clin N Am. 2008;18:451–66, viii.
101. Paramsothy S, Leong RW. Endoscopy: fluorescein contrast in confocal laser endomicroscopy. Nat Rev Gastroenterol Hepatol. 2010;7:366–8.
102. Wallace MB, Fockens P. Probe-based confocal laser endomicroscopy. Gastroenterology. 2009;136:1509–13.
103. Caillol F, Filoche B, Gaidhane M, Kahaleh M. Refined probe-based confocal laser endomicroscopy classification for biliary strictures: the paris classification. Dig Dis Sci. 2013;58:1784–9.
104. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ. AASLD practice guidelines: Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51:660–78.
105. Tischendorf JJ, Hecker H, Kruger M, Manns MP, Meier PN. Characterization, outcome, and prognosis in 273 patients with primary sclerosing cholangitis: a single center study. Am J Gastroenterol. 2007;102:107–14.
106. Stiehl A, Rudolph G, Kloters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. J Hepatol. 2002;36:151–6.
107. Bjornsson E, Lindqvist-Ottosson J, Asztely M, Olsson R. Dominant strictures in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2004;99:502–8.
108. Chapman MH, Webster GJ, Bannoo S, Johnson GJ, Wittmann J, Pereira SP. Cholangiocarcinoma and dominant strictures in patients with primary sclerosing cholangitis: a 25-year single-centre experience. Eur J Gastroenterol Hepatol. 2012;24:1051–8.
109. Okolicsanyi L, Fabris L, Viaggi S, Carulli N, Podda M, Ricci G. Primary sclerosing cholangitis: clinical presentation, natural history and prognostic variables: an Italian multicentre study. The Italian PSC study group. Eur J Gastroenterol Hepatol. 1996;8:685–91.
110. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol. 2004;99:523–6.
111. Bergquist A, Ekbom A, Olsson R, Kornfeldt D, Loof L, Danielsson A, Hultcrantz R, Lindgren S, Prytz H, Sandberg-Gertzen H, Almer S, Granath F, Broome U. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol. 2002;36:321–7.
112. Claessen MM, Vleggaar FP, Tytgat KM, Siersema PD, van Buuren HR. High lifetime risk of cancer in primary sclerosing cholangitis. J Hepatol. 2009;50:158–64.
113. Gonda TA, Glick MP, Sethi A, Poneros JM, Palmas W, Iqbal S, Gonzalez S, Nandula SV, Emond JC, Brown RS, Murty VV, Stevens PD. Polysomy and p16 deletion by fluorescence in situ hybridization in the diagnosis of indeterminate biliary strictures. Gastrointest Endosc. 2012;75:74–9.
114. DeHaan RD, Kipp BR, Smyrk TC, Abraham SC, Roberts LR, Halling KC. An assessment of chromosomal alterations detected by fluorescence in situ hybridization and p16 expression in sporadic and primary sclerosing cholangitis-associated cholangiocarcinomas. Hum Pathol. 2007;38:491–9.
115. Navaneethan U, Njei B, Venkatesh PG, Vargo JJ, Parsi MA. Fluorescence in situ hybridization for diagnosis of cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. Gastrointest Endosc. 2014;79:943–50 e3.
116. Nimura Y. Staging cholangiocarcinoma by cholangioscopy. HPB (Oxford). 2008;10:113–5.
117. Itoi T, Kamisawa T, Igarashi Y, Kawakami H, Yasuda I, Itokawa F, Kishimoto Y, Kuwatani M, Doi S, Hara S, Moriyasu F, Baron TH. The role of peroral video cholangioscopy in patients with IgG4-related sclerosing cholangitis. J Gastroenterol. 2013;48:504–14.
118. 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.

119. Tischendorf JJ, Kruger M, Trautwein C, Duckstein N, Schneider A, Manns MP, Meier PN. Cholangioscopic characterization of dominant bile duct stenoses in patients with primary sclerosing cholangitis. Endoscopy. 2006;38:665–9.
120. Parsi MA. Direct peroral cholangioscopy. World J Gastrointest Endosc. 2014;6:1–5.
121. Slivka A, Gan I, Jamidar P, Costamagna G, Cesaro P, Giovannini M, Caillol F, Kahaleh M. Validation of the diagnostic accuracy of probe-based confocal laser endomicroscopy for the characterization of indeterminate biliary stritures: results of a prospective multicenter international study. Gastrointest Endosc. 2015;81:282–90.
122. Andresen K, Boberg KM, Vedeld HM, Honne H, Jebsen P, Hektoen M, Wadsworth CA, Clausen OP, Lundin KEA, Paulsen V, Foss A, Methisen O, Aabakken L, Schrumpf E, Lothe RA, Lind GE. Four DNA methylation biomarkers in biliary brush samples accurately identify the presence of cholangiocarcinoma. Hepatology. 2015 Jan 16. Epub ahead of print.

Management of Biliary Strictures and Bile Duct Injury

8

Guido Costamagna, Ivo Boškoski, Pietro Familiari and Andrea Tringali

Case Study 1

Initial Presentation

A 67-year-old female without comorbidities presented to the emergency department with new onset painless jaundice. On physical examination there was a palpable gallbladder (positive Courvoisier-Terrier sign). Blood tests were notable for elevated bilirubin 28 times the normal value, and there was also marked elevation of the other liver function tests.

What Is the Differential Diagnosis for This Case?

Painless jaundice, dark urine, pale stools with or without itching are the most common clinical signs of malignancy involving the pancreatobiliary system. On physical examination, the Courvoisier-Terrier sign is positive when there is significant dilatation of the gallbladder due to common bile duct (CBD) obstruction below the cystic duct insertion leading to a painless palpable mass. These, together with painless jaundice, are clinical signs that almost certainly imply malignancy. If a patient presents with pain and/or fever and rigors, the possibility of biliary stones or other benign causes of biliary obstruction is much higher. A history of chronic pancreatitis, severe acute pancreatitis, and recent hepatobiliary surgery may be consistent with a benign biliary stricture.

The principal markers of cholestasis are bilirubin and alkaline phosphatase [1, 2]. In patients with obstructive jaundice the serum bilirubin is principally in conjugated form (the water soluble form of bilirubin), which if persistent, can predispose to postoperative kidney failure and haemostatic abnormalities [3].

Which Diagnostic Tools Are Available to Evaluate Patients with Obstructive Jaundice?

Noninvasive modalities for the study of the biliopancreatic system include transabdominal ultrasound (US), computed tomography (CT scan), magnetic resonance imaging (MRI), and magnetic resonance cholangiopancreatography (MRCP). These tools can detect dilatation of the bile ducts and confirm the presence, site, extent, and cause of obstruction. Assessment of resect-

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ability for malignant biliary obstructive tumors is also performed with these studies.

US is often the first noninvasive imaging technique used in the evaluation of the bile ducts, gallbladder, and pancreas and is usually the test that demonstrates biliary dilation. The sensitivity and specificity of US in the detection of cholelithiasis and biliary dilation are over 90% [4–8]. However, the ability of US to define the site and cause of biliary obstruction is less reliable. US is widely available and inexpensive, but it typically leads to further studies as it is often inconclusive and does not provide adequate staging or surgical information especially in the setting of suspected neoplasms.

CT scan like US may be the initial test demonstrating dilation of the bile ducts. Calcifications and CBD stones can be seen without contrast, while intravenous contrast can provide vascular landmarks and organ opacification to depict the bile ducts [9]. Sensitivity and specificity in defining the level of biliary obstruction, dilation, and etiology can reach up to 97% [9–12].

MRCP is a noninvasive imaging modality of the pancreatobiliary system. MRCP exploits the differences between fluid filled structures and adjacent soft tissues. It has up to 97% sensitivity and specificity in detecting the level and cause of biliary obstruction [13–15], similar to direct cholangiography. The combination of MRCP with conventional T1 and T2 weighted images can accurately evaluate tumor extension, lymph nodes, and metastases [16, 17]. MRCP provides good-quality cholangiopancreatography images without the use of ionizing radiation. Limitations of MRCP include high costs, patient intolerance, and inability to image patients with incompatible metallic and magnetic objects in the body.

EUS (endoscopic ultrasound endoscopic retrograde cholangiopancreatography (ERCP), and direct cholangioscopy are invasive diagnostic and therapeutic procedures for the evaluation of the pancreatobiliary system. EUS enables better visualization of the extrahepatic biliary tree without interference of bowel gas as the CBD passes posterior to the duodenal bulb. Sensitivity and specificity of EUS for choledocholithiasis are 90 and 100%, respectively [18–20]. EUS also allows highly sensitive evaluation of neoplasms and cystic lesions of the pancreas, and accurate visualization of the duodenal wall and ampulla. However, EUS is limited in the evaluation of the biliary hilum and the right hepatic duct. A significant benefit of EUS is the ability to perform fine needle aspiration (FNA) and tissue acquisition without major complications [21]. In recent years EUS has also become a therapeutic tool for various pancreatobiliary interventions including EUS-guided rendezvous and/or transluminal techniques for drainage of malignant biliary obstruction [22].

ERCP is an invasive procedure that provides an anatomic view of the biliary ducts, establishes the cause of obstruction (stricture or stone), permits tissue sampling, and stent insertion. With the advent of MRCP, ERCP has become almost purely therapeutic. For example, MRCP mapping of hilar strictures before performing ERCP gives precious information about the type, site, and extension of the stricture [23]. This approach reduces the risk of contaminating segments of the biliary tree which, if left undrained, may lead to severe cholangitis. At present, percutaneous biliary drainage in patients with biliary strictures should be limited to those who are not candidates for ERCP, or have failed endoscopic biliary drainage. In selected cases EUS-guided biliary drainage can be an alternative. Most common ERCP-related complications are pancreatitis in up to 7% of cases, followed by hemorrhage, perforation, and infectious complications [24].

Cholangioscopy permits the direct endoscopic visualization of the biliary tree, and it is particularly important in cases of indeterminate strictures. Cholangioscopy allows direct tissue sampling as well as lithotripsy of large biliary stones.

Case Continued

On ultrasound there was massive dilation of the CBD with dilated intrahepatic biliary tree. The gallbladder was alithiasic, but hydropic. Exploration of the pancreatic head was limited due to the intense presence of air in the intestine. The patient underwent CT scan and EUS for further diagnosis and staging, and a primary biliary cancer (T1 N0 M0) was diagnosed.

What Are the Indications for Plastic Versus Metal Stent in Malignant Biliary Strictures?

In a patient with a pancreatobiliary malignancy, the first step is to evaluate the stage, extent, resectability, histological nature, and appropriateness of palliative treatment.

Preoperative biliary drainage in operable patients is still a matter of debate. In a recent meta-analysis Y. Fang et al. [25] found no strong evidence to support "routine preoperative biliary drainage." Large clinical trials are needed to determine the threshold level of bilirubin that will indicate which patients should undergo biliary drainage before surgery.

Before ERCP, it is very important to identify the level and complexity of the biliary stricture. Therapeutic implications differ depending on whether the biliary obstruction is proximal or distal. For instance, in patients with a distal obstruction of the CBD a single plastic or metal biliary stent is usually enough to guarantee adequate biliary drainage, whereas a complex hilar stricture may require a more thorough evaluation with MRCP before ERCP.

The European Society of Gastrointestinal Endoscopy has recently published guidelines on indications for biliary stenting and choosing the types of stents [26]. Placement of one or more plastic or metal stents, or percutaneous biliary drainage, may be required either for preoperative biliary drainage of malignant CBD strictures or complex hilar strictures.

Metal stents can be used for preoperative biliary drainage and do not preclude pancreatic resection [26]. Furthermore, if the patient becomes inoperable, the initial placement of a self-expandable metallic stent (SEMS) guarantees better patency and the possibility of adjuvant therapies without interruptions that may occur due to early clogging, which is usually related to plastic stents [26]. Even if SEMS increases the cost of the initial procedure, preoperative biliary drainage with SEMS is not contraindicated and may ultimately lead to cost savings due to fewer repeat procedures for stent clogging [27]. A randomized study of patients with a pancreatic head mass undergoing surgical resection compared the rate of complications in patients who underwent biliary drainage with a plastic stent 4–6 weeks before surgery to those who had resection within 1 week of diagnosis without stenting [28]. Increased complications related to preoperative biliary drainage occurred in patients undergoing stenting (46 versus 2%), mainly due to cholangitis from plastic stent clogging. There was no significant difference in surgery-related complications between the two groups (37 versus 47%). Placement of SEMS may preclude the issues from this trial with its longer patency rates as discussed below. In this setting clinical trials are necessary to compare early surgery versus preoperative biliary drainage with SEMS, whether covered or uncovered.

The type of SEMS should be chosen after factoring several different variables including the site and length of the stricture. It is always better to use stents with larger diameter (10 mm) due to their longer patency rates. Another important issue regarding SEMS is stent covering. Covered SEMS are prone to migration, but less frequently involved by tissue ingrowth through the meshes, while the opposite happens with uncovered SEMS. Uncovered SEMS are mostly placed in malignant strictures while fully covered and partially covered SEMS are suitable for benign and indeterminate strictures. This is because in uncovered stents tissue ingrowth always occurs through the meshes of the stent, which usually prevents SEMS removal. In a recent retrospective cohort study on 749 patients, no significant difference was found in SEMS patency rate or overall survival between covered and uncovered SEMS for malignant distal biliary strictures [29]. There was a significantly higher rate of migration and pancreatitis in patients with covered SEMS compared to those with uncovered SEMS (36 versus 2% for stent migration and 6% versus 1% for pancreatitis). Similarly, in a recent meta-analysis of over 1000 patients Almadi et al. found no clear benefit in the proportion of stents still patent at 6 and 12 months using covered (fully and partially) rather than uncovered SEMS in malignant distal biliary obstruction [30]. However, covered stents remained patent a mean of 68 days longer than uncovered stents. In addition, there was a higher

migration rate with covered SEMS. A meta-analysis of only randomized trials comparing covered (fully and partially covered) to plastic stents in distal biliary obstruction found similar results [31].

Covered SEMS may lead to increased risk of cholecystitis in patients with an intact gallbladder [32]. This could be related to closure of the cystic duct by the SEMS or possibly due to tumor occluding the opening to the cystic duct. Nevertheless, both meta-analyses discussed above found no significant difference in the rate of cholecystitis between covered and uncovered SEMS for distal malignant strictures [30, 31]. Given the currently available data, covered SEMS does not appear to offer advantages over uncovered SEMS in malignant distal biliary strictures. However, when a malignancy has not yet been definitively diagnosed, after tissue sampling has been done, it is better, whenever possible, to place a covered stent that can be easily removed.

In patients with inoperable malignant distal biliary obstruction, the choice of the optimal stent depends mostly on patient survival and disease extent. The choice of stent (plastic versus metal) for palliation of malignant biliary strictures has been the object of many clinical trials. Immediate palliation of jaundice has been observed following placement of both plastic and metal stents in more than 95 % of cases, but what differs is the duration of stent patency. Plastic stents can remain patent up to 5 months while for SEMS, patency increases to 10 months or more [33–35]. Placement of plastic stents in patients with long survival implies the need for additional ERCPs for stent replacement, thus influencing the final costs of the treatment [33–35]. Therefore, for patients with short life expectancies, plastic stents are appropriate while those with longer expected survival (> 6 months) should have SEMS placed.

As far as hilar strictures are concerned, it seems that SEMS are superior to plastic stents for palliation in terms of survival, patency, complications, need for re-interventions, and cost-effectiveness [36–38]. Hilar strictures will be discussed in further detail later in the chapter.

Technique of Plastic Biliary Stent Insertion and Removal

The principle of biliary stenting is to bypass a stricture allowing the passage of bile from the liver into the duodenum. One biliary plastic stent can be enough to guarantee complete biliary drainage in the majority of patients with either benign or malignant distal CBD stricture. It is preferable to place 10 Fr stents in patients with malignant distal biliary strictures since these have superior patency to plastic stents with smaller diameter.

After deep biliary cannulation, a guidewire is left in place and a biliary sphincterotomy may be performed. Sphincterotomy may not be necessary when placing a single plastic stent unlike when inserting multiple stents. Before stent insertion, and when a malignant biliary stricture is suspected, a biliary biopsy and/or brushing can be performed (see Chap. 7 for further discussion on diagnosing biliary strictures). It is rarely necessary to dilate a distal biliary stricture before placement of a single 10 Fr stent, but if multiple stents are being placed, stricture dilation is important. For this purpose a tapered dilating catheter (10–11.5 Fr) or a hydrostatic dilation balloon (4–6 mm) can be used. When inserting multiple plastic biliary stents, a longer stent should be placed first and left one centimeter below the papilla because the friction of the second stent can result in intrabiliary dislocation of the first one. Using lubricants such as silicone spray or paraffin may help prevent stent displacement into the bile duct as well as advancing additional stents slowly into the bile duct.

Generally, when the biliary stricture results from pancreatic cancer, the stent length is 5–7 cm. Too long stents should be avoided because distal migration can rarely lead to the distal end of the stent causing duodenal perforation. The length of the stricture can be measured in different ways. The easiest way is to mark the proximal end of the stricture with fingers on the cannulation catheter while performing the exchange over the wire until the end of the cannula is seen endoscopically outside the papilla. Another way to measure the stricture length uses a Cotton-Huibregtse

catheter (Cook Endoscopy, Winston-Salem, NC) that has two radiopaque markers on the distal end (located 7 cm apart).

With the guidewire deep in the liver, a guiding catheter with the stent preloaded and the pusher catheter lying behind the stent is advanced over the wire until the tip of the guiding catheter is beyond the stricture. The assistant then releases the pusher catheter, which the endoscopist pushes over the guiding catheter to advance the stent forward. During this time, the assistant should keep the guidewire and the guide catheter in balance by holding tension on them in the direction opposite to which the endoscopist is pushing the stent. This maneuver is called "traction" and helps the progression of the stent. Opening and closing the elevator while pushing the stent pusher allows advancing of the stent. The stent can also be pushed with the endoscope using the "shaft torquing maneuver" by dialing up the big wheel of the scope and slightly pulling out the scope while torquing the scope. Attention should be paid not to place the stent intrabiliary nor too far outside the duct. Direct stent visualization can be achieved by turning down the big wheel of the scope when the stent is almost deployed.

When the operator is sure that the stent is in the correct position, the assistant retrieves the guidewire and the guiding catheter from the bile duct while the operator keeps the stent pusher under direct endoscopic vision against the distal end of the stent, and the stent is deployed. Then the pusher catheter is removed. If stent patency and positioning need to be checked, contrast can be injected through the guide catheter after removing the guidewire. Additional stents can be placed with the same technique by cannulating the bile duct alongside the first stent. A nasobiliary drain can be left in place beside the stent to allow flushing of the biliary three with saline. This may be done in cases where there is a concern that sludge may clog the stent immediately after the procedure.

Biliary plastic stents can be easily removed with rat-tooth forceps or a snare. Duodenoscopes with a 4.2-mm channel allow through-the-channel stent extraction for 10 Fr stents. Removing intrabiliary migrated stents is almost always a challenging procedure. It requires patience, a skilled endoscopist, optimal fluoroscopy, knowledge of accessories available to help with removal, and ingenuity. For stents that have migrated just inside the bile duct, a rat-tooth forceps is a very useful tool. This can be gently inserted into the bile duct under fluoroscopic guidance to try to capture the distal end of the stent. Care should be taken not to accidentally push the stent further into the duct. Another option for migrated stent removal is advancing a biliary stone extraction balloon beside the stent as far up and even above the proximal end of the stent if possible, inflating the balloon, and dragging the stent out with the balloon. The Soehendra stent retriever (Cook Endoscopy, Bloomington, IN) can also be helpful, but the distal end of the stent must be cannulated with a wire first using fluoroscopy in order to then attach the device to the stent. This is a wire-guided spring coil catheter with a threaded metal screwlike tip, which can be screwed into the distal end of the plastic stent by rotating the handle of the stent retriever clockwise. Snares, Dormia baskets, and other accessories may also be useful.

Hilar Strictures

The approach to malignant hilar strictures differs from distal biliary strictures. In resectable hilar tumors (Bismuth type I, Fig. 8.1), safer biliary drainage can be obtained with percutaneous biliary drainage, rather than endoscopically [26]. If palliative drainage is planned, MRI should be performed to assess the hepatobiliary anatomy before attempting drainage [26, 39]. Some authors suggested that endoscopic drainage of 25–30% of the hepatic parenchyma is adequate to relieve jaundice [40, 41]. Nevertheless, morbidity and mortality rates have been higher with unilateral compared to bilateral endoscopic biliary drainage [26, 39].

Targeted unilateral endoscopic drainage using a single stent of MRCP-selected ducts has been associated with a reduced risk of post-ERCP cholangitis [23]. However, draining more than 50% of the liver parenchyma is associated with

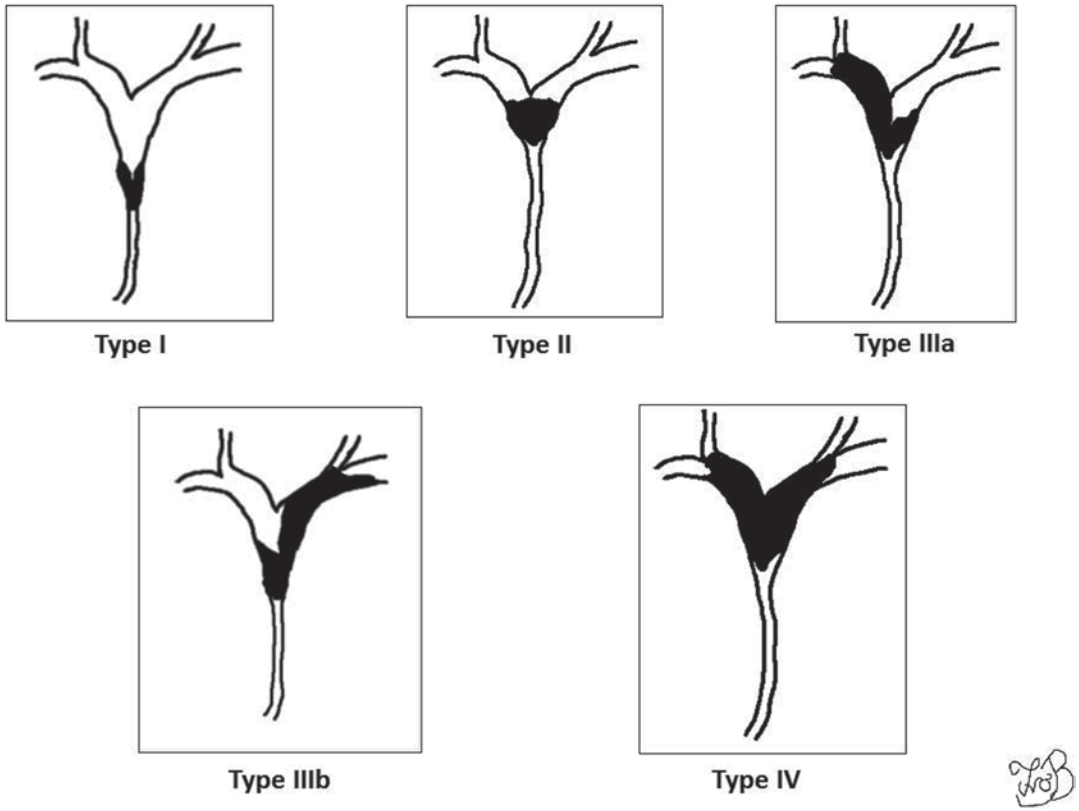

Fig. 8.1 Bismuth and Corlette classification of malignant biliary strictures

higher effectiveness and longer survival [26]. Incomplete biliary drainage, especially if opacified ducts have been left undrained, often leads to cholangitis. To minimize risk of cholangitis, MRCP should be performed to map out the biliary tree before ERCP, a wire can be used rather than contrast to access the intrahepatic ducts, as much bile as possible should be aspirated to decompress the biliary system before contrast injection, and overinjection should be avoided. Some authors have also suggested air cholangiography in lieu of contrast to visualize the biliary system during planned placement of unilateral metal stent [42]. This technique involves aspirating at least 20 cc of bile first and then injecting 10–15 cc of air into the bile duct. Antibiotics should be administered in every patient to minimize the risk of cholangitis before and after ERCP typically for 5–7 days.

The intrahepatic bile ducts in complex malignant hilar strictures generally are drained initially with multiple plastic stents (Fig. 8.2a and b). Negotiation of a complex hilar stricture requires a highly skilled endoscopist, adequate accessories, time, and patience. In some cases, pneumatic or mechanical dilation of the neoplastic stricture can facilitate the placement of multiple stents. The length of the stents in malignant hilar strictures is usually between 12 and 15 cm. During bilateral stent placement whether with plastic or metal stents, it is always better first to drain the left biliary tree due to its anatomy.

Multiple SEMS are usually placed in patients previously treated with plastic stents or percutaneous biliary drainage, and are rarely the initial treatment (especially if more than two SEMS are required due to the small caliber of the CBD below the stricture). Previously placed plastic stents are exchanged to SEMS only in symptomatic patients with clear signs of stent occlusion, and of course always accounting for the patients' general condition and expected survival.

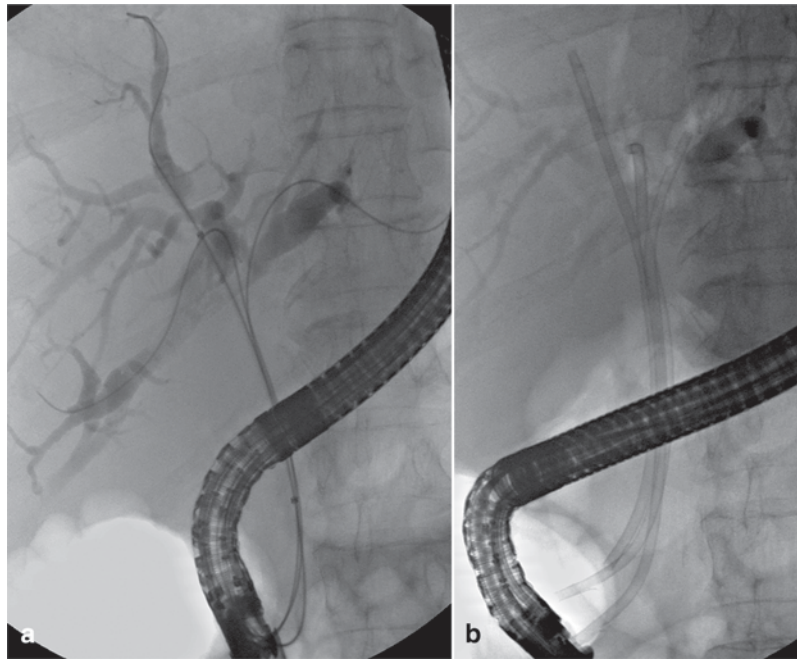

Fig. 8.2 **a** Type III Bismuth and Corlette malignant hilar stricture with three guidewires in place. **b** Placement of three 8.5 French plastic stents

Recently it has been described that SEMS can be used as a bridge to surgery in hilar cholangiocarcinoma without major complications [43].

Technique of Inserting and Removing Self-Expandable Metal Stents

After deep cannulation of the bile ducts, a biliary sphincterotomy may be performed. A recent randomized trial of patients with unresectable pancreatic cancer undergoing partially covered SEMS placement with or without biliary sphincterotomy found no difference in adverse events between the two groups, implying that sphincterotomy is not essential before SEMS insertion [44]. In distal biliary strictures, after gaining access to the bile duct, the guidewire is passed through the stricture. Dilation of the stricture before SEMS placement is rarely necessary because the radial force of the nitinol stents dilates the stricture gradually over 24–72 h. The SEMS is delivered over the guidewire and deployed under endoscopic and fluoroscopic vision. Because the stents have a tendency to move forward into the bile duct during deployment, gentle traction in the opposite direction should be applied by the endoscopist on the stent delivery system to maintain position. Some SEMS deploying systems allows contrast injection through the catheter in order to check immediately the correct position and the patency of the stent.

There are numerous types of SEMS available commercially with variations in length, expanded diameter, presence or absence of covering, design and material of the mesh, ability to reconstrain the stent during deployment, presence of stent shortening following deployment, and size of the delivery system. The endoscopists should be familiar with the stents in their endoscopy unit. Stents that cannot be recaptured during deployment must be carefully and slowly deployed under constant endoscopic and fluoroscopic visualization. For stents that shorten, when possible the stent is deployed with the stricture positioned in the middle of the stent.

Multiple SEMS placement is performed for palliation of complex malignant hilar strictures. This procedure is quite different from single SEMS placement. After selective opacification

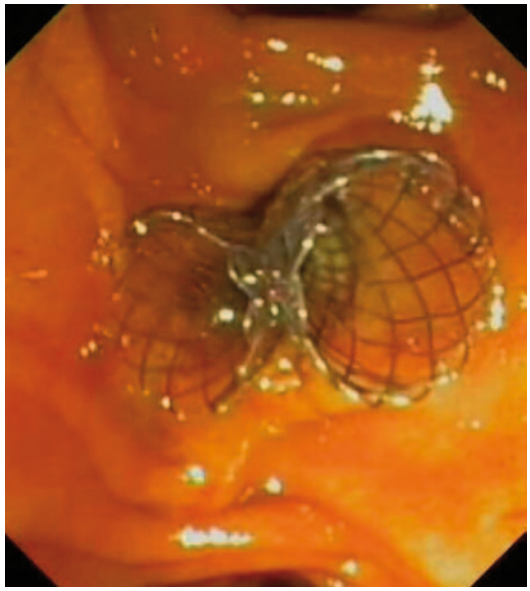

Fig. 8.3 Endoscopic view of two self-expandable metal stents

and cannulation of the intrahepatic ducts above the complex stricture, two to four guidewires are placed through the stricture deeply into the intrahepatic ducts that should be drained. Every metal stent is released under endoscopic and fluoroscopic control and "side-by-side" over the previously placed guidewires. It is advisable to release the stents trans-papillary in order to facilitate future re-interventions for SEMS occlusion (Fig. 8.3). Another reported technique of deploying bilateral hilar metal stents is the stent-within-stent technique using large cell width SEMS [45]. This may be useful for patients with small extrahepatic bile duct diameter which would make deploying multiple SEMS adjacent to each other difficult. Guidewire access to typically the left biliary system is procured followed by SEMS placement into that duct. Wire access to this system is maintained while removing the stent delivery system and advancing an ERCP catheter over the wire. After pulling the wire back into the catheter, it is advanced into the other intrahepatic system by passing the wire in between the interstices of the first stent. The interstices must be dilated using a 4–8-mm hydrostatic balloon dilator or a Soehendra stent retriever. Then the second stent is advanced through the interstices of the first stent into position.

The number of stents that should be placed is usually chosen according to the complexity of the stricture. It is ideal although not always possible to place two SEMS for complete drainage of Bismuth type II stricture, three stents for type III, and three to four stents for type IV. In addition, SEMS for palliative treatment of malignant hilar strictures always must be uncovered in order to avoid occluding the side branches of the bile duct [26].

Multiple SEMS in complex malignant hilar strictures do not impede light delivery for photodynamic therapy but adjustments of the light dose are required [26]. SEMS in malignant hilar strictures can clog due to sludge and tissue ingrowth and/or overgrowth. This can be managed by extracting the sludge and debris with a balloon or, in cases of ingrowth, by the placement of additional SEMS or plastic stents inside the metal one.

Removing covered SEMS is usually straightforward and accomplished by grasping the retrieval loop at the end of the stent with rat tooth forceps, snaring the end of the stent, or using the stent-in-stent technique. This involves placing a second longer covered SEMS within the first stent and removing both about 2 weeks later with the hope that the second stent causes pressure necrosis of the ingrown/overgrown tissue [46]. Other typically more labor-intensive techniques of removing uncovered SEMS have been reported in various case reports and series including the use of endoscopic scissors to cut the distal end of the stent and sequentially remove each wire of the stent, and grasping the proximal end of the stent with rat tooth forceps and then pulling back to invaginate the stent [47, 48].

Case Continued

The patient underwent surgical consultation. Because of very high bilirubin levels, the surgeon preferred to delay surgery. The patient underwent endoscopic preoperative biliary drainage.

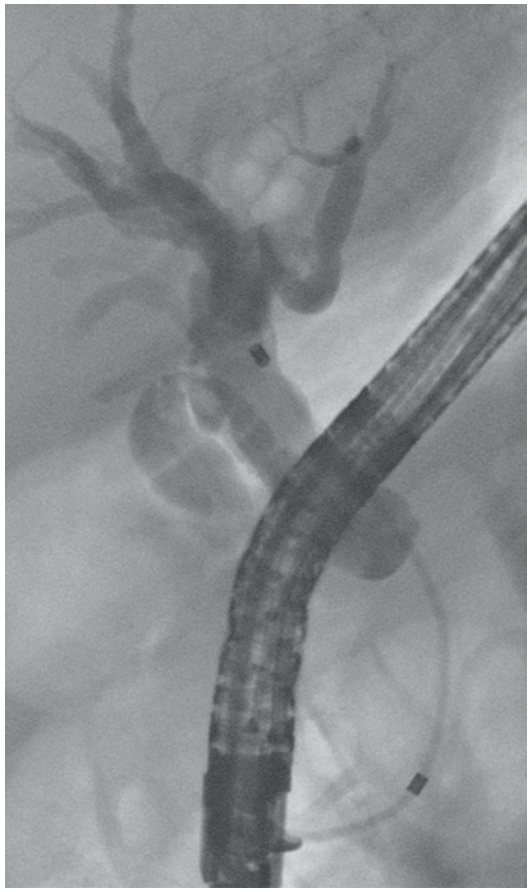

Fig. 8.4 Type I Bismuth and Corlette malignant biliary stricture with dilation of the biliary tree above the stricture

On ERCP (Fig. 8.4) there was a malignant-appearing stricture located in the distal CBD with dilation of the proximal biliary three (Type I Bismuth and Corlette). Biliary forceps biopsy and brushing were performed at the level of the stricture, and one 10 Fr, 5-cm-long plastic stent was placed because the surgeon planned to take the patient to surgery soon. If surgery were to be delayed, a SEMS would have been indicated. The bilirubin level decreased to twice the normal range after 2 days. Biliary histology confirmed cholangiocarcinoma, while cytology was not diagnostic. The patient underwent pancreaticoduodenectomy (Whipple procedure) 1 week after ERCP and on 12 months follow-up was free of disease.

Case Study 2

Initial Presentation

A 35-year-old male presented with itching and dark urine. A laparoscopic cholecystectomy had been performed 6 months before. Liver function tests were all elevated and US showed dilation of the intrahepatic bile ducts. Since post-cholecystectomy bile duct injury was suspected, the patient underwent MRCP. On MRCP a type III Bismuth and Lazorthes [49], postoperative biliary stricture (POBS) was diagnosed. The stricture was located at the level of the main biliary confluence, which was not transected. Metal clips placed during cholecystectomy likely caused the stricture.

How Are Bile Duct Injuries and Postoperative Biliary Strictures Classified?

Injury of the bile ducts may occur during any surgical procedure involving the biliary tract. The main cause of bile duct injuries is laparoscopic cholecystectomy, and it is six times higher compared with open cholecystectomy [50, 51]. A classification of postoperative biliary injuries has been proposed by Bergman et al. in 1996 (Table 8.1) [52].

Postoperative biliary strictures (POBS) usually develop as a consequence of an injury to the bile ducts. Surgical repair with hepatico-jejunistomy is the traditional treatment of POBS. Bismuth et al in 1978 proposed a classification

Table 8.1 Types of bile duct injury according to Bergman et al. [52]

Type A	Cystic duct leak or leakage from aberrant or peripheral hepatic radicles (minor lesions)
Type B	Major bile duct leak with or without concomitant biliary stricture (major lesions)
Type C	Bile duct strictures without bile leakage (major lesions)
Type D	Complete transection of the duct with or without excision of some portion of the biliary tree (major lesions)

Table 8.2 Bismuth and Lazorthes classification of postoperative biliary stricture

Type I	≥2 cm distal to the hepatic bifurcation
Type II	<2 cm distal to the hepatic bifurcation
Type III	At the level of the hepatic bifurcation
Type IV	Involves the right or left hepatic duct
Type V	Extends into the left or right intrahepatic branch ducts

of postoperative biliary stricture that is based on the location of the stricture (Table 8.2) [49]. Endoscopy with placement of multiple biliary stents has become the preferred treatment for POBS [52–54].

Overview of Management of Bile Duct Injuries

With some exceptions, the endoscopic treatment of postoperative biliary injuries and strictures is possible only when the continuity of the bile ducts is maintained and the ducts have not been completely transected. Surgery is usually indicated for complete transection of the CBD (Bergman type D) (Table 8.1, Fig. 8.5) and refractory strictures. The endoscopic treatment of major biliary injuries and strictures mainly consists in the placement of one or more biliary plastic stents (Fig. 8.6) bypassing the site of injury (Video 8.1). Minor bile leaks may be treated by short plastic stent placement to overcome the pressure gradient at the biliary sphincter and allow the bile to flow through the stent into the duodenum rather than out the leak. During initial ERCP, cholangiogram should be performed carefully to examine for choledocholithiasis which is present in about 25% of bile leaks. The stent is usually removed after 1–3 months. After stent removal an occlusion cholangiogram should be performed to assess for complete healing of the bile leak, ongoing choledocholithiasis, and the presence of strictures. Refractory bile leaks may be managed by prolonged plastic stent placement, combination of biliary sphincterotomy with stent, or covered SEMS [55, 56]. If a biliary stricture is identified, the patient should undergo placement of multiple biliary stents to dilate the stricture.

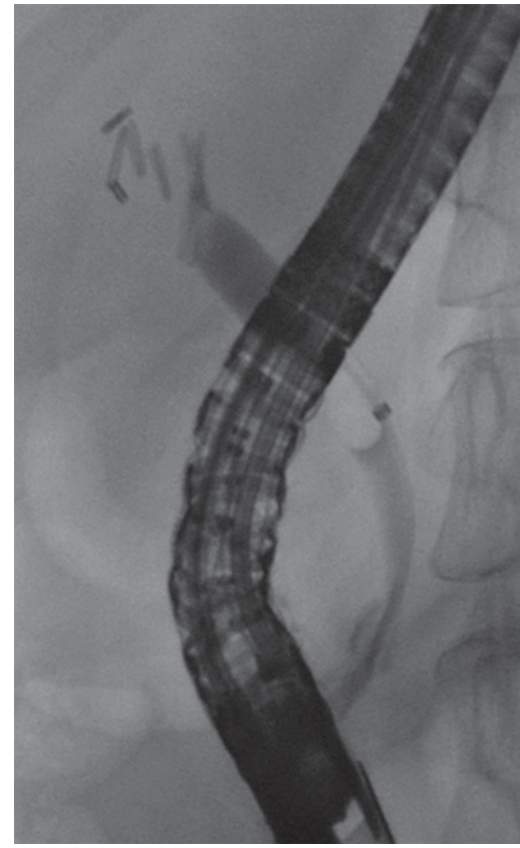

Fig. 8.5 Occlusive cholangiography showing complete transection of the common bile duct with multiple metal clips placed during laparoscopic cholecystectomy (Bergman type D lesion of the common bile duct)

How to Manage Postoperative Biliary Strictures and Other Benign Biliary Strictures

POBS occur frequently after a bile duct injury as a result of fibrotic scarring and generally are diagnosed a few months later. In patients with suspected POBS, an MRCP should be performed to assess the type and morphology of the stricture. CT scan can be useful to evaluate the liver parenchyma for atrophy, especially with long-standing strictures.

Endoscopic treatment of POBS is quite different from the treatment of malignant biliary strictures (Video 8.1). Negotiation of the stricture with a guidewire is usually much more difficult in POBS than in a malignant stricture. This is because POBS are usually short, asymmetric, angu-

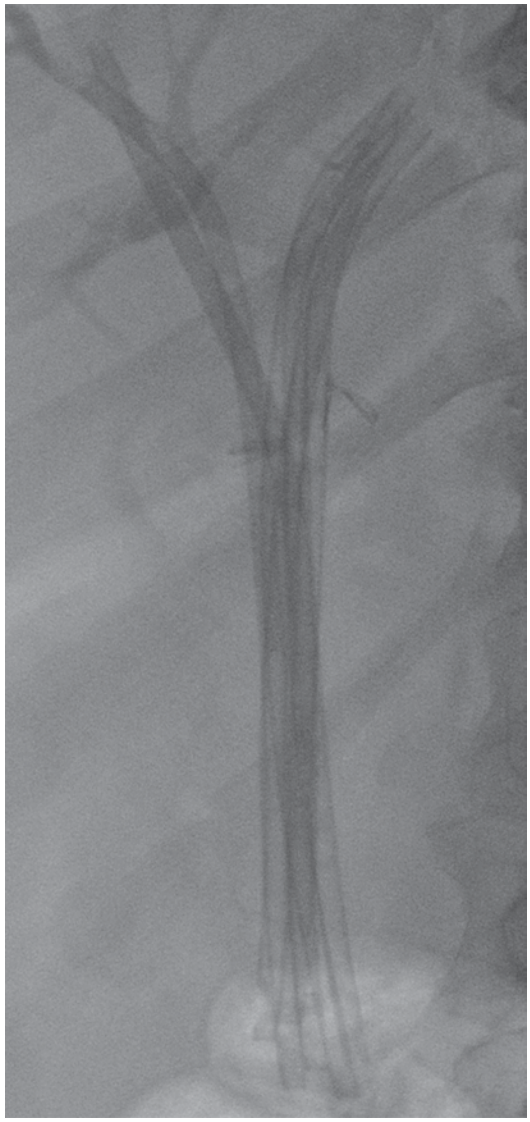

Fig. 8.6 Plain X-ray after placement of six plastic stents for postoperative biliary stricture. Metal clips placed near the hilum during laparoscopic cholecystectomy are also visible. This is the same patient in Fig. 8.7a

lated, and rich with fibrotic tissue. It is preferable to use hydrophilic guidewires (0.035, 0.021, or 0.018 in. in diameter) with a straight or curved (J-shaped) tip. Proper technique for torquing guidewires requires skill, good fluoroscopy, and patience. Torquing guidewires must be done very gently to avoid bile duct perforation and additional injury.

In order to pass the stricture, the direction of the catheter and the wire must be in the same axis as the stricture. Orientation of the guidewire can be achieved by pulling an inflated stone extraction balloon below the stricture. Furthermore, there are different types of rotatable catheters that can be useful in some cases.

Once the stricture has been negotiated with the guidewire, placement of one or two large bore stents (usually 10 French) can suffice as initial treatment, especially in a type I Bismuth and Lazorthes POBS. In complex POBS, especially type III, IV, and V, placement of more stents may be necessary to avoid cholangitis due to undrained opacified ducts (Video 8.1). In these cases thinner stents are often initially placed.

Balloon dilation alone as treatment is immediately effective, but inadequate because of the high restenosis rate (up to 47%) [57–59]. Dilating the stricture is frequently required before stent placement. It is recommended to choose the size of the balloon according to the size of the duct below the stricture in order to avoid perforation. Balloon dilation is usually performed only during the first stenting procedure and should be avoided during subsequent procedures because the forceful tissue disruption provoked by balloons may cause traumatic damage of the bile ducts, leading to the development of additional fibrosis at the level of the stricture.

Currently, one of the most accepted protocols to manage POBS consists of the insertion of as many 10 French plastic stents as possible side-by-side through the stricture. The stents are usually exchanged every 3–5 months. The number of the stents is increased at every ERCP. The treatment is usually continued for 12 months, or until the complete disappearance of any narrowing of the bile duct at cholangiography. [53].

Multiple biliary plastic stent placement is the treatment of choice for POBS, with excellent long-term results [26, 53, 54]. In our center, after mean 7-year follow-up, POBSs recurred in 11% of treated patients, which were retreated with stenting. Following another 7 years on average, no further recurrences were noted. Benign biliary strictures from other etiologies, including chronic pancreatitis and post-liver transplant (Chap. 9),

also respond well to this technique of multiple plastic stenting. Anastomotic strictures following liver transplant resolved in 97 % of patients treated for over 12 months with plastic stenting, and dropped significantly to 78 % in patients stented for less than 12 months [60]. Non-anastomotic strictures do not respond as well with 50–75 % resolution [61]. Chronic pancreatitis-related biliary strictures are also more challenging to treat with small series reporting overall 44–92 % success with this technique [57, 62, 63].

Is There a Role for Fully Covered SEMS in Postoperative Biliary Strictures and Other Benign Biliary Strictures?

Fully covered SEMS may have a role in the management of POBS although they are not FDA approved for use in benign biliary strictures. Many reports have been published in the literature, but usually have included patients with strictures caused by many different diseases (e.g., chronic pancreatitis, liver transplantation, primary sclerosing cholangitis, stones) and with only short follow-up following SEMS removal. Recently a large multicenter study of 187 patients with benign biliary strictures (68 % chronic pancreatitis) treated with covered SEMS followed them for 5 years after stent removal [64]. Covered SEMS were left in for a median 28 months in chronic pancreatitis, 13 months in POBS, and 9 months in liver transplant-related strictures. All stents were removed using rat-tooth forceps to grasp the retrieval loop on the end of the SEMS or snare to grab the distal end of the SEMS with only 3 patients requiring the stent-in-stent technique. Stent migration occurred in 29 %. Strictures had resolved in 76 % of patients at the time of stent removal, and over 5 years, 15 % recurred. Some cases of "de novo strictures" that occurred at the level of the proximal end of the SEMS have been observed. Complications related to the stent and stent removal occurred in 27 % of patients with cholangitis and abdominal pain being most common. Interestingly there was a trend toward increased cholecystitis when the stent covered the cystic duct orifice compared to when it did not (7 % versus 0 %, $p = 0.074$). While these results are

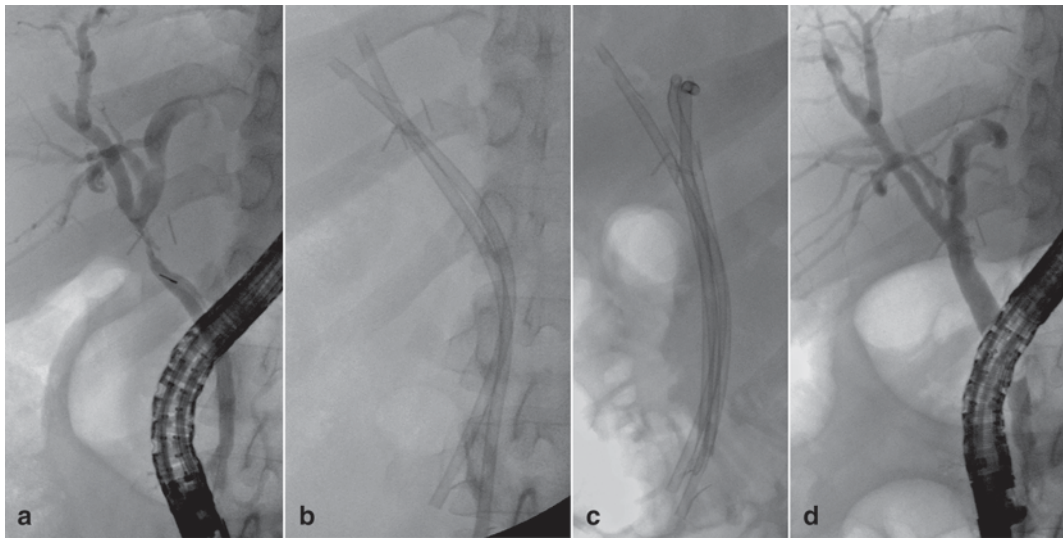

Fig. 8.7 **a** Cholangiography showing type III Bismuth and Lazorthes postoperative biliary stricture with dilation of the intrahepatic biliary tree above the stricture. Note the metal clips placed during laparoscopic cholecystectomy located near the stricture. **b** Placement of two 10 French plastic biliary stents. **c** Placement of increasing number of plastic biliary stents every 3 months over 1 year. **d** Cholangiography showing complete resolution of the type III Bismuth and Lazorthes postoperative biliary stricture

encouraging, the use of fully covered SEMS for benign biliary strictures should be limited to clinical trials or in situations where plastic stenting has failed [26].

Case Continued

The patient underwent ERCP that confirmed a type III Bismuth and Lazorthes stricture and during the first treatment only two plastic stents were placed (Fig. 8.7a and b). The patient underwent three more ERCPs every 3 months over a period of 1 year with multiple plastic stents exchanged (Fig. 8.7c) until complete resolution of the stricture (Fig. 8.7d).

At 2 years follow-up, the patient had normal liver function tests and was in good clinical condition.

Conclusion

The management of biliary strictures and bile duct injuries is challenging, and the optimal treatment for any individual patient should be determined in a multidisciplinary manner. In the future we will have more sophisticated diagnostic tools and accessories that will help to determine the nature of a biliary stricture as well as algorithms that will suggest the best diagnostic and therapeutic approach.

Key Points

- Understanding the nature and morphology of a bile duct stricture is mandatory before ERCP especially with hilar strictures.
- Biliary stents should be chosen on the basis of the pathology and the type of stricture.
- Uncovered metal stents are appropriate preoperatively in surgical candidates with malignant distal biliary strictures.
- In inoperable patients, metal stents offer better patency and allow for other palliative therapies compared to plastic stents.
- Hilar strictures may be difficult to treat and MRCP should be performed before ERCP to visualize the biliary anatomy and plan appropriate treatment.
- Placement of multiple plastic stents is still the treatment of choice in postoperative biliary strictures as well as other benign biliary strictures with excellent long-term results.
- Fully covered SEMS are not FDA approved for use in benign biliary strictures although increasing number of studies are being published suggesting encouraging outcomes with these stents.

Conflict of Interest The authors declare no conflict of interest

Video Caption

Video 8.1 Multiple plastic stents of benign biliary strictures

Benign Biliary Strictures After Laparoscopic Cholecystectomy

- Benign biliary strictures after laparoscopic cholecystectomy can be successfully treated by endoscopy.
- In this case a surgical clip was placed across the common bile duct.
- A 0.018" guidewire was successfully advanced through the clip, and a dilator was passed as a wedge to open the clip. An 11.5 Fr stent was then placed to drain the bile ducts and dilate the stricture.
- Three months later after stent removal, the biliary stricture was not completely dilated, and two 11.5 Fr stents were placed.
- Three months later after the stents were removed, cholangiography showed satisfactory dilation of the stricture.

Benign Biliary Stricture After Surgery for Bile Duct Injury

- In this patient a T tube was placed to repair a section of the common bile duct during laparoscopic cholecystectomy.

- Due to the presence of a stricture two stents were placed after removal of the T tube.
- Three months later the stents were removed and due to a persistent tight stricture, 3 large bore prostheses were placed.
- Three months later the stricture was completely resolved.

Complex Benign Biliary Strictures

- Complex strictures involving the hepatic confluence can also be treated endoscopically.
- In this case, the tight stricture was dilated with a 4 mm balloon, and the number of the stents inserted was increased every 3 months up to three 11.5 Fr prostheses, resulting in resolution of the stricture after removal as seen during occlusion cholangiography.

Simultaneous Benign Biliary Stricture and Leak

- A leak from the common bile duct and bile duct stricture are present in the same case.
- After gently dilation of the stricture with a bougie dilator, one stent was placed mainly to treat the leak.
- Aggressive stricture dilation was attempted 3 months later by balloon dilation and insertion of two stents.
- Three months later 4 stents were placed, leading to resolution of the stricture after stent removal.

References

1. Limdi JK, Hyde GM. Evaluation of abnormal liver function tests. Postgrad Med J. 2003;79:307–12.
2. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology. 2002;123:1367–84.
3. Green J, Better OS. Systemic hypotension and renal failure in obstructive jaundice-mechanistic and therapeutic aspects. J Am Soc Nephrol. 1995;5:1853–71.
4. Cohen SM, Kurtz AB. Biliary sonography. Radiol Clin North Am. 1991;29:1171–98.
5. Blackbourne LH, Earnhardt RC, Sistrom CL, Abbitt P, Jones RS. The sensitivity and role of ultrasound in the evaluation of biliary obstruction. Am Surg. 1994;60:683–90.
6. Harvey RT, Miller WT, Jr. Acute biliary disease: initial CT and follow-up US versus initial US and follow-up CT. Radiology. 1999;213:831–6.
7. Stroszczynski C, Hunerbein M. Malignant biliary obstruction: value of imaging findings. Abdom Imaging. 2005;30:314–23.
8. Laing FC, Jeffrey RB, Jr., Wing VW, Nyberg DA. Biliary dilatation: defining the level and cause by real-time US. Radiology. 1986;160:39–42.
9. Baron RL. Computed tomography of the bile ducts. Semin Roentgenol. 1997;32:172–87.
10. Foley WD, Quiroz FA. The role of sonography in imaging of the biliary tract. Ultrasound Q. 2007;23:123–35.
11. Pedrosa CS, Casanova R, Rodriguez R. Computed tomography in obstructive jaundice. Part I: the level of obstruction. Radiology. 1981;139:627–34.
12. Pedrosa CS, Casanova R, Rodriguez R. Computed tomography in obstructive jaundice. Part I: the level of obstruction. Radiology. 1981;139:627–34.
13. Romagnuolo J, Bardou M, Rahme E, Joseph L, Reinhold C, Barkun AN. Magnetic resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. Ann Intern Med. 2003;139:547–57.
14. Guibaud L, Bret PM, Reinhold C, Atri M, Barkun AN. Bile duct obstruction and choledocholithiasis: diagnosis with MR cholangiography. Radiology. 1995;197:109–15.
15. Magnuson TH, Bender JS, Duncan MD, Ahrendt SA, Harmon JW, Regan F. Utility of magnetic resonance cholangiography in the evaluation of biliary obstruction. J Am Coll Surg. 1999;189:63–71.
16. Barish MA, Soto JA. MR cholangiopancreatography: techniques and clinical applications. AJR Am J Roentgenol. 1997;169:1295–303.
17. Adamek HE, Albert J, Breer H, Weitz M, Schilling D, Riemann JF. Pancreatic cancer detection with magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography: a prospective controlled study. Lancet. 2000;356:190–3.
18. Chen CC. The efficacy of endoscopic ultrasound for the diagnosis of common bile duct stones as compared to CT, MRCP, and ERCP. J Chin Med Assoc. 2012;75:301–2.
19. Canto MI, Chak A, Stellato T, Sivak MV Jr. Endoscopic ultrasonography versus cholangiography for the diagnosis of choledocholithiasis. Gastrointest Endosc. 1998;47:439–48.
20. Amouyal P, Amouyal G, Levy P, Tuzet S, Palazzo L, Vilgrain V, Gayet B, Belghiti J, Fekete F, Bernades P. Diagnosis of choledocholithiasis by endoscopic ultrasonography. Gastroenterology. 1994;106:1062–7.
21. Yusuf TE, Bhutani MS. Role of endoscopic ultrasonography in diseases of the extrahepatic biliary system. J Gastroenterol Hepatol. 2004;19:243–50.
22. Khashab MA, Valeshabad AK, Modayil R, Widmer J, Saxena P, Idrees M, Iqbal S, Kalloo AN, Stavropoulos SN. EUS-guided biliary drainage by using a stan-

dardized approach for malignant biliary obstruction: rendezvous versus direct transluminal techniques (with videos). Gastrointest Endosc. 2013;78:734–41.
23. Hintze RE, Abou-Rebyeh H, Adler A, Veltzke-Schlieker W, Felix R, Wiedenmann B. Magnetic resonance cholangiopancreatography-guided unilateral endoscopic stent placement for Klatskin tumors. Gastrointest Endosc. 2001;53:40–6.
24. Mallery JS, Baron TH, Dominitz JA, Goldstein JL, Hirota WK, Jacobson BC, Leighton JA, Raddawi HM, Varg JJ, Waring JP, Fanelli RD, Wheeler-Harbough J, Eisen GM, Faigel DO. Complications of ERCP. Gastrointest Endosc. 2003;57:633–8.
25. Fang Y, Gurusamy KS, Wang Q, Davidson BR, Lin H, Xie X, Wang C. Meta-analysis of randomized clinical trials on safety and efficacy of biliary drainage before surgery for obstructive jaundice. Br J Surg. 2013;100:1589–96.
26. Dumonceau JM, Tringali A, Blero D, Deviere J, Laugiers R, Heresbach D, Costamagna G. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy. 2012;44:277–98.
27. Cavell LK, Allen PJ, Vinoya C, Eaton AA, Gonen M, Gerdes H, Mendelsohn RB, D'Angelica MI, Kingham TP, Fong Y, Dematteo R, Jarnagin WR, Kurtz RC, Schattner MA. Biliary self-expandable metal stents do not adversely affect pancreaticoduodenectomy. Am J Gastroenterol. 2013;108:1168–73.
28. van der Gaag NA Rauws EA van Eijck CH Bruno MJ van der Harst E Kubben FJ Gerritsen JJ Greve JW Gerhards MF de Hingh IH Klinkenbijl JH Nio CY de Castro SM Busch OR van Gulik TM Bossuyt PM Gouma DJ. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362:129–37.
29. Lee JH, Krishna SG, Singh A, Ladha HS, Slack RS, Ramireddy S, Raju GS, Davila M, Ross WA. 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;78:312–24.
30. 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.
31. Saleem A, Leggett CL, Murad MH, Baron TH. Meta-analysis of randomized trials comparing the patency of covered and uncovered self-expandable metal stents for palliation of distal malignant bile duct obstruction. Gastrointest Endosc. 2011;74:321–327.
32. Yoon WJ, Lee JK, Lee KH, Lee WJ, Ryu JK, Kim YT, Yoon YB. A comparison of covered and uncovered Wallstents for the management of distal malignant biliary obstruction. Gastrointest Endosc. 2006;63:996–1000.
33. Davids PH, Groen AK, Rauws EA, Tytgat GN, Huibregtse K. Randomised trial of self-expanding metal stents versus polyethylene stents for distal malignant biliary obstruction. Lancet. 1992;340:1488–92.
34. Kaassis M, Boyer J, Dumas R, Ponchon T, Coumaros D, Delcenserie R, Canard JM, Fritsch J, Rey JF, Burtin P. Plastic or metal stents for malignant stricture of the common bile duct? Results of a randomized prospective study. Gastrointest Endosc. 2003;57:178–82.
35. 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.
36. Wagner HJ, Knyrim K, Vakil N, Klose KJ. Plastic endoprostheses versus metal stents in the palliative treatment of malignant hilar biliary obstruction. A prospective and randomized trial. Endoscopy. 1993;25:213–8.
37. Mukai T, Yasuda I, Nakashima M, Doi S, Iwashita T, Iwata K, Kato T, Tomita E, Moriwaki H. 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.
38. Perdue DG, Freeman ML, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Overby CS, Ryan ME, Bochna GS, Snady HW, Moore JP. Plastic versus self-expanding metallic stents for malignant hilar biliary obstruction: a prospective multicenter observational cohort study. J Clin Gastroenterol. 2008;42:1040–6.
39. Anderson MA, Appalaneni V, Ben-Menachem T, Decker GA, Early DS, Evans JA, Fanelli RD, Fisher DA, Fisher LR, Fukami N, Hwang JH, Ikenberry SO, Jain R, Jue TL, Khan K, Krinsky ML, Malpas PM, Maple JT, Sharaf RN, Shergill AK, Dominitz JA, Cash BD. The role of endoscopy in the evaluation and treatment of patients with biliary neoplasia. Gastrointest Endosc. 2013;77:167–74.
40. Dowsett JF, Vaira D, Hatfield AR, Cairns SR, Polydorou A, Frost R, Croker J, Cotton PB, Russell RC, Mason RR. Endoscopic biliary therapy using the combined percutaneous and endoscopic technique. Gastroenterology. 1989;96:1180–6.
41. Baer HU, Rhyner M, Stain SC, Glauser PW, Dennison AR, Maddern GJ, Blumgart LH. The effect of communication between the right and left liver on the outcome of surgical drainage for jaundice due to malignant obstruction at the hilus of the liver. HPB Surg. 1994;8:27–31.
42. Sud R, Puri R, Hussain S, Kumar M, Thawrani A. Air cholangiogram: a new technique for biliary imaging during ERCP. Gastrointest Endosc. 2010;72:204–8.
43. Grunhagen DJ, Dunne DF, Sturgess RP, Stern N, Hood S, Fenwick SW, Poston GJ, Malik HZ. Metal stents: a bridge to surgery in hilar cholangiocarcinoma. HPB (Oxford). 2013;15:372–8.
44. Hayashi T, Kawakami H, Osanai M, Ishiwatari H, Naruse H, Hisai H, Yanagawa N, Kaneto H, Koizumi K, Sakurai T, Sonoda T. No benefit of endoscopic sphincterotomy before biliary placement of self-

expandable metal stents for unresectable pancreatic cancer. Clin Gastroenterol Hepatol. 2015 Jan 13. Epub ahead of print.
45. Chahal P, Baron TH. Expandable metal stents for endoscopic bilateral stent-within-stent placement for malignant hilar biliary obstruction. Gastrointest Endosc. 2010;71:195–199.
46. 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.
47. Levy MJ, Wiersema MJ. Endoscopic removal of a biliary Wallstent with a suture-cutting device in a patient with primary pancreatic lymphoma. Endoscopy. 2002;34:835–7.
48. Familiari P, Bulajic M, Mutignani M, Lee LS, Spera G, Spada C, Tringali A, Costamagna G. Endoscopic removal of malfunctioning biliary self-expandable metallic stents. Gastrointest Endosc. 2005;62:903–10.
49. Bismuth H. Postoperative strictures of the bile duct. In: Blumgart LH, editor. The Biliary Tract V. New York: Churchill-Livingstone; 1982. p. 209–18.
50. Deziel DJ, Millikan KW, Economou SG, Doolas A, Ko ST, Airan MC. Complications of laparoscopic cholecystectomy: a national survey of 4292 hospitals and an analysis of 77,604 cases. Am J Surg. 1993;165:9–14.
51. MacFadyen BV, Jr., Vecchio R, Ricardo AE, Mathis CR. Bile duct injury after laparoscopic cholecystectomy. The United States experience. Surg Endosc. 1998;12:315–21.
52. Bergman JJ, van den Brink GR, Rauws EA, de WL, Obertop H, Huibregtse K, Tytgat GN, Gouma DJ. Treatment of bile duct lesions after laparoscopic cholecystectomy. Gut. 1996;38:141–7.
53. Costamagna G, Pandolfi M, Mutignani M, Spada C, Perri V. Long-term results of endoscopic management of postoperative bile duct strictures with increasing numbers of stents. Gastrointest Endosc. 2001;54:162–8.
54. Costamagna G, Tringali A, Mutignani M, Perri V, Spada C, Pandolfi M, Galasso D. Endotherapy of postoperative biliary strictures with multiple stents: results after more than 10 years of follow-up. Gastrointest Endosc. 2010;72:551–7.
55. Canena J, Liberato M, Horta D, Romao C, Coutinho A. Short-term stenting using fully covered self-expandable metal stents for treatment of refractory biliary leaks, postsphincterotomy bleeding, and perforations. Surg Endosc. 2013;27:313–24.
56. Kaffes AJ, Hourigan L, De LN, Byth K, Williams SJ, Bourke MJ. Impact of endoscopic intervention in 100 patients with suspected postcholecystectomy bile leak. Gastrointest Endosc. 2005;61:269–75.
57. Draganov P, Hoffman B, Marsh W, Cotton P, Cunningham J. Long-term outcome in patients with benign biliary strictures treated endoscopically with multiple stents. Gastrointest Endosc. 2002;55:680–6.
58. Smith MT, Sherman S, Lehman GA. Endoscopic management of benign strictures of the biliary tree. Endoscopy. 1995;27:253–66.
59. Foutch PG, Sivak MV Jr. Therapeutic endoscopic balloon dilatation of the extrahepatic biliary ducts. Am J Gastroenterol. 1985;80:575–80.
60. Kao D, Zepeda-Gomez S, Tandon P, Bain VG. Managing the post-liver transplantation anastomotic biliary stricture: multiple plastic versus metal stents: a systematic review. Gastrointest Endosc. 2013;77:679–91.
61. Williams ED, Draganov PV. Endoscopic management of biliary strictures after liver transplantation. World J Gastroenterol. 2009;15:3725–33.
62. Catalano MF, Linder JD, George S, Alcocer E, Geenen JE. 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.
63. Pozsar J, Sahin P, Laszlo F, Forro G, Topa L. Medium-term results of endoscopic treatment of common bile duct strictures in chronic calcifying pancreatitis with increasing numbers of stents. J Clin Gastroenterol. 2004;38:118–23.
64. Deviere J, Nageshwar RD, Puspok A, Ponchon T, Bruno MJ, Bourke MJ, Neuhaus H, Roy A, Gonzalez-Huix LF, Barkun AN, Kortan PP, Navarrete C, Peetermans J, Blero D, Lakhtakia S, Dolak W, Lepilliez V, Poley JW, Tringali A, Costamagna G. Successful management of benign biliary strictures with fully covered self-expanding metal stents. Gastroenterology. 2014;147:385–95.

9 Other Benign Biliary Strictures: Sclerosing Cholangitis, Autoimmune Cholangitis, Post-Liver Transplant

Charles C. Gabbert, Jennifer Chennat and Adam Slivka

Introduction

Within the broad spectrum of biliary pathology, one of the most challenging diagnostic dilemmas is the evaluation of biliary strictures, particularly when imaging and cytopathology results are nondiagnostic. The differential diagnosis for an indeterminate biliary stricture encompasses both benign and malignant processes (Table 9.1). Diagnosis is often delayed due to the indolent disease course of benign etiologies and the slow growth of cholangiocarcinomas, which can have a profound impact on patient morbidity and mortality. While exclusion of malignancy is of principal concern, establishing a definitive diagnosis for benign biliary strictures is also important for appropriate management, but potentially challenging, especially in the setting of hilar and peripheral liver disease. In addition, stricturing diseases can mimic one another on imaging, further contributing to variable interobserver agreement in the interpretation of radiographic findings.

Multiple noninvasive modalities image the biliary tree including transabdominal ultrasound, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP). These low-risk, widely available studies reliably identify biliary ductal dilatation and significant stone disease. For nearly 40 years, endoscopic retrograde cholangiopancreatography (ERCP) has been a principal modality for both the diagnosis and therapy of bile duct pathology [1]. Although MRCP has become the mainstay for initial diagnostic evaluation of the biliary tree, ERCP remains essential for obtaining pathology from biliary strictures despite the poor sensitivity of ERCP techniques, ranging from 54 to 71 % even with combined brush cytology and intraductal biopsies [2–4]. Various adjunct techniques, including direct cholangioscopy and probe-based confocal laser endomicroscopy (pCLE), may potentially improve sensitivity of intraductal sampling, yet are performed at few experienced centers [5–7]. At present, despite multiple efforts in improving the reliability and consistency of such diagnostic techniques, differentiating between benign and malignant biliary strictures can remain a challenge. The biliary gastroenterologist is thus left with the daunting task of interpreting

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Table 9.1 Etiologies for the indeterminate biliary stricture

Benign intrinsic	*Malignant intrinsic*
Iatrogenic injury (i.e., post-surgical)	Cholangiocarcinoma
Primary sclerosing cholangitis	Biliary IPMN
Autoimmune cholangiopathy (i.e., IgG4-associated)	Biliary involvement of ampullary carcinoma
Inflammatory	Chloroma
Ischemic cholangiopathy	Myeloma
Fibroinflammtory biliary stricture (FIBS)	
Chronic choledocholithiasis	
Extrinsic	
Pancreas mass/malignancy	
Hepatic mass/malignancy	
Metastatic disease	
Cystic disease	
Lymphadenopathy	

cholangiographic findings in the context of clinical presentation and serum markers in order to formulate an accurate diagnosis and appropriately guide management.

Case 1

A 70-year-old male nonsmoker with a past medical history significant for coronary artery disease and hypertension is admitted with a 1-month history of fatigue and new-onset jaundice. He denies any abdominal pain, fevers, or weight loss. He is taking no new medications and denies alcohol or drug use. There is no personal or family history of inflammatory bowel disease or gastrointestinal cancers. He underwent a remote cholecystectomy in the past and denies recent travel. Vital signs are stable, and examination reveals scleral icterus with mild jaundice, in the absence of cutaneous stigmata of chronic liver disease. Initial laboratory evaluation reveals the following: total bilirubin 7.2, ALT 229, AST 190, alkaline phosphatase 622, and lipase 27. CBC and coagulation profile are both within normal limits. Hepatitis serologies (A/B/C) are negative and an HIV test is nonreactive. CA 19-9 is moderately elevated at 118 and anti-nuclear antibody is nonreactive. Contrast-enhanced CT scan demonstrates mild intra- and extrahepatic bile duct dilatation in the presence of an ill-defined 4.5 cm lesion in the porta hepatis (Fig. 9.1). There is no evidence of choledocholithiasis or cholelithiasis. A MRCP is ordered and a gastroenterology consult is subsequently placed.

What Benign Biliary Conditions are on the Differential Diagnosis for This Patient?

In Western countries, an isolated benign biliary stricture is frequently iatrogenic, with the majority of cases following operative trauma or cholecystectomy [8]. These stenoses are most often localized and result from scarring at the site of prior surgical resection or anastomosis. While this is an important consideration for our patient, the presence of a porta hepatis lesion and concomitant diffuse ductal dilation argues for an alternate etiology. As such, post-surgical biliary strictures (Chap. 8) shall be largely excluded from this case discussion.

One possible etiology for this patient's presentation is primary sclerosing cholangitis (PSC). PSC is a chronic fibroinflammatory condition that can lead to progressive and diffuse stenoses of both the intra and extrahepatic biliary tree [9]. Up to 80% of PSC cases are associated with inflammatory bowel disease, most frequently ulcerative colitis, although increasingly Crohn's disease as well [10]. Small-duct PSC has also

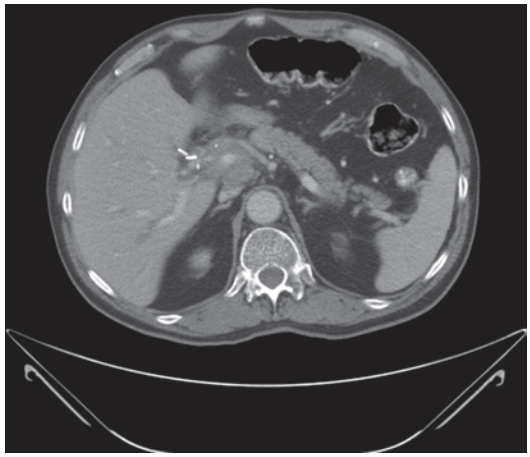

Fig. 9.1 CT abdomen demonstrating a lesion in the porta hepatis and mild biliary ductal dilation

been described [11] and requires liver biopsy for establishing the diagnosis given the paucity of findings on imaging.

PSC more commonly affects men (2:1) and usually presents between ages 30 and 40. If present, initial symptoms are frequently nonspecific and can include malaise, fatigue, and weight loss. Jaundice typically occurs later in the disease process, once stricturing has progressed to cause significant cholestasis. Laboratory evaluation most often reveals an elevated alkaline phosphatase in early stages with hyperbilirubinemia reflecting more advanced disease. Liver biopsy can help support the diagnosis of PSC, especially in cases limited to smaller ducts, yet is not regularly required in clinical practice. Chronic biliary inflammation and cholestasis can progress to cirrhosis, and a significant number of patients will eventually require liver transplantation. The estimated 10-year survival in PSC patients is approximately 65% amidst great variability [12] with a reported incidence of cholangiocarcinoma of 7–9% over the same time period [13, 14].

Aside from variants of cholangiocarcinoma, other conditions may mimic PSC. These include post-operative biliary stricture as mentioned earlier, chronic choledocholithiasis, sequelae of intra-arterial chemotherapy, and even metastatic disease. Mast cell cholangiopathy and eosinophilic cholangitis have also been reported [15, 16]. In these two conditions, where underlying systemic disease is commonly observed, respective mast cell and eosinophilic infiltration of ductal epithelium leads to a fibroinflammatory response that can progress to biliary stricturing. Radiographically, both may appear similar to PSC, thus stressing the need for histology. Another similar benign condition that may mimic both extrahepatic PSC and cholangiocarcinoma is fibroinflammatory biliary stricture (FIBS). FIBS is a rare myofibroblastic lesion with a distinct profile on immunohistochemistry and is frequently diagnosed following extensive resection for presumed cholangiocarcinoma. An increasingly recognized cause of secondary sclerosing cholangitis is IgG4-related disease, referred to here as IgG4-associated cholangitis (IAC). In a 2001 paper by Hamano et al. high serum levels of IgG4 were detected in patients with sclerosing pancreatitis and thus emerged a new classification for autoimmune pancreaticobiliary disease [17]. There have been subsequent reports of IgG4-related disease in a variety of other organs, including both lacrimal and salivary gland involvement [18, 19].

The majority of IAC cases are associated with autoimmune pancreatitis (AIP) (92.5%), although isolated cases of cholangiopathy have been observed [20]. In IAC, parenchymal infiltration by IgG4-positive plasma cells can progress to tissue fibrosis and obliterative phlebitis. Patients are typically older on presentation than those with PSC and most often demonstrate obstructive jaundice. Other features can include weight loss, abdominal pain, and new onset diabetes. Laboratory evaluation typically reveals elevated liver enzymes in a cholestatic pattern with or without abnormal lipase/amylase. Unlike PSC, bilirubin is frequently markedly elevated on diagnosis. The hallmark feature of IAC is a significantly elevated serum IgG4 level (>300 mg/dL), which occurs in 50–80% of patients and may portend a favorable response to corticosteroid therapy [17, 21]. It is important to recognize that serum IgG4 is also moderately elevated in 9% of PSC patients [22]. PSC cases with IgG4 plasma cell infiltration have been described with one study reporting greater than 10 IgG4+cells per

HPF in 23% of explanted livers with PSC [23]. Inflammation was rarely observed surrounding large ducts and other histologic features were more consistent with PSC, despite higher-than-expected levels of serum IgG4. This suggests that serum IgG4 level must be interpreted with caution, particularly when only mildly-to-moderately elevated. Elevated levels should be analyzed in the context of other clinical features and findings in order to more accurately distinguish IAC from both PSC and cholangiocarcinoma. Perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) positivity may help differentiate PSC from IAC as p-ANCA occurs in up to 80% of PSC patients, even in the absence of underlying inflammatory bowel disease [11]. At this time, other autoimmune markers have little role in diagnosing PSC or IAC. In the setting of cholestasis, mild-to-moderate elevations in CA 19-9 can be nonspecific; thus, further evaluation is warranted to exclude underlying malignancy, particularly if levels remain persistently or markedly elevated.

How Do MRCP and ERCP Help Diagnose PSC and IAC?

Abdominal ultrasound and contrast-enhanced CT are often the initial modalities for hepatobiliary imaging. Findings of PSC can be variable and inherently depend on the disease state, ranging from minimal radiologic findings to significant biliary stricturing/dilatation and even cirrhosis. Typically demonstrated on MRCP or ERCP are multifocal stenoses of both intra and extrahepatic bile ducts with intervening normal-appearing or mildly dilated segments to produce a "beaded" ductal appearance. Although high-quality MRCP has good performance characteristics for diagnosing or excluding PSC, ERCP remains the gold standard for the diagnosis of PSC. Various studies on MRCP report a sensitivity of 80–88% in experienced centers [24–27]. Specificity was initially reported in the range of 92–98% [17–19], although recent studies have produced more modest results [20]. While both modalities have demonstrated good interobserver agreement on the degree of intrahepatic stricturing, ERCP exhibits better agreement for extrahepatic strictures [20], particularly those that may warrant endotherapy. At present, MRCP remains suboptimal for predicting need for endotherapy.

Due to the high sensitivity and specificity of MRCP, noninvasive imaging may be sufficient for diagnosis in patients with little concern for underlying malignancy or need for endotherapy. ERCP is generally reserved for patients who cannot undergo MRCP, have nondiagnostic MRCP, or demonstrate dominant stenoses with upstream ductal dilatation. In the latter situation, excluding underlying cholangiocarcinoma with targeted sampling and providing biliary decompression remain the principal reasons for ERCP.

An important radiologic finding in PSC with considerable implication on disease management is the dominant stricture (Fig. 9.2). The definition of dominant strictures in PSC within the literature is variable. Repeated attempts have been made to define dominant strictures in terms of their location within the biliary tree and their respective ductal diameters. At our center, we feel dominant strictures can occur anywhere in the biliary tree and that the status of the upstream bile duct is equally important as the nature of the stricture in determining which strictures warrant therapy. Longitudinal studies have suggested that 33–50% of PSC patients develop a dominant stricture over 8–13 years, stressing the need for improved detection and management [28, 29]. While data have yet to establish specific risk factors for the development of dominant strictures, an association with stage 2–4 fibrosing inflammation on liver biopsy has been reported [29].

A major concern with all dominant strictures is the potential for underlying cholangiocarcinoma. Excluding malignancy can be challenging with MRI and ERCP, especially given the aforementioned limited sensitivity of ERCP biopsies/brushings and unreliable tumor markers in cholestatic disease [30–32]. Greater sensitivity (~80%) has been demonstrated with higher cut-off points for CA 19−9 (≥130 U/mL) in PSC patients [30]. A study of 333 patients with PSC performed at our center reported an even higher

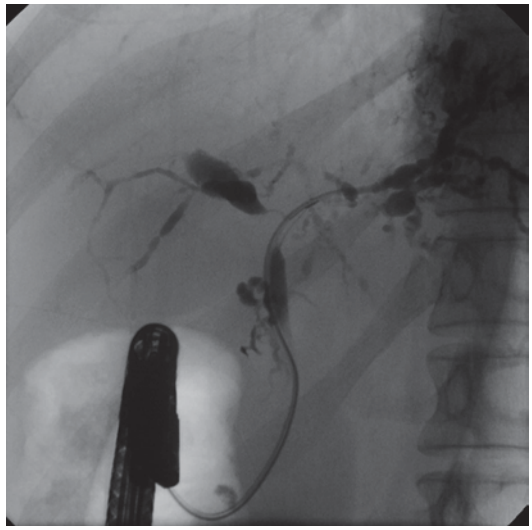

Fig. 9.2 ERCP showing PSC characterized by beading and pruning of intrahepatic branches with dominant stricture in common hepatic duct extending into bifurcation and bilateral main hepatic ducts. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

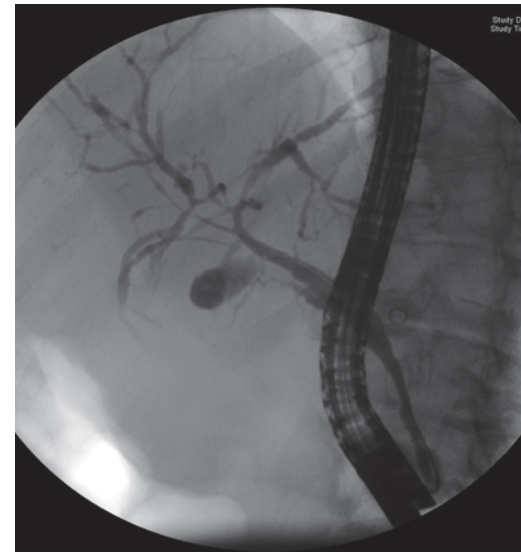

Fig. 9.3 ERCP of a patient diagnosed with IAC characterized by mild beading in intrahepatic ducts with irregular distal common bile duct. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

sensitivity (100%) and nearly 80% specificity for the diagnosis of cholangiocarcinoma when standard brush cytology was combined with abnormal CA 19-9 (>180 U/mL) and CEA (>5.2 ng/mL) levels [32]. More data are required to evaluate the cost-effectiveness of such a strategy and proper screening intervals for symptomatic and asymptomatic PSC. Newer modalities, including 3-dimensional MRI with bile duct reconstruction and direct peroral cholangioscopy with or without confocal endomicroscopy, are being investigated to improve detection of malignancy in dominant strictures.

Similar to PSC, IAC typically affects large bile ducts and can demonstrate diffuse areas of stricturing with either normal or dilated intervening segments on cholangiography. Differentiating between PSC and IAC with current imaging techniques can be challenging (Fig. 9.3). Nishino et al. report a higher incidence of distal bile duct strictures and a more segmental (less beaded) appearance in IAC compared to PSC [33]. Significant intrahepatic stricturing is rarer (less than 10%), yet when present, can be diffuse in IAC. Concomitant pancreatic duct strictures are frequently encountered. There have even been reports of IgG4-related disease causing inflammatory mass-like lesions and subsequent biliary obstruction [34, 35].

Histology obtained during ERCP may help diagnose IAC. One study reports modest sensitivity (52%), despite excellent specificity (97%), for diagnosing IAC from ampullary and intraductal biopsies [36]. When diagnostic, histopathology is most frequently characterized by the typical lymphoplasmacytic infiltrate and transmural fibrosis. Positive stains for IgG4 are further suggestive of IAC. Unlike in PSC, onion-skinned concentric fibrosis is not observed within peri-ductal regions.

Newer techniques, such as cholangioscopy and intraductal ultrasonography (IDUS), have also been investigated in IgG4-related disease, yet their precise roles remain to be defined. IDUS has demonstrated more concentrically thickened bile duct walls with smoother margins in IAC compared to cholangiocarcinoma [37]. In the presence of concomitant pancreatic disease, a core pancreatic biopsy under endoscopic ultrasound guidance can be useful.

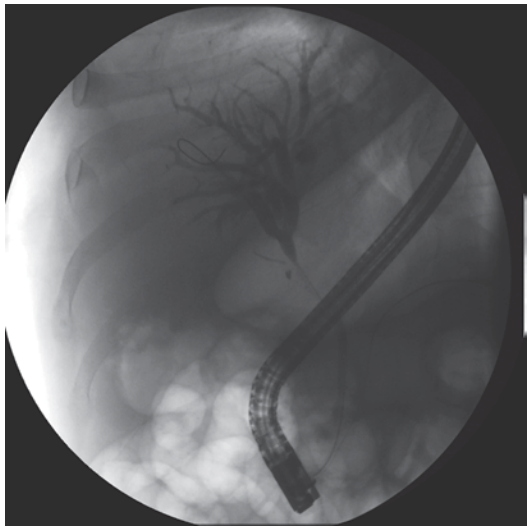

Fig. 9.4 ERCP demonstrating a common hepatic duct stricture and upstream ductal dilation

Case Continued

MRCP reveals moderate dilation of intra and extrahepatic bile ducts with an area of extrahepatic abnormal soft tissue surrounding the main portal vein. A common hepatic duct stricture is noted with associated upstream dilatation. There is no obvious pancreatic head mass. No choledocholithiasis or cholelithiasis is noted. An ERCP is subsequently performed without complication (Fig. 9.4). The patient demonstrates serologic improvement in liver function tests following stent placement. Intraductal biopsies and brushings of the common hepatic duct stricture return negative for malignancy. Serum IgG4 is normal at 87. An endoscopic ultrasound is subsequently performed to obtain tissue from the porta hepatis lesion. Cytopathology results demonstrate mildly atypical epithelial cells without evidence of malignancy.

Diagnosing IAC

The interpretation of findings in the context of suspected autoimmune pancreaticobiliary disease has led to the development of various consensus criteria for its diagnosis. Using the HISORt (histology, imaging, serology, organ involvement, response to therapy) criteria, the diagnosis of IAC requires intrahepatic and/or proximal extrahepatic bile duct stricturing in the context of (1) typical radiologic findings of AIP (encapsulated, sausage-shaped pancreas), (2) supportive radiologic findings of AIP (focal pancreatic enlargement) with abnormal pancreatic ductal imaging and elevated serum IgG4 or other organ involvement (retroperitoneal fibrosis or > 10 IgG4+ cells per hpf from an intraductal or ampullary biopsy obtained during ERCP), (3) clinical and serologic response to steroid therapy with supportive radiologic findings, or (4) histology consistent with AIP from core pancreatic biopsy during EUS [38]. A more recent Japanese consensus criterion has since emerged [39]. Validation of both guidelines will be warranted in future studies.

Given that differentiating between PSC and IAC can be difficult by cholangiography alone, diagnosis largely rests on the patient's history and clinical picture. As previously mentioned, PSC patients tend to be younger males with evidence of mild cholestasis and concomitant inflammatory bowel disease. Rarely do they demonstrate evidence of associated pancreatic disease with the most common cause for this is medication-related sequelae from azathioprine. In older patients without underlying inflammatory bowel disease, IAC receives greater consideration, particularly when evaluation for suspected cholangiocarcinoma is negative on repeat endoscopic examinations. At our center, serum IgG4 levels are not routinely checked in patients with suspected PSC because mild elevations can be observed and may not be clinically relevant. When concomitant autoimmune disease or a family history thereof is observed, serum IgG4 levels and biopsies for IgG4 staining are pursued. In the small subset of patients with concomitant pancreatic disease and/or mass-like lesions that are persistently negative for malignancy on histology, IAC becomes more plausible and thus an empiric trial of steroids is considered prior to advocating for surgical resection.

How Does Management Differ in PSC Versus IAC?

Management options in PSC have included both medical and endoscopic therapies in an effort to prolong (and hopefully obviate) the need for liver transplantation. The American Association for the Study of Liver Diseases (AASLD) currently recommends against the use of ursodiol in managing PSC patients given unclear benefit on transplant-free survival [40]. More recent data from Scandinavia recommend ursodiol (17–23 mg/kg/day) in patients who respond with normalization or significant decreases (≥40 % reduction) in alkaline phosphatase, which was associated with increased survival [41]. Although associated with improvement in liver function testing, the effect of ursodiol on disease progression remains uncertain. Large multi-center studies have investigated both low-dose (10–15 mg/kg/d) and high-dose (17–30 mg/kg/d) ursodiol in PSC, yet neither has been shown to improve histology or lengthen time to liver transplantation [42–44]. In fact, one multicenter trial found high-dose (28–30 mg/kg/d) ursodiol associated with increased mortality and shorter time to transplantation [44]. Recent studies have suggested a possible chemoprotective effect of ursodiol in reducing the risk of colon cancer in patients with concomitant inflammatory bowel disease [45, 46]. Such an effect has yet to be demonstrated for cholangiocarcinoma. Validation of the limited evidence is necessary prior to recommending ursodiol for chemoprevention. Immunomodulator and steroid therapy have also been trialed without demonstrated benefit [47], except in overlap syndromes of PSC and autoimmune hepatitis and/or IgG4+ infiltrate on liver biopsy [48, 49].

Acute episodes of cholangitis are treated with usual antibiotic therapy targeted at enteric pathogens, particularly gram-negative and anaerobic organisms. In patients who suffer from repeated episodes of cholangitis, suppressive antibiotic therapy may be considered as a bridge to liver transplantation. In these patients, a Model for End Stage Liver Disease (MELD) score exception may be granted and more urgent transplantation indicated.

Endoscopic management of PSC usually occurs later in the disease and relies heavily on the endoscopist to accurately recognize a dominant stricture. Endotherapy with balloon dilation and/or stenting is indicated to alleviate biliary outflow obstruction and possible resultant hepatocellular injury. Since the original report of endoscopic decompression in PSC in 1982 [50], multiple studies (mostly retrospective) have investigated the role of balloon dilation and stenting in this patient population [51–54]. One prospective study by Stiehl et al demonstrated improved survival following endoscopic management of dominant strictures compared to the predicted survival derived from the Mayo Clinic survival model prior to ERCP in 106 PSC patients on ursodiol [29]. However, the Mayo Clinic model was not validated in highly selected PSC patients with acute obstructive jaundice. Because it is heavily weighted to the serum bilirubin level, it should be applied to patients immediately after endoscopic interventions and then followed long term. Regardless of these limitations, improved patient outcomes can be seen in selected patients with obstructive jaundice and PSC following endoscopic intervention [29, 55, 56].

In order to access the biliary tree and facilitate techniques for biliary evaluation and decompression, a small sphincterotomy is often performed. Following cannulation of the bile duct, recognition of potentially treatable strictures becomes of paramount importance. Short-segment (≤2 cm long) dominant strictures of the common bile duct (CBD) were the first to be successfully treated endoscopically. Subsequent efforts over the years have investigated the role of endotherapy in long-segment CBD strictures and strictures within distal hepatic ducts. In a prospective study of 171 patients on ursodiol followed for 20 years, 96 patients underwent endotherapy for either dominant strictures or cholangitis [57]. Both CBD strictures greater than 2 cm in length and short strictures within 2 cm of the bifurcation may be effectively treated with dilation and/or stenting. Significant stricturing of the intrahepatic system proximal to this 2-cm mark may be difficult to treat endoscopically and thus may warrant more prompt transplant referral.

The dilemma of balloon dilation alone versus dilation with placement of a "short-interval" biliary stent continues to be better defined. Longer-term stent placement has been associated with a high complication rate around 20% [56]. Debris can occlude biliary stents and the stents can block opposing peripheral bile ducts. These complications can inevitably lead to cholestasis and sepsis. For these reasons, a "short-interval" biliary stent is generally recommended. In a retrospective study of 32 patients treated with biliary stents removed after a mean of 11 days, clinical improvement was observed in 80% of the population [58]. Perhaps even more significant, 60% of patients did not require repeat intervention at 3-year follow-up. This suggests that short-term stent placement may yield the desired clinical and biochemical response.

Balloon dilation remains a mainstay of endotherapy in PSC, as it allows for graded dilation of the biliary tree. The balloon diameter must match the smaller diameter of the downstream bile duct to avoid iatrogenic injury. Once the balloon is inflated, pressure is maintained for a period of 30–60 s in order to achieve adequate response. Some advocate the use of short-term stents following balloon dilation while others try to avoid stent placement all together. At our center, 10 French plastic stents are uniformly placed for patients with episodes of acute bacterial cholangitis following therapy with balloon dilation. Patients are instructed to return for reevaluation and stent removal in 2 weeks. In patients with evidence of recurrent cholangitis (>3 episodes) and/or progressive stricturing that becomes dependent on endotherapy to alleviate persistent obstruction, transplant referral is once again the most appropriate next step in management. Surgical reconstruction prior to liver transplantation leads to worse outcomes and should be avoided if possible.

Peri-procedural antibiotic prophylaxis is universally recommended, as mere injection of contrast during the procedure can result in sepsis and/or infection within more peripheral bile ducts. Patients are generally given ciprofloxacin 500 mg twice daily for 3–5 days following the procedure with longer durations (7–14 days) advocated in those with systemic constitutional symptoms or evidence of pus on endoscopic evaluation. The complication rate of ERCP in PSC patients is suspected to be slightly higher than in patients with CBD stones or solitary malignant strictures. Clinically significant complications have been observed in 7–14% of PSC patients [29, 53, 59, 60], mostly due to increased rates of cholangitis. Other series have reported even higher complication rates, although these findings may be attributable to longer and/or greater number of stent placement prior to removal.

Unlike PSC, where steroids have no reported benefit, the first line of therapy in IAC is an extended taper of prednisone starting at 40 mg daily. This is usually tapered by 5 mg weekly, after which a maintenance dose of 5 mg daily for 3–6 months is recommended. Azathioprine, mycophenolate mofetil, and rituximab have been utilized as maintenance regimens in steroid-resistant disease [20, 61, 62]. Lab parameters (specifically liver function tests, glucose, and IgG4 levels) should be followed throughout the treatment period. In patients who demonstrate clinical worsening and/or laboratory deterioration while on corticosteroids, therapy should be tapered and further evaluation for malignancy should ensue. Biliary stents are frequently placed for interval decompression during initial steroid treatment and often removed after 1–2 months. Repeated dilations and stenting may be warranted in refractory disease. Peri-procedural antibiotic prophylaxis is generally recommended, particularly in the setting of hilar strictures and intrahepatic involvement.

Case Continued

Given suspicion for IAC and lack of evidence of malignancy, the patient is started on an extended course of steroids. He is followed closely and continued to demonstrate both clinical and serologic improvement while on steroid therapy. Repeat imaging is performed 1 month following initiation of steroid therapy (Fig. 9.5). Repeat ERCP reassesses the disease process following a course of steroids for possible stent removal/exchange (Fig. 9.6).

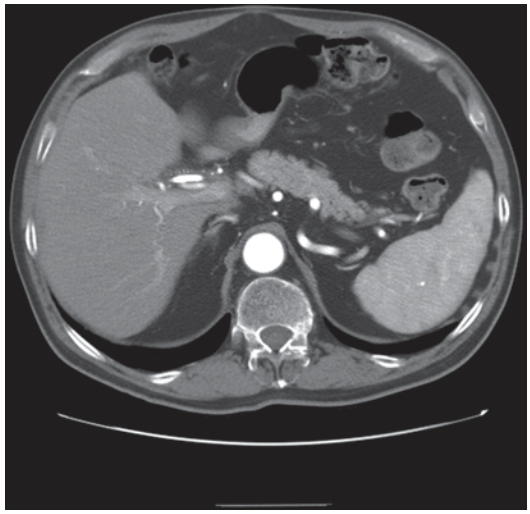

Fig. 9.5 CT abdomen reveals near resolution of porta hepatis mass and ductal dilation following initiation of steroids for presumed IAC

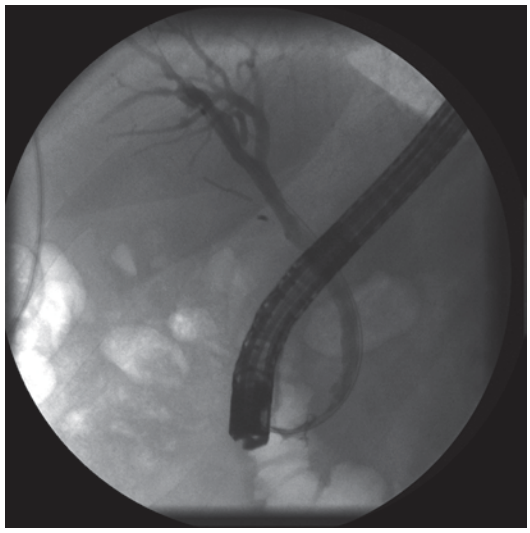

Fig. 9.6 Repeat ERCP confirms resolution of common hepatic duct stricture

Case 2

A 55-year-old male with a past medical history significant for hepatitis C cirrhosis status post orthotopic liver transplantation 2 years ago presents for evaluation of abnormal liver function tests. His operative course was uncomplicated and the patient has had no issues following his transplant. He denies jaundice, abdominal pain, and fever. Vital signs are stable and physical exam is largely unremarkable. Laboratory evaluation reveals the following: total bilirubin 2.9, ALT 202, AST 121, and alkaline phosphatase 1000. CBC and coagulation profile are within normal limits. An abdominal ultrasound with Doppler shows patent vessels and no evidence of ductal dilation. An MRCP is subsequently ordered.

What Biliary Complications Can Occur Following Liver Transplant?

Liver transplantation has become a principal treatment modality in eligible patients for a variety of conditions; the most common remain end-stage liver disease, hepatocellular carcinoma (HCC), and acute liver failure. A donor-to-recipient choledocho-choledochostomy is created in 75–88 % of liver transplants in the United States [63–65], with the remaining cases being a Roux-en-Y choledochojejunostomy (primarily for PSC and pediatric cases). Biliary complications are frequently encountered following liver transplantation, affecting 5–25 % of the post-transplant population [66–68]. Early complications occur within 30 days of transplant and are often attributed to surgical manipulation proper or vascular compromise. The most common early complications include bile leaks and extrahepatic biliary obstruction. While the latter is frequently a consequence of post-surgical edema/inflammation, other etiologies include anastomotic narrowing, vascular insufficiency, and even torsion. Late complications generally occur after 1 month following liver transplantation. Ductopenic rejection and hepatic artery thrombosis are two important diagnostic possibilities to consider in this population; both may be suggested by cholestasis alone. Other possible etiologies for late cholestasis include recurrent liver disease, choledocholithiasis, biliary cast syndrome, and/or post-transplant ampullary dysfunction. Similar to ischemic cholangiopathy that is associated with the development of hepatic artery thrombosis following transplant, biliary cast syndrome is most-

ly observed in patients with some degree of vascular insufficiency and is more frequent in those with hilar strictures. This uncommon phenomenon, which may be related to both intra-operative ischemia times and/or the presence of concomitant acute cellular rejection, often requires repeat attempts at endoscopic therapy (sphincterotomy and balloon sweeping) to achieve ductal clearance. Another late etiology for cholestasis is post-transplant ampullary dysfunction. These patients typically lack the pain associated with sphincter of Oddi dysfunction, presumably due to a denervated biliary tree. Filling defects are not observed on cholangiography and the degree of ductal dilation is typically uniform upstream of the papillary orifice. Efficient treatment is achieved with biliary sphincterotomy. Given the observed variability in the onset of biliary diseases following liver transplantation, recognition of temporal relationships can have a profound impact on patient morbidity and mortality.

What Are the Principal Differences Between Anastomotic and Nonanastomotic Strictures?

One complication that can occur at any time following liver transplantation, and is often amenable to endoscopic therapy, is post-transplant anastomotic biliary stricture. Strictures represent 40–45% of all biliary complications after liver transplantation [69, 70] and occur in higher frequency among patients who receive a living-donor-related transplant. Biliary strictures are observed in up to 32% of such transplants [71] compared to 5–15% with deceased-donor livers [71–73]. Post-transplant strictures most frequently involve the duct-to-duct anastomosis where a choledocho-choledochostomy was performed, yet can also occur distal to the anastomosis within the biliary tree. Strictures may also involve the biliary-enteric anastomosis in patients with a Roux-en-Y hepaticojejunostomy. While these biliary strictures may result from localized post-operative inflammation and fibrosis, other possible causes include ischemia and disease recurrence (i.e., PSC).

Patients with a biliary stricture can present variably, ranging from asymptomatic to cholangitic with new onset jaundice in the presence of abdominal pain and/or fever. Laboratory evaluation classically reveals elevated liver enzymes in a cholestatic pattern with direct hyperbilirubinemia. Biliary strictures are most frequently evaluated first with abdominal ultrasound, contrast-enhanced CT, or MRCP. These modalities may reveal areas of stricturing with concomitant dilation of donor ducts. An added benefit of ultrasonography is the performance of Doppler evaluation to exclude hepatic artery thrombosis. Ultrasound and CT are limited by their suboptimal sensitivities and specificities in diagnosing post-transplant strictures. MRCP appears comparable to ERCP in its accuracy for evaluating post-transplant complications, including strictures [74–76]. Recent data suggest sensitivity and specificity greater than 95% for MRCP in diagnosing biliary complications following liver transplant [76]. Thus, MRCP remains an effective noninvasive modality for imaging the post-transplant biliary tree prior to endoscopic intervention.

Post-transplant biliary strictures are generally classified as anastomotic or nonanastomotic, as determined by their location and length. Strictures involving the biliary anastomosis are usually short-segment strictures that occur within 1 year of liver transplantation. Older recipient age, history of prior bile leak, prolonged intra-operative warm/cold ischemia times, and active smoking have been identified as possible risk factors for the development of anastomotic strictures [77–79]. Higher rates of late-onset anastomotic strictures have also been reported in patients with recurrent hepatitis C infection and in those with a history of HCC requiring trans-arterial chemoembolization prior to transplant [80]. These strictures are typically diagnosed by abdominal ultrasound or MRCP, both of which can demonstrate anastomotic narrowing with upstream dilatation of donor ducts. It is important to differentiate an anastomotic stricture from size mismatch between donor and recipient bile ducts. In the latter situation, either donor or recipient ducts can appear “dilated,” yet this may simply reflect

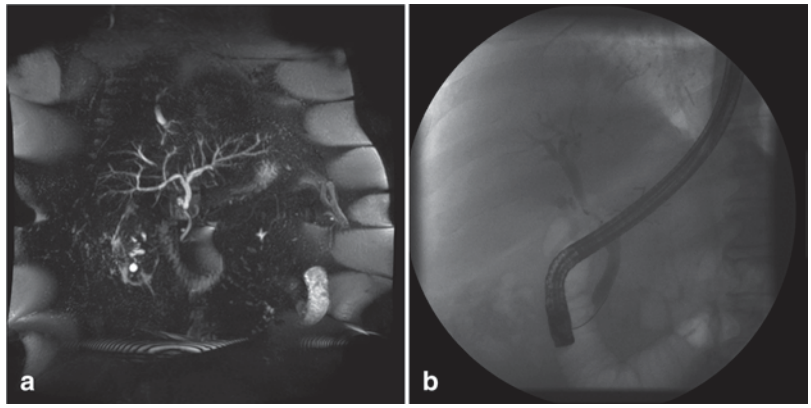

Fig. 9.7 **a** MRCP demonstrating a short-segment stricture at the level of the duct-to-duct anastomosis following orthotopic liver transplantation. **b** ERCP with an anastomotic stricture

a duct-to-duct size discrepancy in the absence of true narrowing at the anastomosis.

Nonanastomotic strictures are defined as strictures greater than 5 mm proximal to the surgical anastomosis and represent more than 20% of post-transplant biliary strictures [81]. The most common etiologies for nonanastomotic strictures are ischemic cholangiopathy, vascular injury/thrombosis (i.e., hepatic artery thrombosis), and disease recurrence (i.e., PSC). Cases of viral cholangiopathy and ductopenic rejection leading to biliary strictures have also been reported [82, 83]. Nonanastomotic strictures are frequently diffuse, multiple, and proximal to the hilum within the intrahepatic biliary tree. Development of these strictures has been associated with donors after cardiac death, prolonged intra-operative ischemia times, and need for extended vasopressor support during transplantation [83–85]. Detection of nonanastomotic biliary strictures following transplant should prompt a complete vascular evaluation with Doppler ultrasonography and/or angiography to ensure adequate perfusion of the allograft.

Case Continued

MRCP reveals a short-segment nonvisualization of the extrahepatic bile duct, likely in the region of the biliary anastomosis. Intrahepatic bile ducts and the donor common hepatic duct are also mildly dilated (Fig. 9.7a). An ERCP is subsequently scheduled for further evaluation and management. A 6-mm biliary stricture at the level of the anastomosis is appreciated (Fig. 9.7b).

What Endoscopic Therapies Are Available for Post-Transplant Strictures?

Endotherapy for anastomotic strictures is highly effective, with success rates ranging from 65 to 100% [71, 72, 86, 87]. Anastomotic strictures may recur in roughly 20% of patients following endoscopic management. In patients who undergo liver transplantation with a choledochocholedochostomy, conventional access to the biliary tree is performed via ERCP. After passing a standard duodenoscope, a biliary sphincterotomy may be performed to facilitate intraductal therapy. Endoscopic techniques have included both balloon dilation and stenting, with the former being avoided in patients less than 1 month post-transplant due to concerns over a tenuous anastomosis and the presence of post-operative edema which may resolve over time.

In patients greater than 1 month post-transplant, balloon dilation is generally performed with balloon size matched to the diameter of the smaller duct on either side of the anastomosis. After 30–60 s, the balloon is deflated and plastic biliary stents (10 Fr) are conventionally de-

ployed. These stents are often exchanged every 3 months over the course of a full year, as they tend to occlude with debris over time. Overall success rates with endoscopic management of anastomotic strictures have been reported to range from 70 to 100 % [74], and multiple studies have demonstrated that balloon dilation plus stenting is more effective than balloon dilation alone [71, 88–95] In a 2006 paper by Zoepf et al., recurrence rates following balloon dilation alone (62 %) were higher than those who underwent balloon dilation and stenting (31 %) [95]. In certain circumstances, particularly larger strictures and larger duct sizes, multiple plastic stents may be inserted to achieve adequate dilation and biliary drainage. Studies report long-term success rates greater than 90 % with this technique of placing as many plastic stents as possible across the anastomotic stricture [91, 92]. Patients may require fewer procedures to achieve stricture resolution with this approach. Newer studies have investigated the off label use of fully covered self-expandable metal stents in this patient population. A recent prospective study of 54 patients demonstrated high rates of stent migration despite an overall success rate of 75 % [93]. Another study reported an almost 40 % migration rate with fully covered metal stents for the treatment of refractory strictures or bile leak following transplant, although limitations included small sample size and the use of stents without anti-migration flanges [94]. Nonetheless, given these data, deployment of a fully covered metal stent is generally reserved for refractory disease [93]. When endoscopic or percutaneous treatment has failed to resolve the stricture, surgical intervention with creation of a hepaticojejunostomy may be necessary. Drastic cases may require re-transplantation.

Nonanastomotic strictures can be much more difficult to treat endoscopically, as they frequently involve the hilum and proximal intrahepatic ducts. Smaller duct size and variations in anatomy often preclude the endoscopist from achieving effective stent drainage. Studies report biliary stenting to be effective in 50–75 % of selected patients with nonanastomotic strictures [73, 86, 95, 96], a response rate considerably lower than anastomotic strictures. In the majority of cases, endotherapy for nonanastomotic strictures also utilizes balloon dilation whether or not a stent is placed. Retrospective data have suggested that cholangitis rates may be lower following balloon dilation alone (12 %) compared with concomitant stenting (25 %) in nonanastomotic strictures, although further investigations are warranted [97]. Nonetheless, stents are often deployed to maintain duct patency, at the risk of occluding more proximal ducts that oppose the stent itself. Severe disease may necessitate percutaneous biliary drainage, interventional procedures to achieve adequate hepatic artery flow, and even re-listing for transplant. More data are necessary to better elucidate the most effective endoscopic technique in this subset of patients in order to improve patient and graft survival.

Liver transplantation utilizing a donor-to-recipient choledocho-choledochostomy is advantageous because it maintains intestinal integrity and promotes a greater degree of biliary sterility and continuity. Preservation of intestinal anatomy also facilitates biliary access for the performance of ERCP. Patients with anastomotic strictures following liver transplantation with a Roux-en-Y choledochojejunostomy may be difficult to treat endoscopically. Endoscopic access to the anastomosis often requires a variety of deep enteroscopy techniques. Single-balloon and spiral-overtube-assisted enteroscopy have both been employed with variable success rates. In a recent retrospective review of 31 post-transplant patients with Roux-en-Y reconstruction, ERCP was successfully performed in 22 (71 %) cases using a pediatric colonoscope in the majority of patients [98]. When biliary access is granted, anastomotic strictures are similarly treated as described above with balloon dilation and/or temporary stenting depending on the age of the anastomosis. When identification of the anastomosis is difficult and technically infeasible endoscopically, percutaneous approaches may be warranted.

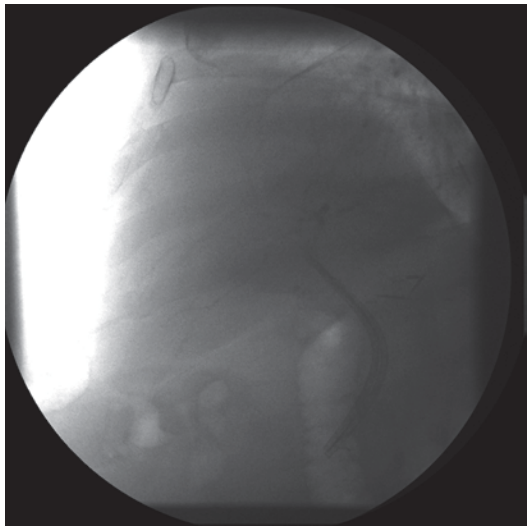

Fig. 9.8 Successful placement of two 10 Fr × 9 cm biliary stents following biliary sphincterotomy

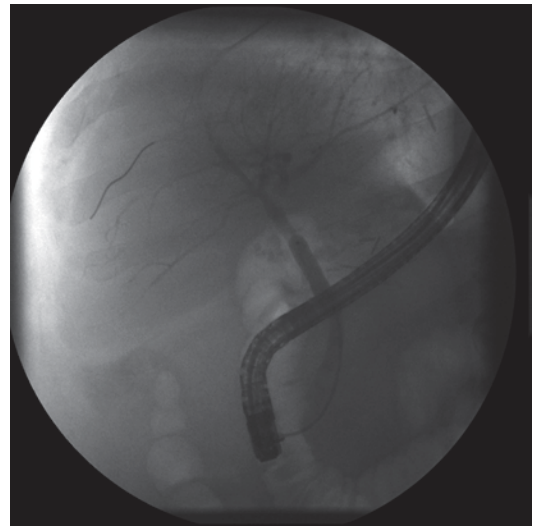

Fig. 9.9 Balloon dilation of anastomotic stricture

Case Continued

After performing an 8-mm biliary sphincterotomy, the anastomotic stricture is dilated with a 6-mm balloon dilator. Two 10 Fr - 9-cm biliary stents with internal and external flaps are then placed 8.5 cm into the bile duct (Fig. 9.8). The procedure is accomplished without difficulty and the patient is discharged home. LFTs normalize shortly after stent placement. He does well for the next 3 months without complications and is scheduled for repeat ERCP. During his subsequent procedure, clinical improvement is noted and the patient undergoes repeated balloon dilation (Fig. 9.9). No biliary stent is replaced given near resolution of the anastomotic stricture. The patient continues to follow up with transplant hepatology as an outpatient and liver function testing has remained normal.

Conclusion

While the greatest concern for a biliary stricture is the underlying possibility of cholangiocarcinoma, a number of benign conditions exist that can have similar clinical presentation. Included among these are post-surgical causes for biliary strictures, PSC, IAC, chronic choledocholithiasis, and even sequelae from prior chemotherapy. Each condition may demonstrate characteristic findings upon serologic and radiographic evaluation, yet they also may mimic one another, particularly on cholangiography. Advances in noninvasive imaging techniques have resulted in MRCP becoming the principal diagnostic modality for assessment of biliary strictures, including in patients following liver transplantation. Once stricturing disease is identified, ERCP remains instrumental in diagnosis and treatment despite variable sensitivity and specificity in providing tissue diagnoses. Cholangiographic findings and tissue sampling can frequently be nondiagnostic following endoscopic evaluation and thus should be interpreted in the context of clinical presentation and laboratory results to allow accurate diagnosis and effective management. Endoscopic intervention continues to be the cornerstone in the treatment of most benign biliary strictures.

Key Points

- Success rates of biliary endoscopy in sclerosing disorders may best correlate with the location of intervened-upon segments depending on the disease process, which requires deeper

understanding of the underlying etiology and natural history of the diseases.

- MRCP is the noninvasive diagnostic imaging of choice for assessing biliary strictures.
- In patients with primary sclerosing cholangitis (PSC), the degree of upstream ductal dilatation is of utmost importance in defining a stricture as dominant and determining whether the identified stricture should be evaluated and treated endoscopically.
- Balloon dilation remains the mainstay of endoscopic management in PSC, while deployment of short-interval stents may be most beneficial in patients with episodes of acute bacterial cholangitis and/or evidence of persistently obstructed biliary outflow despite balloon dilation.
- The majority of cases of autoimmune cholangiopathy are associated with concomitant pancreatic inflammation, and high serum levels of IgG4 may imply a favorable response to corticosteroid therapy.
- Endoscopic management of anastomotic strictures following liver transplant is successful in 70–100% of cases with long-term data suggesting that recurrence may be minimized with the placement of temporary stents following balloon dilation.

References

1. Cohen S, Bacon BR, Berlin JA, Fleischer D, Hecht GA, Loehrer PJ Sr, McNair AE Jr, Mulholland M, Norton NJ, Rabeneck L, Ransohoff DF, Sonnenberg A, Vannier MW. National Institutes of Health State-of-the-Science Conference Statement: ERCP for diagnosis and therapy, January 14–16, 2002. Gastrointest Endosc. 2002;56(6):803–9.
2. Ponchon T, Gagnon P, Berger F, Labadie M, Liaras A, Chavaillon A, Bory R. Value of endobiliary brush cytology and biopsies for the diagnosis of malignant bile duct stenosis: results of a prospective study. Gastrointest Endosc. 1995;42(6):565–72.
3. Schoefl R, Haefner M, Wrba F, Pfeffel F, Stain C, Poetzi R, Gangl A. Forceps biopsy and brush cytology during endoscopic retrograde cholangiopancreatography for the diagnosis of biliary stenoses. Scand J Gastroenterol. 1997;32(4):363–8.
4. Rosch T, Hofrichter K, Frimberger E, Meining A, Born P, Weigert N, Allescher HD, Classen M, Barbur M, Schenck U, Werner M. ERCP or EUS for tissue diagnosis of biliary strictures? A prospective comparative study. Gastrointest Endosc. 2004;60(3):390–6.
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. Gastrointest Endosc. 2011;74(5):961–8.
6. Fukuda Y, Tsuyuguchi T, Sakai Y, Tsuchiya S, Saisyo H. Diagnostic utility of peroral cholangioscopy for various bile-duct lesions. Gastrointest Endosc. 2005;62(3):374–82.
7. Shah RJ, Langer DA, Antillon MR, Chen YK. Cholangioscopy and cholangioscopic forceps biopsy in patients with indeterminate pancreaticobiliary pathology. Clin Gastroenterol Hepatol. 2006;4(2):219–25.
8. Vecchio R, Ferrara M, Pucci L, Meli G, Latteri S. Treatment of iatrogenic lesions of the common bile duct. Minerva Chir. 1995;50(1/2):29–38.
9. Broome U, Olsson R, Loof L, Bodemar G, Hultcrantz R, Danielsson A, Prytz H, Sandberg-Gertzen H, Wallerstedt S, Lindberg G. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut. 1996;38(4):610–5.
10. Rasmussen HH, Fallingborg JF, Mortensen PB, Vyberg M, Tage-Jensen U, Rasmussen SN. Hepatobiliary dysfunction and primary sclerosing cholangitis in patients with Crohn's disease. Scand J Gastroenterol. 1997;32(6):604–10.
11. Bjornsson E, Olsson R, Bergquist A, Lindgren S, Braden B, Chapman RW, Boberg KM, Angulo P. The natural history of small-duct primary sclerosing cholangitis. Gastroenterology. 2008;134(4):975–80.
12. Bambha K, Kim WR, Talwalkar J, Torgerson H, Benson JT, Therneau TM, Loftus EV Jr, Yawn BP, Dickson ER, Melton LJ 3rd. Incidence, clinical spectrum, and outcomes of primary sclerosing cholangitis in a United States community. Gastroenterology. 2003;125(5):1364–9.
13. Burak K, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol. 2004;99(3):523–6.
14. Claessen MM, Vleggaar FP, Tytgat KM, Siersema PD, van Buuren HR. High lifetime risk of cancer in primary sclerosing cholangitis. J Hepatol. 2009;50(1):158–64.
15. Baron TH, Koehler RE, Rodgers WH, Fallon MB, Ferguson SM. Mast cell cholangiopathy: another cause of sclerosing cholangitis. Gastroenterology. 1995;109(5):1677–81.
16. Chen WH, Yu CC, Wu CC, Jan YJ. Eosinophilic cholangitis with obstructive jaundice mimicking bile duct carcinoma. J Hepatobiliary Pancreat surg. 2009;16(2):242–5.
17. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med. 2001;344(10):732–8.

18. Ohara H, Nakazawa T, Sano H, Ando T, Okamoto T, Takada H, Hayashi K, Kitajima Y, Nakao H, Joh T. Systemic extrapancreatic lesions associated with autoimmune pancreatitis. Pancreas. 2005;31(3):232–7.
19. Ishida M, Hotta M, Kushima R, Shibayama M, Shimizu T, Okabe H. Multiple IgG4-related sclerosing lesions in the maxillary sinus, parotid gland and nasal septum. Pathol Int. 2009;59(9):670–5.
20. Ghazale A, Chari ST, Zhang L, Smyrk TC, Takahashi N, Levy MJ, Topazian MD, Clain JE, Pearson RK, Petersen BT, Vege SS, Lindor K, Farnell MB. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology. 2008;134(3):706–15.
21. Ghazale A, Chari ST, Smyrk TC, Levy MJ, Topazian MD, Takahashi N, Clain JE, Pearson RK, Pelaez-Luna M, Petersen BT, Vege SS, Farnell MB. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol. 2007;102(8):1646–53.
22. Mendes FD, Jorgensen R, Keach J, Katzmann JA, Smyrk T, Donlinger J, Chari S, Lindor KD. Elevated serum IgG4 concentration in patients with primary sclerosing cholangitis. Am J Gastroenterol. 2006;101(9):2070–5.
23. Zhang L, Lewis JT, Abraham SC, Smyrk TC, Leung S, Chari ST, Poterucha JJ, Rosen CB, Lohse CM, Katzmann JA, Wu TT. IgG4 + plasma cell infiltrates in liver explants with primary sclerosing cholangitis. Am J Surg Pathol. 2010;34(1):88–94.
24. Fulcher AS, Turner MA, Franklin KJ, Shiffman ML, Sterling RK, Luketic VA, Sanyal AJ. Primary sclerosing cholangitis: evaluation with MR cholangiography-a case-control study. Radiology. 2000;215(1):71–80.
25. Angulo P, Pearce DH, Johnson CD, Henry JJ, LaRusso NF, Petersen BT, Lindor KD. Magnetic resonance cholangiography in patients with biliary disease: its role in primary sclerosing cholangitis. J Hepatol. 2000;33(4):520–7.
26. Berstad AE, Aabakken L, Smith HJ, Aasen S, Boberg KM, Schrumpf E. Diagnostic accuracy of magnetic resonance and endoscopic retrograde cholangiography in primary sclerosing cholangitis. Clin Gastroenterol Hepatol. 2006;4(4):514–20.
27. Moff SL, Kamel IR, Eustace J, Lawler LP, Kantsevoy S, Kalloo AN, Thuluvath PJ. Diagnosis of primary sclerosing cholangitis: a blinded comparative study using magnetic resonance cholangiography and endoscopic retrograde cholangiography. Gastrointest Endosc. 2006;64(2):219–23.
28. Stiehl A, Rudolph G, Sauer P, Benz C, Stremmel W, Walker S, Theilmann L. Efficacy of ursodeoxycholic acid treatment and endoscopic dilation of major duct stenoses in primary sclerosing cholangitis. An 8-year prospective study. J Hepatol. 1997;26(3):560–6.
29. Stiehl A, Rudolph G, Kloters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. J Hepatol. 2002;36(2):151–6.
30. Levy C, Lymp J, Angulo P, Gores GJ, Larusso N, Lindor KD. The value of serum CA 19—9 in predicting cholangiocarcinomas in patients with primary sclerosing cholangitis. Dig Dis Sci. 2005;50(9):1734–40.
31. 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(4):1106–17.
32. Siqueira E, Schoen RE, Silverman W, Martin J, Rabinovitz M, Weissfeld JL, Abu-Elmaagd K, Madariaga JR, Slivka A. Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. Gastrointest Endosc. 2002;56(1):40–7.
33. Nishino T, Oyama H, Hashimoto E, Toki F, Oi I, Kobayashi M, Shiratori K. Clinicopathological differentiation between sclerosing cholangitis with autoimmune pancreatitis and primary sclerosing cholangitis. J Gastroenterol. 2007;42(7):550–9.
34. Zen Y, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, Kurumaya H, Katayanagi K, Masuda S, Niwa H, Morimoto H, Miwa A, Uchiyama A, Portmann BC, Nakanuma Y. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? Am J Surg Pathol. 2004;28(9):1193–203.
35. Kanno A, Satoh K, Kimura K, Masamune A, Asakura T, Unno M, Matsuno S, Moriya T, Shimosegawa T. Autoimmune pancreatitis with hepatic inflammatory pseudotumor. Pancreas. 2005;31(4):420–3.
36. Kawakami H, Zen Y, Kuwatani M, Eto K, Haba S, Yamato H, Shinada K, Kubota K, Asaka M. IgG4-related sclerosing cholangitis and autoimmune pancreatitis: histological assessment of biopsies from Vater's ampulla and the bile duct. J Gastroenterol Hepatol. 2010;25(10):1648–55.
37. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Tanaka H, Okumura F, Takahashi S, Joh T. Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. J Gastroenterol. 2009;44(11):1147–55.
38. Chari ST, Takahashi N, Levy MJ, Smyrk TC, Clain JE, Pearson RK, Petersen BT, Topazian MA, Vege SS. A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer. Clin Gastroenterol Hepatol. 2009;7(10):1097–103.
39. Okazaki K, Kawa S, Kamisawa T, Shimosegawa T, Tanaka M, Research Committee for Intractable Pancreatic D, Japan Pancreas S. Japanese consensus guidelines for management of autoimmune pancreatitis: I. Concept and diagnosis of autoimmune pancreatitis. J Gastroenterol. 2010;45(3):249–65.
40. Chapman R, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ, American Association for the Study of Liver D. Diagnosis and

management of primary sclerosing cholangitis. Hepatology. 2010;51(2):660–78.
41. Lindstrom L, Hultcrantz R, Boberg KM, Friis-Liby I, Bergquist A. Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis. Clin Gastroenterol Hepatol. 2013;11(7):841–6.
42. Lindor KD. Ursodiol for primary sclerosing cholangitis. Mayo Primary Sclerosing Cholangitis-Ursodeoxycholic Acid Study Group. N Engl J Med. 1997;336(10):691–5.
43. Olsson R, Boberg KM, de Muckadell OS, Lindgren S, Hultcrantz R, Folvik G, Bell H, Gangsoy-Kristiansen M, Matre J, Rydning A, Wikman O, Danielsson A, Sandberg-Gertzen H, Ung KA, Eriksson A, Loof L, Prytz H, Marschall HU, Broome U. High-dose ursodeoxycholic acid in primary sclerosing cholangitis: a 5-year multicenter, randomized, controlled study. Gastroenterology. 2005;129(5):1464–72.
44. Lindor KD, Kowdley KV, Luketic VA, Harrison ME, McCashland T, Befeler AS, Harnois D, Jorgensen R, Petz J, Keach J, Mooney J, Sargeant C, Braaten J, Bernard T, King D, Miceli E, Schmoll J, Hoskin T, Thapa P, Enders F. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology. 2009;50(3):808–14.
45. Tung BY, Emond MJ, Haggitt RC, Bronner MP, Kimmey MB, Kowdley KV, Brentnall TA. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Ann Intern Med. 2001;134(2):89–95.
46. Pardi DS, Loftus EV Jr, Kremers WK, Keach J, Lindor KD. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. Gastroenterology. 2003;124(4):889–93.
47. Culver EL, Chapman RW. Systematic review: management options for primary sclerosing cholangitis and its variant forms—IgG4-associated cholangitis and overlap with autoimmune hepatitis. Alimen Pharmacol Ther. 2011;33(12):1273–91.
48. Floreani A, Rizzotto ER, Ferrara F, Carderi I, Caroli D, Blasone L, Baldo V. Clinical course and outcome of autoimmune hepatitis/primary sclerosing cholangitis overlap syndrome. Am J Gastroenterol. 2005;100(7):1516–22.
49. Webster GJ, Pereira SP, Chapman RW. Autoimmune pancreatitis/IgG4-associated cholangitis and primary sclerosing cholangitis–overlapping or separate diseases? J Hepatol. 2009;51(2):398–402.
50. Huibregtse K, Tytgat GN. Palliative treatment of obstructive jaundice by transpapillary introduction of large bore bile duct endoprosthesis. Gut. 1982;23(5):371–5.
51. Johnson GK, Geenen JE, Venu RP, Schmalz MJ, Hogan WJ. Endoscopic treatment of biliary tract strictures in sclerosing cholangitis: a larger series and recommendations for treatment. Gastrointest Endosc. 1991;37(1):38–43.
52. Lee JG, Schutz SM, England RE, Leung JW, Cotton PB. Endoscopic therapy of sclerosing cholangitis. Hepatology. 1995;21(3):661–7.
53. van Milligen de Wit AW van Bracht J Rauws EA Jones EA Tytgat GN Huibregtse K. Endoscopic stent therapy for dominant extrahepatic bile duct strictures in primary sclerosing cholangitis. Gastrointest Endosc. 1996;44(3):293–9.
54. Kaya M, Petersen BT, Angulo P, Baron TH, Andrews JC, Gostout CJ, Lindor KD. Balloon dilation compared to stenting of dominant strictures in primary sclerosing cholangitis. Am J Gastroenterol. 2001;96(4):1059–66.
55. van den Hazel SJ, Wolfhagen EH, van Buuren HR, van de Meeberg PC, Van Leeuwen DJ. Prospective risk assessment of endoscopic retrograde cholangiography in patients with primary sclerosing cholangitis. Dutch PSC Study Group. Endoscopy. 2000;32(10):779–82.
56. Baluyut AR, Sherman S, Lehman GA, Hoen H, Chalasani N. Impact of endoscopic therapy on the survival of patients with primary sclerosing cholangitis. Gastrointest Endosc. 2001;53(3):308–12.
57. Gotthardt DN, Rudolph G, Kloters-Plachky P, Kulaksiz H, Stiehl A. Endoscopic dilation of dominant stenoses in primary sclerosing cholangitis: outcome after long-term treatment. Gastrointest Endosc. 2010;71(3):527–34.
58. Ponsioen CY, Lam K, van Milligen de Wit AW, Huibregtse K, Tytgat GN. Four years experience with short term stenting in primary sclerosing cholangitis. Am J Gastroenterol. 1999;94(9):2403–7.
59. Gluck M, Cantone NR, Brandabur JJ, Patterson DJ, Bredfeldt JE, Kozarek RA. A twenty-year experience with endoscopic therapy for symptomatic primary sclerosing cholangitis. J Clin Gastroenterol. 2008;42(9):1032–9.
60. Bangarulingam SY, Gossard AA, Petersen BT, Ott BJ, Lindor KD. Complications of endoscopic retrograde cholangiopancreatography in primary sclerosing cholangitis. Am J Gastroenterol. 2009;104(4):855–60.
61. Topazian M, Witzig TE, Smyrk TC, Pulido JS, Levy MJ, Kamath PS, Chari ST. Rituximab therapy for refractory biliary strictures in immunoglobulin G4-associated cholangitis. Clin Gastroenterol Hepatol. 2008;6(3):364–6.
62. Mannion M, Cron RQ. Successful treatment of pediatric IgG4 related systemic disease with mycophenolate mofetil: case report and a review of the pediatric autoimmune pancreatitis literature. Pediatr Rheumatol Online J. 2011;9(1):1.
63. Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation (1). N Engl J Med. 1989;321(15):1014–22.
64. Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation (2). N Engl J Med. 1989;321(16):1092–9.
65. Akamatsu N, Sugawara Y, Hashimoto D. Biliary reconstruction, its complications and management of biliary complications after adult liver transplantation: a systematic review of the incidence, risk factors and outcome. Transpl Int. 2011;24(4):379–92.

66. Stratta RJ, Wood RP, Langnas AN, Hollins RR, Bruder KJ, Donovan JP, Burnett DA, Lieberman RP, Lund GB, Pillen TJ et al. Diagnosis and treatment of biliary tract complications after orthotopic liver transplantation. Surgery. 1989;106(4):675–83; discussion 83–4.
67. Thethy S, Thomson B, Pleass H, Wigmore SJ, Madhavan K, Akyol M, Forsythe JL, James Garden O. Management of biliary tract complications after orthotopic liver transplantation. Clin Transpl. 2004;18(6):647–53.
68. Krok KL, Cardenas A, Thuluvath PJ. Endoscopic management of biliary complications after liver transplantation. Clin Liver Dis. 2010;14(2):359–71.
69. Pascher A, Neuhaus P. Biliary complications after deceased-donor orthotopic liver transplantation. J Hepatobiliary Pancreat Surg. 2006;13(6):487–96.
70. Sossenheimer M, Slivka A, Carr-Locke D. Management of extrahepatic biliary disease after orthotopic liver transplantation: review of the literature and results of a multicenter survey. Endoscopy. 1996;28(7):565–71.
71. Sharma S, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. Liver Transpl. 2008;14(6):759–69.
72. Verdonk RC, Buis CI, Porte RJ, van der Jagt EJ, Limburg AJ, van den Berg AP, Slooff MJ, Peeters PM, de Jong KP, Kleibeuker JH, Haagsma EB. Anastomotic biliary strictures after liver transplantation: causes and consequences. Liver Transpl. 2006;12(5):726–35.
73. Thuluvath PJ, Pfau PR, Kimmey MB, Ginsberg GG. Biliary complications after liver transplantation: the role of endoscopy. Endoscopy. 2005;37(9):857–63.
74. Novellas S, Caramella T, Fournol M, Gugenheim J, Chevallier P. MR cholangiopancreatography features of the biliary tree after liver transplantation. AJR Am J Roentgenol. 2008;191(1):221–7.
75. Kitazono MT, Qayyum A, Yeh BM, Chard PS, Ostroff JW, Coakley FV. Magnetic resonance cholangiography of biliary strictures after liver transplantation: a prospective double-blind study. J Magn Reson Imaging. 2007;25(6):1168–73.
76. Boraschi P, Donati F, Gigoni R, Volpi A, Salemi S, Filipponi F, Falaschi F. MR cholangiography in orthotopic liver transplantation: sensitivity and specificity in detecting biliary complications. Clin Transpl. 2010;24(4):E82–7.
77. Park JB, Kwon CH, Choi GS, Chun JM, Jung GO, Kim SJ, Joh JW, Lee SK. Prolonged cold ischemic time is a risk factor for biliary strictures in duct-to-duct biliary reconstruction in living donor liver transplantation. Transplantation. 2008;86(11):1536–42.
78. Kim BW, Bae BK, Lee JM, Won JH, Park YK, Xu WG, Wang HJ, Kim MW. Duct-to-duct biliary reconstructions and complications in 100 living donor liver transplantations. Transpl Proc. 2009;41(5):1749–55.
79. Mathur AK, Ranney DN, Patel SP, Lee DS, Bednar F, Lynch RJ, Welling TH, Englesbe MJ. The effect of smoking on biliary complications following liver transplantation. Transpl Int. 2011;24(1):58–66.
80. Fujita S, Fujikawa T, Mizuno S, Reed AI, Kim RD, Howard RJ, Firpi RJ, Nelson DR, Hemming AW. Is early recurrence of hepatitis C associated with biliary anastomotic stricture after liver transplantation? Transplantation. 2007;84(12):1631–5.
81. Dacha S, Barad A, Martin J, Levitsky J. Association of hepatic artery stenosis and biliary strictures in liver transplant recipients. Liver Transpl. 2011;17(7):849–54.
82. Halme L, Hockerstedt K, Lautenschlager I. Cytomegalovirus infection and development of biliary complications after liver transplantation. Transplantation. 2003;75(11):1853–8.
83. Maheshwari A, Maley W, Li Z, Thuluvath PJ. Biliary complications and outcomes of liver transplantation from donors after cardiac death. Liver Transpl. 2007;13(12):1645–53.
84. Suarez F, Otero A, Solla M, Arnal F, Lorenzo MJ, Marini M, Vazquez-Iglesias JL, Gomez M. Biliary complications after liver transplantation from maastricht category-2 non-heart-beating donors. Transplantation. 2008;85(1):9–14.
85. Abt P, Crawford M, Desai N, Markmann J, Olthoff K, Shaked A. Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. Transplantation. 2003;75(10):1659–63.
86. Graziadei IW, Schwaighofer H, Koch R, Nachbaur K, Koenigsrainer A, Margreiter R, Vogel W. Long-term outcome of endoscopic treatment of biliary strictures after liver transplantation. Liver Transpl. 2006;12(5):718–25.
87. Seo JK, Ryu JK, Lee SH, Park JK, Yang KY, Kim YT, Yoon YB, Lee HW, Yi NJ, Suh KS. Endoscopic treatment for biliary stricture after adult living donor liver transplantation. Liver Transpl. 2009;15(4):369–80.
88. Morelli J, Mulcahy HE, Willner IR, Cunningham JT, Draganov P. Long-term outcomes for patients with post-liver transplant anastomotic biliary strictures treated by endoscopic stent placement. Gastrointest Endosc. 2003;58(3):374–9.
89. Schwartz DA, Petersen BT, Poterucha JJ, Gostout CJ. Endoscopic therapy of anastomotic bile duct strictures occurring after liver transplantation. Gastrointest Endosc. 2000;51(2):169–74.
90. Kulaksiz H, Weiss KH, Gotthardt D, Adler G, Stremmel W, Schaible A, Dogan A, Stiehl A, Sauer P. Is stenting necessary after balloon dilation of post-transplantation biliary strictures? Results of a prospective comparative study. Endoscopy. 2008;40(9):746–51.
91. Costamagna G, Pandolfi M, Mutignani M, Spada C, Perri V. Long-term results of endoscopic management of postoperative bile duct strictures with increasing numbers of stents. Gastrointest Endosc. 2001;54(2):162–8.
92. Tabibian JH, Asham EH, Han S, Saab S, Tong MJ, Goldstein L, Busuttil RW, Durazo FA. Endoscopic

treatment of postorthotopic liver transplantation anastomotic biliary strictures with maximal stent therapy (with video). Gastrointest Endosc. 2010;71(3):505–12.
93. Tarantino I, Traina M, Mocciaro F, Barresi L, Curcio G, Di Pisa M, Granata A, Volpes R, Gridelli B. Fully covered metallic stents in biliary stenosis after orthotopic liver transplantation. Endoscopy. 2012;44(3):246–50.
94. Traina M, Tarantino I, Barresi L, Volpes R, Gruttadauria S, Petridis I, Gridelli B. Efficacy and safety of fully covered self-expandable metallic stents in biliary complications after liver transplantation: a preliminary study. Liver Transpl. 2009;15(11):1493–8.
95. Rerknimitr R, Sherman S, Fogel EL, Kalayci C, Lumeng L, Chalasani N, Kwo P, Lehman GA. Biliary tract complications after orthotopic liver transplantation with choledochocholedochostomy anastomosis: endoscopic findings and results of therapy. Gastrointest Endosc. 2002;55(2):224–31.
96. Rizk RS, McVicar JP, Emond MJ, Rohrmann CA Jr, Kowdley KV, Perkins J, Carithers RL Jr, Kimmey MB. Endoscopic management of biliary strictures in liver transplant recipients: effect on patient and graft survival. Gastrointest Endosc. 1998;47(2):128–35.
97. Zoepf T, Maldonado de Dechene EJ, Dechene A, Malago M, Beckebaum S, Paul A, Gerken G, Hilgard P. Optimized endoscopic treatment of ischemic-type biliary lesions after liver transplantation. Gastrointest Endosc. 2012;76(3):556–63.
98. Chahal P, Baron TH, Poterucha JJ, Rosen CB. Endoscopic retrograde cholangiography in post-orthotopic liver transplant population with Roux-en-Y biliary reconstruction. Liver Transpl. 2007;13(8):1168–73.

Choledochal Cysts: Evaluation and Management

10

James Stayner and Douglas G. Adler

Introduction

Choledochal cysts are rare congenital dilations of the biliary tree. Most are diagnosed in infancy or childhood, though the incidence of adult diagnosis is increasing. Early recognition and appropriate treatment are important due to risk of malignant transformation. Endoscopic retrograde cholangiopancreatography (ERCP) has a central role in diagnosis, surveillance, and even definitive therapy in a subtype of cysts. This chapter will review the presentation and diagnosis of choledochal cysts as well as their clinical classification and management.

Case Presentation

A 55-year-old man without previous medical comorbidities was evaluated for episodes of intense right upper quadrant (RUQ) pain associated with nausea and vomiting. The patient's liver function tests (LFTs) were normal at the time of evaluation. In between episodes, the patient feels well and is in his usual state of good health. The patient had a benign physical examination. An upper endoscopy was negative. A computed tomography (CT) of the abdomen was obtained, which revealed a cystic dilation of the mid to distal common bile duct (CBD). The patient saw a hepatobiliary surgeon, but was not interested in surgery despite a discussion of the risks of a potential choledochal cyst. The patient was referred for ERCP.

How Common Are Choledochal Cysts Worldwide?

Choledochal cysts were initially described in the 1700s. Cystic dilation of intra- or extrahepatic bile ducts is usually diagnosed in childhood with more than 60 % of choledochal cysts diagnosed in the first decade of life. An increasing number are diagnosed in adulthood, often in asymptomatic individuals [29, 50, 55]. Despite increased frequency in adulthood, the incidence of true cystic biliary dilation identified in patients undergoing ERCP remains very low, at less than one-tenth of a percent [47, 55]. The disease is more common in females, with female to male ratios three to eight times higher [55]. The incidence in western populations has traditionally been reported between 1:100,000 and 1:150,000, although it has been reported as high as 1:13,500 in the USA and 1:15,000 in Australia [50]. Asian countries, particularly Japan, have the highest reported incidence of choledochal cysts with rates as high as one in 1000 births [39, 50].

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Why Do Choledochal Cysts Develop?

Many of the theories to explain the etiology of choledochal cysts propose that abnormalities during embryogenesis allow for the variant anatomy to develop. Early differentiation of structures destined for the hepatobiliary tract and pancreas occurs at the end of the 3rd week of gestation. An endodermal outpouching from the midgut, known as the pars hepatica or hepatic diverticulum (HD), will become the liver, gallbladder, extrahepatic ducts, and pancreas [44].

The HD begins to develop liver parenchyma as endodermal cells invade the cranial portion of the mesoderm and begin to differentiate. Further differentiation at the cranial end leads to the liver and the common hepatic duct (CHD) while the caudal end divides into two buds, a superior bud (pars cystica), which eventually differentiates into the gallbladder and cystic duct, and an inferior bud, which becomes the ventral pancreas. After 6 weeks of gestation, all the components of the biliary tree are recognizable and have rotated into their definitive positions [3]. At 8 weeks, the liver precursor cells differentiate into the ductal plate that undergoes remodeling to form the biliary ducts.

Multiple theories have been proposed to explain how choledochal cysts develop. The common channel theory proposed by Babbit suggests that an aberrant pancreatic bud causes a longer (usuallys >8 mm) common channel and an abnormal pancreaticobiliary junction (APBJ) [18]. Thus, the bile duct and pancreatic duct (PD) unite outside the duodenal wall. The long channel, along with an ineffective sphincter of Oddi, is thought to allow mixing of biliary and pancreatic juices, which activates pancreatic enzymes leading to inflammation, deterioration of structural proteins and biliary duct wall, and further duct dilation. Opponents to this theory note that it only accounts for Todani type I and Todani type IV cysts. Numerous studies have identified incomplete concordance between identified APBJ and the presence of choledochal cysts [1, 26]. About 50–80% of these choledochal cysts are accompanied by APBJ. Another theory suggests that choledochal cysts are part of a spectrum of embryological malformations of the pancreaticobiliary system.

What Is the Most Common Classification for Choledochal Cysts?

The first classification schema for choledochal cysts to gain wide acceptance was introduced by Alonso-Lei in 1959 [2]. Three distinct types were initially described: congenital cystic dilation, congenital diverticulum of the CBD, and congenital choledochocele. This classification was later expanded to five types by Todani et al. in 1977 [62, 65]. Though there have been further permutations, this is still the most widely recognized classification scheme. Todani's classification includes five subtypes, detailed below.

Todani type I cysts are characterized by areas of segmental intra- or extrahepatic bile duct dilation (Figs. 10.1 and 10.2). These are the most commonly observed choledochal cysts, representing >80–90% of reported cases. Type I choledochal cysts are further subdivided based on the appearance of the dilation into subtypes A–D. Type IA cysts are usually characterized by

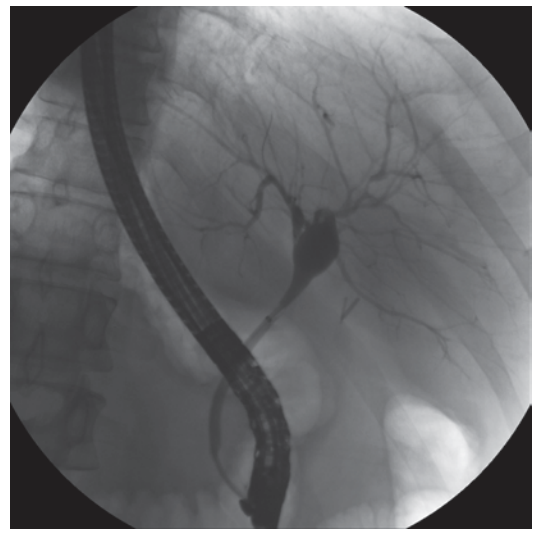

Fig. 10.1 ERCP cholangiogram revealing a variant of a type I choledochal cyst, with cystic dilation of the proximal extrahepatic biliary tree just below the bifurcation. *ERCP* endoscopic retrograde cholangiopancreatography

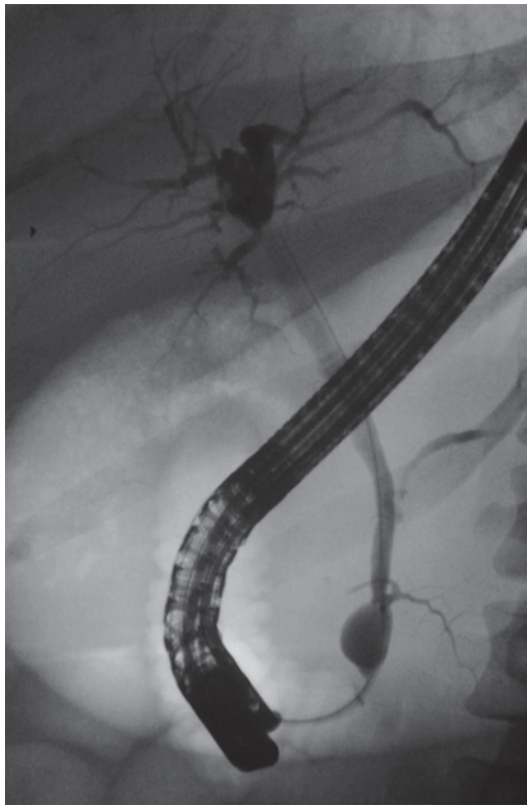

Fig. 10.2 ERCP cholangiogram demonstrating type IB choledochal cyst with anomalous pancreaticobiliary junction. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA). *ERCP* endoscopic retrograde cholangiopancreatography

a pronounced cystic dilation of the CBD without intrahepatic dilation, with the cystic duct and gallbladder arising from the dilated CBD. Type IB cysts have focal, segmental dilation of the extrahepatic bile duct, usually in the distal CBD with the cystic duct typically arising from the normal CBD. In type IC cysts, the entire extrahepatic duct, including both the CBD and CHD, is characterized by a smooth fusiform dilation usually extending into the intrahepatic ducts (which is less spheroid than type IA cysts). Type ID cysts were recently described as dilation of the CBD, CHD, and proximal portion of the cystic duct as well [34].

Todani type II cysts are rare diverticuli arising from the extrahepatic bile duct. These cystic outpouchings are connected by a thin stalk to an otherwise normal bile duct. They occur equally in males and females and may be discovered at any age. The absence of communication with the cystic duct or gallbladder distinguishes Todani type II cysts from gallbladder duplications and peribiliary cysts, which are small noncommunicating retention cysts adjacent to intrahepatic ducts [7, 35]. Imaging becomes important when attempting to establish whether the fluid-filled diverticulum communicates with the gallbladder or CBD and requires surgical intervention, or is a benign fluid collection. ERCP is preferred over MRCP (magnetic resonance cholangiopancreatography), largely because identifying small communications on MRCP is less sensitive compared with ERCP, where the communication opacifies with contrast.

Todani type III cysts are rare cystic dilations of the distal CBD within the duodenal wall (Fig. 10.3a). These lesions are often seen to bulge into the lumen of the duodenum (Fig.10.3b). They are also known as choledochoceles (given their similarities to ureteroceles before the Todani classification was created) [9, 26]. There is an ongoing debate as to whether choledochoceles should be considered true choledochal cysts given the significant differences in the age and symptoms at presentation, and presumed reduced risk of malignancy [74].

Choledochoceles were further divided by Scholz into type IIIA cysts if the PD and CBD drained into the choledochocele, or type IIIB if the dilation is a diverticulum of the CBD within the wall of the duodenum [48]. Further classification schemes have been proposed that categorize cysts according to the relationship between the papilla of Vater (PV), the PD, and the CBD [45]. However, since the management for all Todani type III cysts is nearly the same, this scheme is not commonly used in clinical practice [50].

Todani type IV lesions are multiple cystic dilations of the extrahepatic ducts with or without intrahepatic involvement (Fig. 10.4). Type IVA lesions are multiple cystic dilations of both intra- and extrahepatic ducts. The dilated ducts may be any combination of fusiform or cystic dilations. Type IVB lesions only involve the extrahepatic ducts with multiple dilated segments, and appear

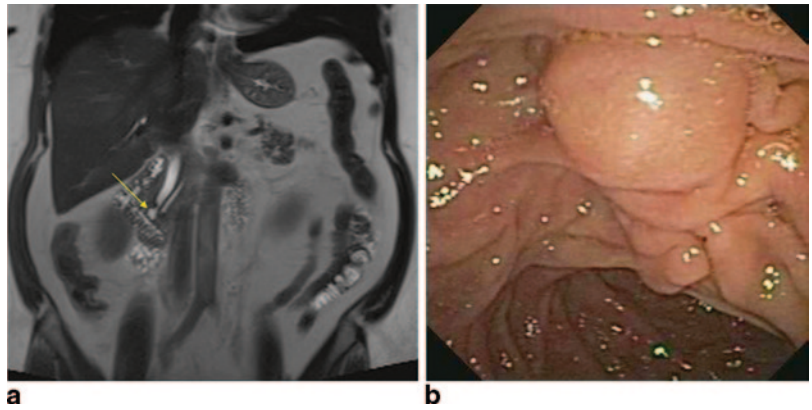

Fig. 10.3 **a** Coronal T2 weighted MRI pancreas showing type III choledochal cyst (*arrow*). **b** Endoscopic view of type III choledochal cyst (choledochocele) with bulging ampulla. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA). *MRI* magnetic resonance imaging

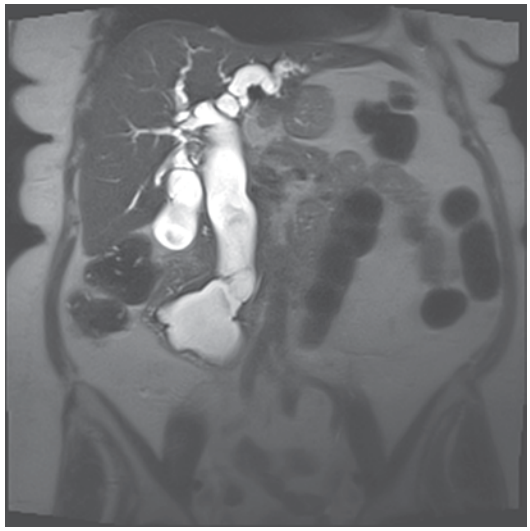

Fig. 10.4 Coronal T2 weighted MRCP image demonstrating a massively enlarged common duct and proximal intrahepatic ducts, consistent a type IVA choledochal cyst. (Courtesy of Marta Heilbrun, MD). *MRCP* magnetic resonance cholangiopancreatography

radiographically as a string of beads or bunch of grapes.

Todani type V cysts, also known as Caroli disease, are single or multiple nonobstructive dilations of the intrahepatic bile ducts [27]. Most of the intrahepatic dilations of Todani type V cysts are multiple segmental saccular dilations, giving a characteristic "beaded" appearance [26]. If there is extrahepatic duct dilation, it is mild and fusiform, compared with the large cystic dilations seen in type IVA cysts [45]. Caroli syndrome is when Caroli disease dilations are associated with congenital hepatic fibrosis, polycystic kidney disease, and other congenital disorders [26, 49]. Cholangitis is common in both conditions, though only Caroli syndrome will progress to liver fibrosis, portal hypertension, and eventual liver failure.

Histologically, choledochal cysts have varying degrees of dysplasia, though there are no pathognomonic histologic findings of the bile duct wall unique to Todani I–IV choledochal cysts. Ductal plate malformations with persisting embryonic features, inflammation, and dilation of the intrahepatic bile ducts characterize Todani V cysts [45]. Malformations confined to the larger intrahepatic ducts form Caroli disease, while patients with abnormalities limited to the small interlobular ducts develop congenital hepatic fibrosis. When both patterns are present, patients have Caroli syndrome, which involves all intrahepatic bile ducts.

Although not included in the Todani classification, forme fruste cysts are characterized by an abnormal pancreaticobiliary duct junction without bile duct dilation [28, 50]. They share many of the same presenting symptoms—histologic changes and potential for malignant transformation—like the other choledochal cysts [18].

How Do Patients Present with Choledochal Cysts?

Patients with choledochal cysts present with a wide variety of symptoms, usually complications of the cysts such as cholangitis, cholecystitis, and pancreatitis, or may remain completely asymptomatic with incidental discovery of the lesion(s) [4, 57]. Between 50 and 80 % of patients with choledochal cysts are diagnosed in the first decade of life [29, 51]. The classic triad of abdominal pain, jaundice, and a palpable abdominal mass is more common in younger patients. Although over 60 % of patients have two out of three symptoms, only 20 % will have all three [2, 55, 57]. In younger patients, obstructive jaundice and a palpable abdominal mass are the most common symptoms. In older patients, symptoms related to mass effect or bile stasis within the cyst, such as RUQ abdominal pain, nausea, vomiting, and fever, are more common. Bile stasis can lead to stone formation and infection, which may result in secondary biliary cirrhosis [42]. These patients may present with signs and symptoms of cirrhosis including variceal bleeding, splenomegaly, and pancytopenia. Portal hypertension may also occur without cirrhosis due to the choledochal cyst causing mechanical obstruction of the portal vein. Rarely, patients present with life-threatening complications such as cyst rupture (1–12 %), variceal bleeding from portal hypertension, liver abscesses, or sepsis [23, 57]. Cyst rupture presents with abdominal pain, sepsis, and bile peritonitis with abdominal ultrasound (US) potentially demonstrating a normal biliary tree if the cyst decompressed following rupture. A hepatobiliary iminodiacetic acid (HIDA) scan will show contrast entering the peritoneal cavity.

While patients with choledochoceles may have symptoms similar to other choledochal cysts, they are often asymptomatic. Type III choledochal cysts can also rarely present with gastric outlet obstruction if a large intramural cyst bulges into the duodenal lumen [41, 57].

Although many patients are asymptomatic, many adult patients will develop complications from choledochal cysts [28]. Symptoms may arise in any part of the biliary tract, often due to mechanical obstruction either from mass effect by the cyst or from stones in the ducts, which can lead to ascending cholangitis or pancreatitis [57]. The severity of recurrent episodes of inflammation and infection is likely to escalate if left untreated. Secondary changes, including portal hypertension, cirrhosis, and malignancy, occur much more often in adults than in children [55].

What Is the Risk of Malignancy with Choledochal Cysts?

Cancer is common in patients with choledochal cysts (Table 10.1). Cholangiocarcinoma accounts for nearly two-third of these malignancies followed by gallbladder cancer, with rare occurrences of hepatocellular carcinoma, and pancreatic cancer [57]. Cancer typically develops within the choledochal cysts and in the gallbladder of patients with forme fruste cysts. While all choledochal cysts are premalignant, and cancer has been reported in all Todani classes, types I and IV account for the vast majority of cancers (68 and 21 %, respectively) [63]. The overall incidence of malignancy in patients with choledochal cysts is between 2.5 and 28 %, which is 20 to 120 times greater than the general population

Table 10.1 Frequency of choledochal cysts and frequency of each type of cyst in choledochal cyst-associated cancers. [18, 50, 23]

Todani classification	Frequency of type of cyst (%)	Frequency of type of cyst in cancers arising from choledochal cysts
I	80–90	50–80
II	2	2–5
III	4–5	1.4–4.5
IV	19	15–35
V	20	7–15

Table 10.2 Age and frequency of cancer [18, 54]

Age (years)	Incidence of choledochal malignancy (%)
<10	<1
10–30	0
31–50	19
51–70	50
>75	75

[38, 55, 57]. In addition, patients with choledochal cysts are typically diagnosed with malignancy 10–20 years earlier than the general population, and have a worse prognosis with few surviving beyond 2 years from diagnosis [54, 57, 70].

The risk of malignancy in patients with choledochal cysts increases with age (Table 10.2). In patients younger than 10, the cancer risk is less than 1% [18]. The risk of cancer increases to 2.3% in patients over 20, over 10% by age 30, and 75% by age 70 [5, 50]. Even after surgical resection of a choledochal cyst, patients are at increased risk for developing cancer. Assuming the cyst is completely excised, there is negligible risk of malignancy for the first three decades following surgery. The risk then rises with each decade after resection to 19% between 30 and 50 years and 50% for patients 50–70 years following surgery [36]. The literature suggests this is due to the remnant cyst tissue or subclinical malignant disease not detected or excised at the time of surgery [18].

What Tools Are Available to Diagnose Choledochal Cysts?

Serum liver chemistries are generally not useful in the diagnosis of choledochal cysts, as there is no pathognomonic laboratory pattern for choledochal cysts. They may be normal, although elevations of transaminases or bilirubin from cholangitis are common. Without pathognomonic physical examination findings or laboratory values, imaging becomes the definitive tool for diagnosis of choledochal cysts. The goals of imaging studies include determining whether the cyst communicates with the bile duct, and evaluating for the presence of a mass. Numerous imaging modalities, both invasive and noninvasive, can be utilized to characterize the choledochal cysts. Noninvasive imaging with transabdominal US, CT, magnetic resonance imaging (MRI), and MRCP, as well as invasive imaging modalities such as ERCP, endoscopic ultrasound (EUS), and percutaneous transhepatic cholangiography (PTC) are used to diagnose choledochal cysts. The most common cause of bile duct dilation is obstruction, not biliary cysts. Biliary cysts communicate with the biliary tract, and do not result from distal obstruction [26]. Cholangiographic studies, including ERCP, MRCP, and PTC, are used to show continuity with the biliary tract, rule out obstruction, define the anatomy of the biliary tree, and more fully characterize the choledochal cyst.

Transabdominal ultrasound is often the first modality used to evaluate patients who present with abdominal pain and jaundice. Characteristic findings of choledochal cysts are a nonobstructive mass in the RUQ that communicates with the biliary tract [22]. US can be used to evaluate the size and shape of the cysts, its relationship to other components of the biliary tract, and whether there are stones or sludge present within the cyst. The sensitivity of US to diagnose choledochal cysts ranges between 71 and 97%, though limited by many factors, including the skill of the technician and the patient's body habitus, gas pattern, and overlying structures [14, 16]. The "central dot" sign (dilated duct surrounding a portal bundle) seen only in Todani type V cysts is nearly pathognomonic for Caroli disease. Todani type III cysts are difficult to identify on transabdominal ultrasound because of their smaller size, location within or at the level of the duodenal wall, and less dilated CBD [57]. Although more invasive than transabdominal US, EUS is not affected by the factors that limit transabdominal US imaging, and is particularly useful for visualizing the intrapancreatic portion of the CBD as is desired in patients with type III cysts [53, 57]. EUS can provide more detailed imaging of the pancreaticobiliary junction as well.

Antenatal US has been used to diagnose choledochal cysts in utero well before symptoms manifest [31]. It is a useful tool to distinguish choledochal cysts from other masses in the RUQ-like biliary atresia, which usually require emergent surgery [18, 66].

CT scan visualizes the continuity between the cysts and the biliary tree in all five Todani classes, and is superior to US at characterizing the intrahepatic biliary system, distal bile duct, and the head of the pancreas [57]. Extrahepatic malignancies can appear as a mass or focal wall thickening [37]. CT scan also shows the architecture of the liver and intrahepatic lesions, which in type IV or V cysts can be useful in preoperative planning to determine if segmental lobectomy is feasible. It may be superior to MRI for postoperative monitoring as well [33]. Computed tomographic cholangiopancreatography (CTCP) utilizes CT images with infusion of iodipamide meglumine that is absorbed by hepatocytes and excreted into the bile to visualize the biliary tract [19]. Though highly sensitive (>90%) for visualizing the biliary tree and diagnosing both choledochal cysts and cholelithiasis, it is inferior to MRCP, EUS, and ERCP in visualizing the intrahepatic and pancreatic ducts [13, 25]. Further shortcomings of CT and CTCP include radiation exposure and potential nephrotoxicity from the intravenous contrast.

HIDA scan is a nuclear medicine study used to demonstrate continuity between the cysts and the biliary tract. Dye absorbed by hepatocytes collects in bile and fills the cyst with delayed emptying into the bowel [18, 57]. The sensitivity is nearly 100% for identifying extrahepatic cysts but decreases significantly to 67% with intrahepatic cysts [36]. HIDA scan can be particularly useful for distinguishing choledochal cysts from biliary atresia in the neonate with excretion seen in cysts and retention of contrast in biliary atresia.

MRCP is a noninvasive evaluation of the biliary tract with very high sensitivity for diagnosing choledochal cysts, reported between 90 and 100%. MRCP has been used for diagnosis, preoperative planning, and postoperative monitoring and is typically performed before ERCP. Compared to ERCP, MRCP is safer with no radiation exposure or risk of pancreatitis and cholangitis, and image acquisition is not operator dependent. Secretin stimulation may increase diagnostic accuracy, and newer, faster sequencing techniques minimize motion artifacts, make image acquisition more tolerable for adults, and allow children to be imaged without anesthesia [8, 12, 33, 72]. Although MRCP is considered by some to have replaced ERCP as the gold standard for diagnosing choledochal cysts, it does not allow direct evaluation of biliary epithelium, tissue sampling, or therapeutic maneuvers [33, 40, 55, 57]. In addition, MRCP is inferior at evaluating highly tortuous ducts, small structures, small stones, and the pancreaticobiliary junction, with sensitivity as low as 46–60% [24]. Therefore, the diagnosis of APBJ and small choledochoceles is limited with MRCP.

ERCP is the gold standard for diagnosing choledochal cysts with sensitivity approaching 100% [21]. It detects stones and filling defects, identifies malignancy, and characterizes abnormal pancreaticobiliary junctions. In addition to being highly sensitive, ERCP allows the operator to pursue further imaging, such as pancreatography, cholangioscopy, or intraductal and/or EUS in the same session. Perhaps the greatest benefit of ERCP is the ability to perform therapeutic interventions such as sphincterotomy (as is commonly performed for type III cysts). However, the incidence of post-ERCP pancreatitis is much higher in patients with choledochal cysts, with some reports as high as 87% [56]. In addition, large cysts require larger dye loads, which can dilate the cyst resulting in overestimation of cyst size and obscuring mucosal defects including ulcers and malignancies [32, 57].

Cholangioscopy involves passing a small fiber optic camera during ERCP into the bile duct to more fully evaluate the biliary tree [61]. It can be used diagnostically to evaluate cyst shape and size and biopsy from the bile duct or therapeutically to break up and remove stones. Compared to traditional ERCP with brush biopsy, cholangioscopic-guided biopsy has higher sensitivity and specificity for diagnosing cholangiocarcinoma in patients with congenital cystic dilations [11, 36]. Intraductal ultrasound (IDUS) has also been used to diagnose early malignant changes in choledochal cysts [73]. The procedure is performed during ERCP over a guidewire to characterize the pancreatic and bile ducts [20]. The probe has a penetration depth of around 2.0 cm, and is very sensitive at visualizing luminal ab-

normalities. The maneuverability of the probe may be hindered by strictures within the duct.

Patients should undergo MRCP preferably to further evaluate possible choledochal cysts that were detected on abdominal US and/or abdominal CT. If uncertainty remains over whether the cyst communicates with the bile duct, HIDA scan should likely be the next step although ERCP can be performed as well. For suspected type III cysts, ERCP should be pursued for both diagnostics and therapeutics. ERCP can also be used if MRCP cannot be performed or is inadequate, biliary obstruction cannot be ruled out, or there are concerns about malignant transformation. Cholangioscopy and IDUS can be used to examine the bile duct walls during ERCP and look for concerning areas that would warrant biopsy and brushing. In general, the authors do not advocate random brushings of normal appearing choledochal cyst walls, as this likely has a very low yield. Type I choledochal cysts may be difficult to differentiate from biliary obstruction, leading to secondary biliary dilation and may require further evaluation with EUS or ERCP. Clues supporting a diagnosis of biliary obstruction include presence of stones, stricture, mass, abnormal LFTs, and improvement of biliary dilation after treatment. On the other hand, presence of APBJ implies a choledochal cyst.

PTC may aid in preoperative planning to define the extent of the dilations in both the intra- and extrahepatic biliary tree and as an adjunct when other modalities have been unable to fully characterize the cyst, although this is uncommon nowadays [46, 58]. In addition to diagnostic uses, PTC has been used therapeutically to decompress the biliary tract and successfully perform sphincterotomy in patients whose anatomy makes traditional endoscopic sphincterotomy technically difficult [17].

Case Continued

The patient underwent an ERCP, which revealed a cystic dilation of the mid to distal CBD to the level of the ampulla (Fig. 10.5). The cyst was felt to have features of both a type I and a type III choledochal cyst. After discussion with the patient's hepatobiliary surgeon, the decision was made to perform a biliary sphincterotomy given features suggestive of a type III cyst. This was performed without incident. The patient then underwent cholangioscopy, which revealed smooth bile duct walls and no signs of precancerous lesions.

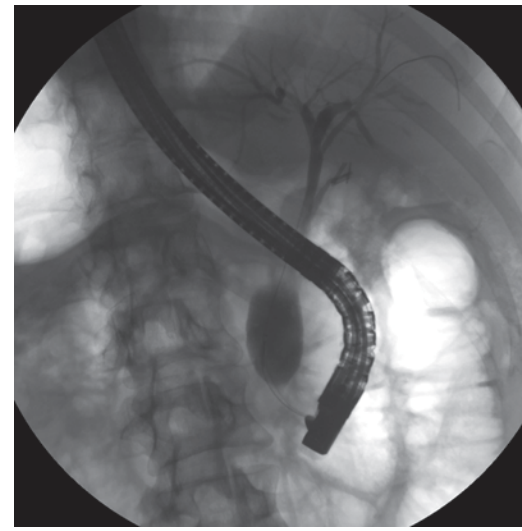

Fig. 10.5 ERCP cholangiogram revealing a choledochal cyst with features of both a type I and a type III cyst. The cystic area reaches to the level of the duodenal wall and extends proximally to involve the CBD. *ERCP* endoscopic retrograde cholangiopancreatography, *CBD* common bile duct

How Should Choledochal Cysts Be Managed?

Most choledochal cysts are managed surgically. Previously, internal drainage by cystenterostomy or partial cyst excision was performed for symptomatic relief. This approach has been abandoned due to high rates of morbidity mainly from recurrent cholangitis, anastomotic stricture, and 30% risk of malignancy within the wall of the cyst [21, 64, 68]. The risk of malignancy in patients with incomplete excision is high enough that reoperation for complete resection of cyst and biliary diversion is recommended in asymptomatic patients who had a previous cystenterostomy [69].

Todani type I cysts are treated via complete excision in good surgical candidates [17]. Optimal management consists of complete surgical excision of the dilated extrahepatic malformation, removing stones and sludge from the intrahepatic and common ducts, and surgical anastomosis to allow biliary drainage into the alimentary tract [16, 71]. Several surgical techniques have been successfully performed, including minimally invasive laparoscopic procedures, which may lead to reduced recovery time and adhesions, though these are less widely available [67]. Roux-en-Y hepaticojejunostomy (RYHJ), originally described in 1924, is preferred to hepaticoduodenostomy (HD) for type I cysts in most western countries. The complication rate, including malignancy, is significantly higher (42%) following HD than RYHJ (7%) [21, 52]. RYHJ is successful in over 92% of cases, and provides initial relief to most symptomatic patients with low perioperative morbidity [59]. Late complications, most commonly related to stricture formation at the anastomosis or malignancy, may require repeat procedures. Malignancy occurs in up to 6% of patients postoperatively and is attributed to cyst tissue or malignancy not appreciated at the time of surgery.

Both Todani type II and III cysts have lower incidence of malignant transformation than Todani I or IV, with less than 5% of all cancers associated with types II and III [58]. With low rates of malignancy, type II choledochal cysts can be simply excised by ligation at the neck without the need for bile duct reconstruction [6]. Type III cysts were historically treated with transduodenal excision and sphincteroplasty. In the current era, most of these lesions are managed via endoscopic sphincterotomy to allow drainage of biliary sludge and stones and reduce stasis within the cyst [67]. Sphincterotomy is recommended even in asymptomatic patients. Biopsies of the inner cyst lining should be performed to evaluate for dysplasia and whether the mucosa is duodenal or biliary because biliary tissue is associated with higher malignancy rates. Patients with large choledochoceles are at risk for duodenal or gastric obstruction, and may merit surgical excision and duodenostomy, although this finding is rare [68].

Patients with Todani type IV cysts are at higher risk for developing malignancy, and, like Type I cysts, complete excision of extrahepatic lesions with wide hilar hepaticoenterostomy is recommended. If the intrahepatic lesions are localized to one lobe, then the patient should be considered for a full hepatic lobectomy [17, 64]. As more lobes are involved, surgical resection may not be possible. In these patients, symptoms are managed with long-term stenting or percutaneous hepaticojejunostomy as needed [55, 64, 68].

Todani type V cysts, including patients with both Caroli disease and Caroli syndrome are treated in a similar manner to patients with type IV cysts. Extrahepatic lesions are treated with complete surgical excision [64]. Treatment of intrahepatic lesions depends on the degree of involvement and the severity of associated liver disease. Recurrent cholangitis and intrahepatic stones can be treated conservatively with prophylactic antibiotics, and endoscopic or percutaneous lithotripsy. Ursodeoxycholic acid has been used to decrease the burden of intrahepatic stones [43]. Intrahepatic lesions, including ductal strictures, dilations, or abscess confined to one lobe, are treated with segmental lobectomy [68]. Diffuse cystic disease with evidence of liver disease, including liver failure, cirrhosis, portal hypertension, or recurrent cholangitis, is best treated with orthotopic liver transplant [60, 64, 67]. Transplanted patients with Caroli disease and Caroli syndrome have graft and overall survival comparable to patients transplanted for other reasons, although the 5-year graft survival is superior in Caroli disease (86%) than Caroli syndrome (71%) [10, 15].

Patients with forme fruste cysts should undergo at least a cholecystectomy. There is debate over whether the CBD should also be excised with a hepaticoenterostomy.

What Are Surveillance Recommendations After Surgical Resection?

All patients, regardless of Todani classification, will need lifelong cancer surveillance. Compared to the general population, patients with chole-

dochal cysts have a 20–30-fold increased risk of developing cholangiocarcinoma with a lifetime cancer rate between 2.5 and 30% [64]. Malignancy has a grim prognosis and many patients are unresectable at the time of diagnosis [68]. Complete surgical excision of the precancerous cysts will decrease but not eliminate the risk of malignant transformation [30, 67]. Radiographic changes and serum markers have been used to monitor malignancy but cannot be relied upon as a definitive screening modality [18, 57, 60]. Although CEA, CA 19-9, CA-125 can be elevated in cholangiocarcinoma, they are not specific and can be elevated in inflammatory diseases. The most appropriate modality and frequency of surveillance in patients with choledochal cysts are not well defined in the literature. Current recommendations include lifelong abdominal US with LFT, CEA, and CA 19-9 levels every 6–12 months [18].

Case Follow Up

The patient's symptoms resolved following ERCP with sphincterotomy. Because he continued to refuse surgery, the patient is undergoing periodic MRI/MRCP to monitor the cyst, with ERCP and/or EUS as needed. There are no definitive guidelines for performing surveillance in patients with choledochal cysts who undergo no or partial resection of the cyst. It seems reasonable to pursue annual MRCP or CT to evaluate for malignant changes.

Conclusion

Choledochal cysts are congenital dilations of the biliary tract. Most are diagnosed and treated surgically in infancy or childhood with diagnosis in adults becoming more common. Although MRCP has gained increased support for initial diagnosis, ERCP plays a key role in diagnosis and presurgical planning for most Todani cyst classes. In Todani type III cysts, ERCP with sphincterotomy is the recommended definitive management.

Key Points

- Choledochal cysts most commonly present in childhood, although they are increasingly diagnosed in adults.
- Malignant potential is greatest with Todani types I and IV and with increasing age.
- Surgical resection is the mainstay of treatment for most choledochal cysts except type III (choledochocele), which may be managed endoscopically due to its low risk of malignancy.
- MRCP should be the initial diagnostic imaging with ERCP performed in cases of diagnostic uncertainty, concern for malignancy or biliary obstruction, inability to perform MRI, or choledochoceles.
- Surveillance for malignancy must continue even following surgical resection due to ongoing risk of malignancy which increases with time.

References

1. Alkhatib AA, Hilden K, Adler DG. Incidental pancreatography via ERCP in patients with anomalous pancreaticobiliary junction does not result in pancreatitis in a North American population. Dig Dis Sci. 2012;57(4):1064–8. doi:10.1007/s10620-011-1964-8. Epub 2011 Nov 12. PubMed PMID: 22080418.
2. Alonso-Lej F, Rever WB, Jr, Pessagno DJ. Congenital choledochal cyst, with a report of 2, and an analysis of 94, cases. Int Abstr Surg. 1959;108(1):1–30. PubMed PMID: 13625059.
3. Ando H. Embryology of the biliary tract. Dig Surg. 2010;27(2):87–9. doi:10.1159/000286463. Epub 2010 Jun 10. Review. PubMed PMID: 20551648.
4. Atkinson HD, Fischer CP, de Jong CH, Madhavan KK, Parks RW, Garden OJ. Choledochal cysts in adults and their complications. HPB (Oxford). 2003;5(2):105–10. doi:10.1080/13651820310001144. PubMed PMID: 8332966; PubMed Central PMCID: PMC2020569.
5. Benjamin IS. Biliary cystic disease: the risk of cancer. J Hepatobiliary Pancreat Surg. 2003;10(5):335–9. Review. PubMed PMID: 14598132.
6. Bhavsar MS, Vora HB, Giriyappa VH. Choledochal cysts: a review of literature. Saudi J Gastroenterol. 2012;18(4):230–6. doi:10.4103/1319-3767.98425. Review. PubMed PMID: 22824764; PubMed Central PMCID: PMC3409882.

7. Coakley FV. Pearls and pitfalls in abdominal imaging. Cambridge: Cambridge University Press; 2010. pp. 72–5.
8. Dabbas N, Davenport M. Congenital choledochal malformation: not just a problem for children. Ann R Coll Surg Engl. 2009;91(2):100–5. doi:10.1308/003588409X391947. Review. PubMed PMID: 19317933; PubMed Central PMCID: PMC2749342.
9. de Courcy Wheeler WI. An unusual case of obstruction to the common bile-duct (choledochocele?). Br J Surg. 1940;27:446–8. doi:10.1002/bjs.18002710705.
10. De Kerckhove L, De Meyer M, Verbaandert C, Mourad M, Sokal E, Goffette P, Geubel A, Karam V, Adam R, Lerut J. The place of liver transplantation in Caroli's disease and syndrome. Transpl Int. 2006;19(5):381–8. PubMed PMID:16623873.
11. Draganov PV, Chauhan S, Wagh MS, Gupte AR, Lin T, Hou W, Forsmark CE. 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(2):347–53. doi:10.1016/j.gie.2011.09.020. PubMed PMID: 22248602.
12. Fitoz S, Erden A, Boruban S. Magnetic resonance cholangiopancreatography of biliary system abnormalities in children. Clin Imaging. 2007;31(2):93–101. PubMed PMID: 17320775.
13. Fumino S, Ono S, Kimura O, Deguchi E, Iwai N. Diagnostic impact of computed tomography cholangiography and magnetic resonance cholangiopancreatography on pancreaticobiliary maljunction. J Pediatr Surg. 2011;46(7):1373–8. doi:10.1016/j.jpedsurg.2011.01.026. PubMed PMID: 21763837.
14. Haliloglu M, Akata D, Gurel S, Ozmen MN, Akhan O. Choledochal cysts in children: evaluation with three-dimensional sonography. J Clin Ultrasound. 2003;31(9):478–80. PubMed PMID: 14595738.
15. Harring TR, Nguyen NT, Liu H, Goss JA, O'Mahony CA. Caroli disease patients have excellent survival after liver transplant. J Surg Res. 2012;177(2):365–72. doi:10.1016/j.jss.2012.04.022. Epub 2012 Apr 29. PubMed PMID: 22640887.
16. Huang SP, Wang HP, Chen JH, Wu MS, Shun CT, Lin JT. Clinical application of EUS and peroral cholangioscopy in a choledochocele with choledocholithiasis. Gastrointest Endosc. 1999;50(4):568–71. PubMed PMID: 10502185.
17. Itoi T, Shinohara Y, Takeda K, Nakamura K, Sofuni A, Itokawa F, Moriyasu F, Tsuchida A. A novel technique for endoscopic sphincterotomy when using a percutaneous transhepatic cholangioscope in patients with an endoscopically inaccessible papilla. Gastrointest Endosc. 2004;59(6):708–11. PubMed PMID:15114320.
18. Jabłońska B. Biliary cysts: etiology, diagnosis and management. World J Gastroenterol. 2012;18(35):4801–10. Review. PubMed PMID: 23002354; PubMed Central PMCID: PMC3447264.
19. Kamisawa T, Okamoto A. Biliopancreatic and pancreatobiliary refluxes in cases with and without pancreaticobiliary maljunction: diagnosis and clinical implications. Digestion. 2006;73(4):228–36. Epub 2006 Aug 28. Review. PubMed PMID: 16940726.
20. Kamisawa T, Takuma K, Itokawa F, Itoi T. Endoscopic diagnosis of pancreaticobiliary maljunction. World J Gastrointest Endosc. 2011;3(1):1–5. doi:10.4253/wjge.v3.i1.1. PubMed PMID: 21258599; PubMed Central PMCID: PMC3024475.
21. Keil R, Snajdauf J, Rygl M, Pycha K, Kotalová R, Drábek J, Stovícek J, Procke M. Diagnostic efficacy of ERCP in cholestatic infants and neonates—a retrospective study on a large series. Endoscopy. 2010;42(2):121–6. doi:10.1055/s-0029-1215372. Epub 2010 Feb 5. PubMed PMID: 20140829.
22. Kim OH, Chung HJ, Choi BG. Imaging of the choledochal cyst. Radiographics. 1995;15(1):69–88. Review. PubMed PMID: 7899614.
23. Kiresi DA, Karabacakoğlu A, Dilsiz A, Karaköse S. Spontaneous rupture of choledochal cyst presenting in childhood. Turk J Pediatr. 2005;47(3):283–6. PubMed PMID: 16250318.
24. Krausé D, Cercueil JP, Dranssart M, Cognet F, Piard F, Hillon P. MRI for evaluating congenital bile duct abnormalities. J Comput Assist Tomogr. 2002;26(4):541–52. PubMed PMID: 12218818.
25. Lam WW, Lam TP, Saing H, Chan FL, Chan KL. MR cholangiography and CT cholangiography of pediatric patients with choledochal cysts. AJR Am J Roentgenol. 1999;173(2):401–5. PubMed PMID: 10430145.
26. Levy AD, Rohrmann CA, Jr. Biliary cystic disease. Curr Probl Diagn Radiol. 2003;32(6):233–63. Review. PubMed PMID: 14647122.
27. Levy AD, Rohrmann CA, Jr, Murakata LA, Lonergan GJ. Caroli's disease: radiologic spectrum with pathologic correlation. AJR Am J Roentgenol. 2002;179(4):1053–7. PubMed PMID: 12239064.
28. Lilly JR, Stellin GP, Karrer FM. Forme fruste choledochal cyst. J Pediatr Surg. 1985;20(4):449–51. PubMed PMID: 4045674.
29. Liu CL, Fan ST, Lo CM, Lam CM, Poon RT, Wong J. Choledochal cysts in adults. Arch Surg. 2002;137(4):465–8. PubMed PMID: 11926955.
30. Liu YB, Wang JW, Devkota KR, Ji ZL, Li JT, Wang XA, Ma XM, Cai WL, Kong Y, Cao LP, Peng SY. Congenital choledochal cysts in adults: twenty-five-year experience. Chin Med J (Engl). 2007;120(16):1404–7. PubMed PMID: 17825168.
31. Makin E, Davenport M. Understanding choledochal malformation. Arch Dis Child. 2012;97(1):69–72. doi:10.1136/adc.2010.195974. Epub 2011 Mar 27. Review. PubMed PMID: 21444296.
32. Matos C, Nicaise N, Devière J, Cassart M, Metens T, Struyven J, Cremer M. Choledochal cysts: comparison of findings at MR cholangiopancreatography and endoscopic retrograde cholangiopancreatography in eight patients. Radiology. 1998;209(2):443–8. PubMed PMID: 9807571.

33. Metcalfe MS, Wemyss-Holden SA, Maddern GJ. Management dilemmas with choledochal cysts. Arch Surg. 2003;138(3):333–9. Review. PubMed PMID: 12611583.
34. Michaelides M, Dimarelos V, Kostantinou D, Bintoudi A, Tzikos F, Kyriakou V Rodokalakis G, Tsitouridis I. A new variant of Todani type I choledochal cyst. Imaging evaluation. Hippokratia. 2011;15:174–7.
35. Motoo Y, Yamaguchi Y, Watanabe H, Okai T, Sawabu N. Hepatic peribiliary cysts diagnosed by magnetic resonance cholangiography. J Gastroenterol. 2001;36(4):271–5. PubMed PMID: 11324732.
36. Nicholl M, Pitt HA, Wolf P, Cooney J, Kalayoglu M, Shilyansky J, Rikkers LF. Choledochal cysts in western adults: complexities compared to children. J Gastrointest Surg. 2004;8(3):245–52. PubMed PMID: 15019916.
37. Nonomura A, Mizukami Y, Matsubara F, Ueda H. A case of choledochal cyst associated with adenocarcinoma exhibiting sarcomatous features. J Gastroenterol. 1994;29(5):669–75. PubMed PMID: 8000520.
38. Ohtsuka T, Inoue K, Ohuchida J, Nabae T, Takahata S, Niiyama H, Yokohata K, Ogawa Y, Yamaguchi K, Chijiiwa K, Tanaka M. Carcinoma arising in choledochocele. Endoscopy. 2001;33(7):614–9. PubMed PMID: 11473335.
39. O'Neill JA, Jr. Choledochal cyst. Curr Probl Surg. 1992;29(6):361–410. Review. PubMed PMID: 1582241.
40. Park DH, Kim MH, Lee SK, Lee SS, Choi JS, Lee YS, Seo DW, Won HJ, Kim MY. Can MRCP replace the diagnostic role of ERCP for patients with choledochal cysts? Gastrointest Endosc. 2005;62(3):360–6. PubMed PMID: 16111952.
41. Ramos A, Castelló J, Pinto I. Intestinal intussusception as a presenting feature of choledochocele. Gastrointest Radiol. 1990;15(3):211–4. PubMed PMID: 2340996.
42. Rao KLN, Chowdhary SK, Kumar D. Choledochal cyst associated with portal hypertension. Pediatr Surg Int. 2003;19:729–32.
43. Ros E, Navarro S, Bru C, Gilabert R, Bianchi L, Bruguera M. Ursodeoxycholic acid treatment of primary hepatolithiasis in Caroli's syndrome. Lancet. 1993;342(8868):404–6. PubMed PMID: 8101905.
44. Santiago I, Loureiro R, Curvo-Semedo L, Marques C, Tardáguila F, Matos C, Caseiro-Alves F. Congenital cystic lesions of the biliary tree. AJR Am J Roentgenol. 2012;198(4):825–35. doi:10.2214/AJR.11.7294. Review. Erratum in: AJR Am J Roentgenol. 2012 May;198(5):1232. PubMed PMID: 22451547.
45. Sarris GE, Tsang D. Choledochocele: case report, literature review, and a proposed classification. Surgery. 1989;105(3):408–14. Review. PubMed PMID: 2646745.
46. Savader SJ, Venbrux AC, Benenati JF, Mitchell SE, Widlus DM, Cameron JL, Osterman FA, Jr. Choledochal cysts: role of noninvasive imaging, percutaneous transhepatic cholangiography, and percutaneous biliary drainage in diagnosis and treatment. J Vasc Interv Radiol. 1991;2(3):379–85. PubMed PMID: 1799785.
47. Schmidt HG, Bauer J, Wiessner V, Schönekäs H. Endoscopic aspects of choledochoceles. Hepatogastroenterology. 1996;43(7):143–6. PubMed PMID: 8682450.
48. Scholz FJ, Carrera GF, Larsen CR. The choledochocele: correlation of radiological, clinical and pathological findings. Radiology. 1976;118(1):25–8. PubMed PMID: 1244667.
49. Shedda S, Robertson A. Caroli's syndrome and adult polycystic kidney disease. ANZ J Surg. 2007;77(4):292–4. Review. PubMed PMID: 173888390.
50. Singham J, Yoshida EM, Scudamore CH. Choledochal cysts: part 1 of 3: classification and pathogenesis. Can J Surg. 2009;52(5):434–40. Review. PubMed PMID: 19865581; PubMed Central PMCID: PMC2769090.
51. Singham J, Yoshida EM, Scudamore CH. Choledochal cysts: part 2 of 3: diagnosis. Can J Surg. 2009;52(6):506–11. Review. PubMed PMID: 20011188; PubMed Central PMCID: PMC2792398.
52. Singham J, Yoshida EM, Scudamore CH. Choledochal cysts. Part 3 of 3: management. Can J Surg. 2010;53(1):51–6. Review. PubMed PMID: 20100414; PubMed Central PMCID: PMC2810009.
53. Sood A, Senthilnathan MS, Deswal S, Pradhan PK, Das BK, Kumar R. Spontaneous rupture of a choledochal cyst and the role of hepatobiliary scintigraphy. Clin Nucl Med. 2004;29(6):392–3. PubMed PMID: 15166894.
54. Søreide K, Søreide JA. Bile duct cyst as precursor to biliary tract cancer. Ann Surg Oncol. 2007;14(3):1200–11. Epub 2006 Dec 23. Review. PubMed PMID: 17187167.
55. Söreide K, Körner H, Havnen J, Söreide JA. Bile duct cysts in adults. Br J Surg. 2004;91(12):1538–48. Review. PubMed PMID: 15549778.
56. Sugiyama M, Haradome H, Takahara T, Abe N, Tokuhara M, Masaki T, Mori T, Hachiya J, Atomi Y. Anomalous pancreaticobiliary junction shown on multidetector CT. AJR Am J Roentgenol. 2003;180(1):173–5. PubMed PMID: 12490498.
57. Swisher SG, Cates JA, Hunt KK, Robert ME, Bennion RS, Thompson JE, Roslyn JJ, Reber HA. Pancreatitis associated with adult choledochal cysts. Pancreas. 1994;9(5):633–7. PubMed PMID: 7809018.
58. Tamada K, Yasuda Y, Tomiyama T, Oohashi A, Kanai N, Aizawa T, Wada S, Tano S, Miyata T, Satoh Y, Ido K, Kimura K. Preoperative assessment of congenital bile duct dilatation using intraductal US. Gastrointest Endosc. 1999;49(4 Pt 1):488–92. PubMed PMID: 10202064.
59. Tao KS, Lu YG, Wang T, Dou KF. Procedures for congenital choledochal cysts and curative effect analysis in adults. Hepatobiliary Pancreat Dis Int. 2002;1(3):442–5. PubMed PMID: 14607724.

60. Taylor AC, Palmer KR. Caroli's disease. Eur J Gastroenterol Hepatol. 1998;10(2):105–8. PubMed PMID: 9581983.
61. Terheggen G, Neuhaus H. [Cholangioscopy]. Internist (Berl). 2013;54(3):302–8. doi:10.1007/s00108-012-3180-9 German. PubMed PMID: 23420024.
62. Todani T, Watanabe Y, Narusue M, Tabuchi K, Okajima K. Congenital bile duct cysts: classification, operative procedures, and review of thirty-seven cases including cancer arising from choledochal cyst. Am J Surg. 1977;134(2):263–9. PubMed PMID: 889044.
63. Todani T, Tabuchi K, Watanabe Y, Kobayashi T. Carcinoma arising in the wall of congenital bile duct cysts. Cancer. 1979;44(3):1134–41. Review. PubMed PMID: 383269.
64. Todani T, Watanabe Y, Toki A, Urushihara N. Carcinoma related to choledochal cysts with internal drainage operations. Surg Gynecol Obstet. 1987;164(1):61–4. PubMed PMID: 3026058.
65. Todani T, Watanabe Y, Toki A, Morotomi Y. Classification of congenital biliary cystic disease: special reference to type Ic and IVA cysts with primary ductal stricture. J Hepatobiliary Pancreat Surg. 2003;10(5):340–4. PubMed PMID: 14598133.
66. Tongprasert F, Traisrisilp K, Tongsong T. Prenatal diagnosis of choledochal cyst: a case report. J Clin Ultrasound. 2012;40(1):48–50. doi:10.1002/jcu.20856. Epub 2011 Jun 17. PubMed PMID: 21688273.
67. Ure BM, Schier F, Schmidt AI. Laparoscopic resection of congenital choledochal cyst, choledochojejunostomy, and extraabdominal Roux-en- Y anastomosis. Surg Endosc. 2005;19:1055–7.
68. Wang DC, Liu ZP, Li ZH, Li DJ, Chen J, Zheng SG, He Y, Bie P, Wang SG. Surgical treatment of congenital biliary duct cyst. BMC Gastroenterol. 2012;12:29. doi:10.1186/1471-230X-12-29. PubMed PMID: 22458359; PubMed Central PMCID: PMC3352298.
69. Watanabe Y, Toki A, Todani T. Bile duct cancer developed after cyst excision for choledochal cyst. J Hepatobiliary Pancreat Surg. 1999;6(3):207–12. PubMed PMID: 10526053.
70. Weyant MJ, Maluccio MA, Bertagnolli MM, Daly JM. Choledochal cysts in adults: a report of two cases and review of the literature. Am J Gastroenterol. 1998;93(12):2580–3. Review. PubMed PMID: 9860432.
71. Woon CY, Tan YM, Oei CL, Chung AY, Chow PK, Ooi LL. Adult choledochal cysts: an audit of surgical management. ANZ J Surg. 2006;76(11):981–6. PubMed PMID: 17054547.
72. Yamataka A, Kuwatsuru R, Shima H, Kobayashi H, Lane G, Segawa O, Katayama H, Miyano T. Initial experience with non-breath-hold magnetic resonance cholangiopancreatography: a new noninvasive technique for the diagnosis of choledochal cyst in children. J Pediatr Surg. 1997;32(11):1560–2. PubMed PMID: 9396525.
73. Yazumi S, Takahashi R, Tojo M, Watanabe N, Imamura M, Chiba T. Intraductal US aids detection of carcinoma in situ in a patient with a choledochal cyst. Gastrointest Endosc. 2001;53(2):233–6. PubMed PMID: 11174304.
74. Ziegler KM, Zyromski NJ. Choledochoceles: are they choledochal cysts? Adv Surg. 2011;45:211–24. Review. PubMed PMID: 21954689.

Part III
Pancreatic Cases

Acute Biliary Pancreatitis: Image, Intervene, or Observe?

11

Faris M. Murad and Steve Edmundowicz

Introduction

When managing patients with acute biliary pancreatitis, establishing the presence of persistent biliary obstruction and/or the presence of concomitant cholangitis is essential [1, 2]. While the literature is conflicted regarding the role of early endoscopic retrograde cholangiopancreatography (ERCP) for all patients with biliary pancreatitis, it appears that early intervention benefits patients with severe acute pancreatitis complicated by persistent pancreaticobiliary obstruction, especially when accompanied by cholangitis [3–5]. In this context, a clinician must utilize and prioritize the multitude of diagnostic resources at hand to risk stratify patients in a manner that translates to expedient and cost-effective care delivery. Due to the heterogeneity of patient presentations, it is important to manage patients with biliary pancreatitis through a risk-stratification system. This chapter will review different case scenarios with focused questions regarding the cases and discussion of risk stratification.

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Case 1

A 72-year-old male presents with acute onset abdominal pain. His lipase is elevated to 15,000 consistent with acute pancreatitis. Biochemical liver function testing demonstrates a total bilirubin of 4.7 mg/dL, alkaline phosphatase of 273 IU/L, and transaminases are elevated with an ALT 118 and AST 165. The patient denied significant alcohol use. A right upper quadrant ultrasound demonstrates cholelithiasis (Fig. 11.1) and mild dilation of the extrahepatic bile duct (8 mm in diameter). On presentation the patient is tachycardic to 110 beats/min and has an elevated white blood cell (WBC) count of 18,000. His blood pressure is stable and renal function is normal. He was given 4 L of IV fluids within the first 8 h of his admission and subsequently was noted to have normal vital signs.

Questions:

1. Which of the aforementioned liver function test abnormalities are most important for medical decision making for this patient?
2. Does this patient require further imaging?
3. Should an ERCP be performed in this patient at this time?

How to Risk Stratify for Choledocholithiasis

Biochemical abnormalities and transabdominal ultrasonography are often the first (and can be the most important) data a clinician utilizes to

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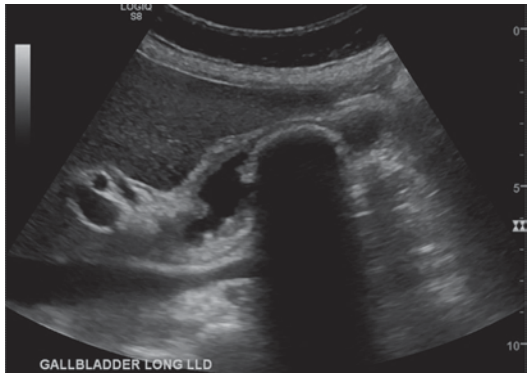

Fig. 11.1 Transabdominal ultrasound showing hyperechoic structure with post-acoustic shadowing representing cholelithiasis

risk stratify a patient when deciding whether biliary endoscopy is indicated in the setting of acute pancreatitis. A study of more than 1000 patients evaluating biochemical parameters as predictors for choledocholithiasis prior to laparoscopic cholecystectomy found that presence of at least one abnormal liver function test (LFT) of the five (ALT, AST, alkaline phosphatase, total bilirubin, and GGT) had a sensitivity of 87.5% [6]. Conversely, completely normal liver function testing had a negative predictive value for a positive ERCP of 97%. Among biochemical testing, total bilirubin had the highest specificity (87.5%), with a probability ratio of 3.9. Total bilirubin and alkaline phosphatase level were also demonstrated on multivariate analysis to be independent predictors for choledocholithiasis on ERCP although the positive predictive value of all the liver function tests was only 15% [2]. Therefore, LFTs are most helpful when normal for excluding choledocholithiasis while even elevated total bilirubin and alkaline phosphatase may be false positives.

Similarly a normal bile duct on abdominal ultrasound rules out choledocholithiasis with 95–96% negative predictive value. Of course the finding of a common bile duct (CBD) stone on ultrasound has very high specificity. Without a definite stone seen on imaging, the presence of multiple predictors for choledocholithiasis increases the positive predictive value. Predictors for choledocholithiasis were studied in patients presenting for laparoscopic cholecystectomy. This study found that an elevated bilirubin approaching 2 mg/dL combined with a patient age of 55 or greater and CBD dilation on ultrasound greater than 6 mm demonstrated a 75% probability of predicting choledocholithiasis at the time of ERCP [6].

An ASGE position statement recommends risk stratification of patients with cholelithiasis based on biochemical liver testing and ultrasonography to categories of high, intermediate, and low risk for choledocholithiasis to determine who needs ERCP [2]. These categories stem from evidence-based predictors that are identified as "very strong" (CBD stone on transabdominal ultrasound, clinical ascending cholangitis, or bilirubin >4 mg/dL), "strong" (CBD>6 mm with gallbladder in situ on ultrasound, bilirubin level 1.8–4 mg/dL), and "moderate" (any abnormal biochemical liver test other than bilirubin, age greater than 55, and clinical gallstone pancreatitis) for identifying patients with choledocholithiasis on ERCP. Patients with the presence of any "very strong" predictor or two "strong" predictors are high risk with a greater than 50% chance of choledocholithiasis and should proceed to ERCP. Patients without any predictors may not require any further workup as they have less than 10% probability of choledocholithiasis. Patients with an intermediate likelihood are those with a combination of predictors that do not meet the high-risk category. Further evaluation prior to ERCP for this group of patients may be reasonable. Specifically, this represents a group of patients that would benefit from further evaluation with endoscopic ultrasound (EUS) or magnetic resonance cholangiopancreatography (MRCP) [2].

In this case our patient demonstrated a "very strong" predictor with a bilirubin greater than 4 mg/dL, a "strong" predictor with a CBD>6 mm on ultrasonography and a "moderate" predictor with acute pancreatitis in the setting of cholelithiasis. He was identified as high probability for choledocholithiasis and the next step of management was ERCP. EUS or MRCP would not provide any additional useful information and would

only delay definitive therapy along with adding additional costs for the patient.

Case Follow-Up

At the time of biliary endoscopy, the lower third of the main bile duct contained multiple stones, the largest of which was 12 × 10 mm in size. The CBD was dilated to 12 mm on cholangiogram as well. Stones were extracted with endoscopic biliary sphincterotomy and balloon sweep (Video 11.1).

Case 2

A 55-year-old female presents to the emergency room with unrelenting abdominal pain after an evening meal. The patient underwent a cholecystectomy for symptomatic cholelithiasis approximately 1 year prior to her presentation to the emergency department. She reports subsequent intermittent, self-limited episodes of right upper quadrant abdominal pain associated with nausea, emesis, and diaphoresis. An outpatient upper endoscopy was negative. She reports consumption of alcohol at a level of 2–3 drinks per day, 4 days per week. On admission the patient's lipase is elevated at 2130, her liver function panel reveals an AST of 140, ALT of 250, and total bilirubin is 1.5. A right upper quadrant ultrasound demonstrated an extrahepatic CBD measuring 8 mm in maximal diameter and no evidence for choledocholithiasis. On admission she is afebrile, vital signs are stable. The patient does not have evidence of organ failure or systemic inflammatory response syndrome. In the days following her admission and following conservative management, her pain improves to the point that she requests a diet. However, on admission day 3 her liver function transaminases remain elevated at AST 124, ALT 180 and her total bilirubin is 1.8. She experiences an episode of similar pain when she attempts oral intake.

Questions:

1. What is your differential diagnosis for this patient's episode of acute pancreatitis?
2. How would you risk stratify this patient for persistent pancreaticobiliary obstruction?
3. What additional imaging would be helpful in evaluating this patient at this time?
4. Should this patient proceed straight to ERCP?

EUS or MRCP for Intermediate Probability Choledocholithiasis?

In contrast to the first case, here there are multiple considerations when deciding if the patient is presenting with biliary pancreatitis, and if biliary pancreatitis is complicated by ongoing pancreaticobiliary obstruction. First, the patient reports a significant history of alcohol use, which is a possible explanation for both pancreatitis and even elevated transaminases. Transient biliary obstruction due to pancreatic edema and peripancreatic fluid can also cause dynamic liver function abnormalities in the setting of acute pancreatitis. Supporting biliary pancreatitis is the patient's preceding history of cholelithiasis, recurrent episodes of biliary type pain following cholecystectomy, and both the presence and pattern of elevated abnormal transaminases at the time of presentation. Alcoholic pancreatitis may present with similar biochemical abnormalities, but in the setting of the patient's history of cholelithiasis; this has to remain high on the differential.

Overall, this patient lacks the previously discussed findings associated with a high pretest probability for choledocholithiasis (cholangitis, elevated bilirubin, and/or bile duct dilation on imaging) which would justify proceeding directly with ERCP. At best this patient has a moderate probability of persistent pancreaticobiliary obstruction. Further workup would be prudent at this time.

EUS is an established, safe modality for the diagnosis of biliary stone disease. Prospective studies have demonstrated EUS to be sensitive,

specific, and to possess the same diagnostic accuracy as ERCP for the detection of choledocholithiasis; yet possesses a substantially lower risk profile [7]. One prospective study of 36 patients with biliary pancreatitis who underwent EUS prior to ERCP found that EUS had a high diagnostic accuracy of 97% and negative predictive value of 95% for choledocholithiasis. EUS can identify patients who have choledocholithiasis and require ERCP while avoiding possible ERCP-related complications in those without choledocholithiasis [8, 9]. A meta-analysis encompassing 2673 patients undergoing EUS in the evaluation of choledocholithiasis demonstrated pooled sensitivities of 89–94% and specificity of 94–95% for the detection of choledocholithiasis [10, 11].

The typical findings of choledocholithiasis on EUS are a hyperechoic structure/focus with or without post-acoustic shadowing. These hyperechoic structures can be seen anywhere in the biliary system including the ampulla, extrahepatic bile duct, cystic duct, and gallbladder. Bile duct sludge and microlithiasis can also be visualized endosonographically. Sludge is typically hypoechoic to isoechoic and may layer within the biliary system. Microlithiasis typically appears as tiny hyperechoic foci within sludge. In performing endosonographic examination of the biliary system, one method is to advance the echoendoscope just distal to the major papilla and apply a slow withdrawal of the echoendoscope until the pancreatic duct is visualized in the ventral anlage. The scope is then slightly rotated counterclockwise until the distal extrahepatic bile duct is visualized. The extrahepatic bile duct is an anechoic tubular structure without flow on Doppler. The ampulla is then easily examined. Keeping the extrahepatic bile duct in sonographic view, the extrahepatic bile duct can be easily evaluated by slowly withdrawing the echoendoscope.

MRCP is also an effective tool when evaluating patients at moderate pretest probability for pancreaticobiliary obstruction. The one clear advantage of MRCP over EUS is it is noninvasive. A systematic review of five studies demonstrated no overall statistical difference between EUS and MRCP for the detection of biliary stone disease with an aggregate sensitivity of 85% and specificity of 93% [12]. However, limitations of MRCP include the need for expert interpretation, potential for false negative and positive results due to imaging artifact and processing, diminished ability to identify small stones (<6 mm) and sludge, and potential variable accuracy for stone detection by duct diameter and when stone disease is present at the level of the ampulla [13–15].

Either of these two modalities would be appropriate to risk stratify this patient depending upon availability and local expertise. A third option that was recently evaluated in a randomized trial is cholecystectomy and intraoperative cholaniography (IOC) followed by ERCP if indicated [16]. This study randomized patients with gallstones and intermediate probability CBD stones to cholecystectomy and IOC within 48 h of admission followed by ERCP if necessary or initial EUS or MRCP followed by ERCP if indicated and then cholecystectomy with the primary outcome being hospital length of stay. Hospital stay was significantly shorter in the cholecystectomy and IOC group (median 5 versus 8 days, $p<0.001$) with fewer EUS performed as well (10 versus 54, $p<0.001$). Issues with this study include: the performance of EUS and any indicated ERCPs on separate days for most patients; although not statistically significant, the median time from admission to EUS trended longer at 1.5 days [interquartile range (IQR) 1–2.75] compared to 1 day (IQR 1–2) for the surgery with IOC group. While readmissions did not differ amongst the two groups, there is lack of adequate follow-up data regarding recurrent biliary symptoms. Therefore, starting with cholecystectomy and IOC represents another viable option for the management of patients with intermediate probability of choledocholithiasis.

Case Follow-Up

An EUS was performed. One 6-mm stone was visualized in the distal CBD at the level of the ampulla (Fig. 11.2). A subsequent ERCP demonstrated choledocholithiasis. The stone was

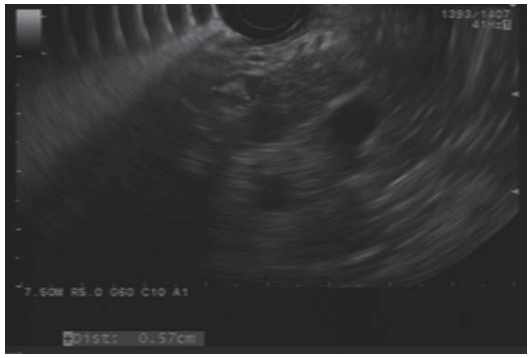

Fig. 11.2 EUS revealing hyperechoic structure with post-acoustic shadowing in distal extrahepatic bile duct. This was a retained small bile duct stone

extracted utilizing endoscopic biliary sphincterotomy and balloon sweep.

Case 3

A 42-year-old female presents with acute cholecystitis, suspected NASH cirrhosis, and has a short history of recurrent episodic biliary pancreatitis. The patient presents to the hospital with right upper quadrant and epigastric pain. Her lipase is 434, WBC 12,500, hemoglobin 9.8, and platelet count 68,000. Her bilirubin is elevated to 3.8 with elevated transaminases in the 200 s and elevated alkaline phosphatase of 450. Her international normalized ratio (INR) is also high at 3.26. She undergoes a computed tomography (CT) scan which reveals a distended gallbladder with mild gallbladder wall thickening, and adjacent hepatic hyperemia suggestive of acute cholecystitis. A transabdominal ultrasound scan is then performed which reveals a distended gallbladder and thickened wall without gallstones. Her extrahepatic bile duct measures 7 mm. There are several prominent vessels running along the gallbladder wall. Her vital signs on presentation to the emergency department were temperature 36.8, pulse 112, respiratory rate 18, and blood pressure 102/67. Her oxygen saturations were 100% on 4 L of oxygen. She was started on IV fluids and broad spectrum antibiotics and transferred to the medical intensive care unit (MICU).

Questions:

1. What is the role of surgery, interventional radiology, or ERCP at this time?
2. What is the role of prophylactic endoscopic biliary sphincterotomy if she is not a candidate for cholecystectomy?
3. What is the timing of cholecystectomy in patients after an attack of gallstone pancreatitis?

Surgery or ERCP to Prevent Recurrent Gallstone Pancreatitis?

In this situation, the patient requires aggressive supportive care as it is not clear if she has concomitant ascending cholangitis or her presentation is exacerbated from her suspected NASH cirrhosis. A surgery consult was obtained along with consultations from interventional radiology and interventional endoscopy. It was felt after hepatobiliary surgery consult that the patient was too high risk for a laparoscopic cholecystectomy due to her suspected cirrhosis and several prominent vessels surrounding the gallbladder. Interventional radiology also felt that the patient was too high risk for percutaneous cholecystostomy tube due to the prominent vessels surrounding the gallbladder. Both services requested ERCP for possible endoscopic biliary sphincterotomy and possible transpapillary stent placement into the gallbladder. After discussion with the MICU team, it was decided to proceed with ERCP after the INR was reversed.

The current recommendations for patients who present with mild biliary pancreatitis is to undergo a cholecystectomy during the initial hospitalization to prevent recurrent episodes of pancreatitis [17, 18]. The Society of American Gastrointestinal and Endoscopic Surgeons recommends cholecystectomy for mild and self-limited gallstone pancreatitis after symptoms have subsided and laboratory values have normalized [19]. A number of studies have described a wide range of recurrent gallstone pancreatitis, between 2.5 and 21.1% in patients who did not have a cholecystectomy [20, 21]. Patients who undergo cholecystectomy have a significantly decreased risk of gallstone pancreatitis, reported from 1 to

1.7% [22]. This data has led to the recommendation that patients undergo cholecystectomy soon after their initial episode of mild gallstone pancreatitis. Following cholecystectomy patients are still at risk for recurrent gallstone pancreatitis, but the risk is significantly less than those who do not undergo cholecystectomy [23]. For patients with severe gallstone pancreatitis, cholecystectomy should be delayed until full recovery.

In some studies, ERCP with endoscopic biliary sphincterotomy (EBS) has been suggested as an alternative to laparoscopic cholecystectomy for high-risk surgical patients and the elderly [21, 24, 25]. The rate of recurrent episodes of gallstone pancreatitis range from 0 to 6.4% following ERCP with EBS. The British Society of Gastroenterology guidelines suggest that patients who are not fit for surgery should undergo EBS [26]. Kaw et al. [23] compared EBS alone to cholecystectomy in the treatment of gallstone pancreatitis in a small study of patients followed up prospectively. In the EBS group, the observed rate of recurrent pancreatitis was 2.9% compared with 2.4% ($p > 0.05$) in the cholecystectomy group after a mean follow-up of almost 3 years. Patients who underwent EBS followed by laparoscopic cholecystectomy had the lowest rate of recurrent pancreatitis (1.2%) over a 5-year follow-up period. There was a nonsignificant trend towards overall increased rate of any biliary complication in the EBS only group compared to the cholecystectomy patients (11.6% versus 3.6%, $p = 0.19$).

Endoscopic sphincterotomy has also been recommended by the International Association of Pancreatology (IAP) as an alternative to cholecystectomy in patients who are not fit to undergo surgery or in the elderly to reduce the chances of recurrent biliary pancreatitis [17]. This recommendation was irrespective of the presence or absence of CBD stones.

Case Follow-Up

The patient underwent ERCP with a small biliary sphincterotomy (<4 mm) and balloon sweep. No stones were identified on cholangiogram or balloon sweep (Fig. 11.3). The cystic duct was also cannulated and contrast was noted to pass into the gallbladder. There was no evidence of obstruction of the cystic duct. Due to the ongoing cholecystitis, a 7 French (Fr) plastic double pigtail stent was placed across the papilla and into the gallbladder. The patient improved clinically and was transferred out of the MICU after 24 h.

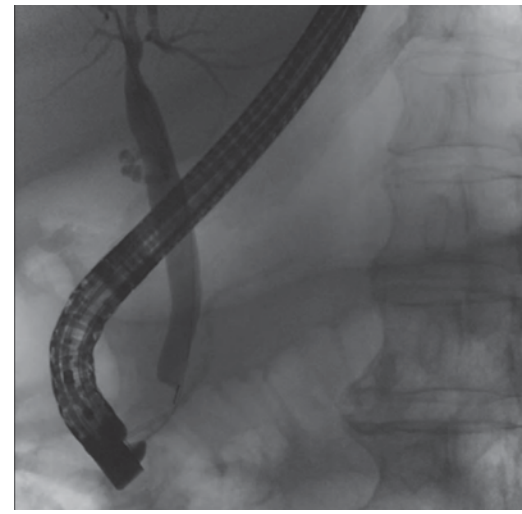

Fig. 11.3 Normal cholangiogram without filling defects

Biliary Pancreatitis and the Bariatric Surgery Patient

The incidence of cholelithiasis in patients after Roux-en-Y gastric bypass (RYGB) varies widely; however, in the literature it has been reported to be as high as 30–50% [27, 28]. Prophylactic cholecystectomy in patients undergoing bariatric surgery is not currently recommended unless patients are symptomatic prior to or at the time of surgery. Prophylactic cholecystectomy has failed to demonstrate a clear benefit in patients undergoing bariatric surgery, and complications due to gallstone disease post bariatric surgery is limited [29]. Since prophylactic cholecystectomy is not performed routinely at the time of bariatric surgery, managing biliary pancreatitis in post-RYGB surgical anatomy can be complex

and will remain an issue faced by many institutions [30].

Endoscopic procedures in patients with RYGB anatomy can be challenging. ERCP in these patients has been performed utilizing a multitude of techniques. These techniques fall into two broad categories that utilize either enteroscopy or laparoscopic-assisted access through the gastric remnant to reach the papilla. However, limitations to the enteroscopy-assisted technique include failure to complete the procedure to the point of desired biliary intervention (as high as 30–40 %), thus requiring surgical/endoscopic access to the gastric remnant, and long procedure times for both modalities. Percutaneous access to the gastric remnant also has the late complications such as persistent gastrocutaneous fistula, and the complexity of coordinating patient care across endoscopic and surgical teams for a single intervention [31–33]. In the setting of patients with suspected biliary pancreatitis and RYGB anatomy, it is imperative that there is proof of biliary obstruction before embarking on combined surgical/endoscopic procedure to perform ERCP or enteroscopy-assisted ERCP.

Case 4

A 59-year-old male with a past medical history of diabetes and RYGB presents with a self-limited episode of abdominal pain and nausea following ingestion of a fatty meal. On admission, his lipase was elevated to 960 (ULN 99), total bilirubin was 1.5, alkaline phosphatase 302, AST 93, and ALT 308. His WBC was 11.2. The patient is hemodynamically stable and afebrile. An abdominal ultrasound demonstrates cholelithiasis, gallbladder wall thickening, and no pericholecystic fluid. The extrahepatic bile duct and intrahepatic ducts are without significant dilation, and there is no clear evidence of choledocholithiasis. An MRCP revealed a CBD diameter of 9 mm without evidence of choledocholithiasis.

A review of this patient's history in the medical chart reveals prior episodes of acute pancreatitis associated with elevated liver function tests. The workup during prior admissions included abdominal ultrasonography, which was negative for gallstones. Prior episodes were associated with rapid resolution of symptoms. The patient elected to defer cholecystectomy when offered on prior admissions.

Questions:

1. Why is this patient's history of Roux-en-Y gastric bypass important?
2. What are the options for further management of this patient?
3. What is the role for surgical intervention in this patient?

What Is the Role of Intraoperative Cholangiography?

This patient presents with recurrent acute pancreatitis with the likely etiology being biliary pancreatitis. The patient has known cholelithiasis and an intact gallbladder. While his liver function tests are elevated on presentation, his total bilirubin is less than 2, and the extrahepatic bile duct does not reveal choledocholithiasis despite being dilated to 9 mm. His post-RYGB surgical anatomy is problematic for gaining easy access to the major papilla for performing an ERCP, and the tools available for ERCP in a length that can be used through the enteroscope are limited. As he will need a cholecystectomy, an IOC can be performed to assess for filling defects within the extrahepatic bile duct.

Intraoperative cholangiography is performed by placing a small catheter into the cystic duct at the time of cholecystectomy. Fluoroscopic images are interpreted by the surgeon during the operation. This test is specific and adds approximately 16–20 min to a laparoscopic cholecystectomy procedure [34]. Literature supporting the routine use of IOC during laparoscopic cholecystectomy suggests no clear benefit. As such, its use and availability during laparoscopic cholecystectomy for all indications is variable [35, 36]. However, a recent prospective study found that a selective approach to the utilization of IOC based on preprocedure risk factors resulted in a superior positive predictive value (PPV). The presence of acute pancreatitis, dilated CBD, or jaundice

at the time of surgery yielded a PPV of 26, 45 and 86 % respectively; combinations of abnormal liver function tests with dilated CBD increased the PPV compared to either alone [37]. It is now clear that IOC remains a recommended part of the algorithm for the workup of patients with an intermediate suspicion for choledocholithiasis in the setting of acute pancreatitis [2]. In the context of this case, a positive study can be followed by laparoscopic CBD exploration or intraoperative ERCP. Laparoscopic bile duct exploration has been demonstrated in randomized trials to have equivalent efficacy and outcomes as preoperative and postoperative ERCP. Intraoperative bile duct exploration as an added intervention for choledocholithiasis may even be associated with lower costs and shorter hospital stay compared with patients who require an additional procedure in the form of an ERCP [38, 39].

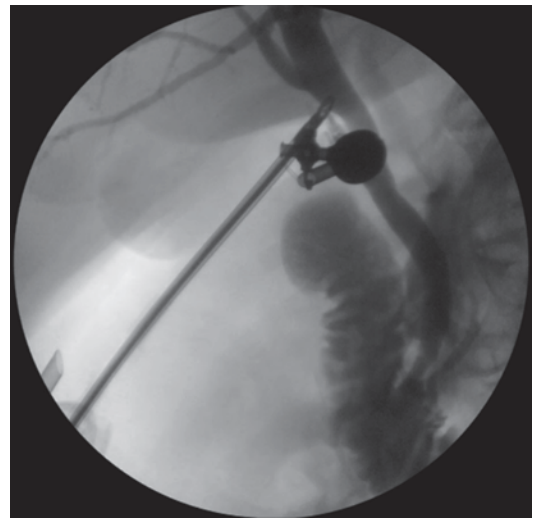

Fig. 11.4 Normal IOC. Contrast readily passes from the extrahepatic bile duct to the duodenum with no filling defects visualized

Case Follow-Up

As this patient required a cholecystectomy for repeated episodes of suspected biliary pancreatitis, the decision was made to proceed with cholecystectomy plus IOC. A positive IOC would have led to the surgeon attempting to clear the extrahepatic bile duct, and if not successful, the patient would have been managed with laparoscopic surgical access to the gastric remnant to allow ERCP. The laparoscopic cholecystectomy was performed with a negative IOC (Fig. 11.4). Final pathology demonstrated cholelithiasis with acute and chronic cholecystitis. A lengthy, complex combined surgical/endoscopic procedure was thus avoided by careful use of preoperative assessment and IOC, and the costs as well as potentially complications were minimized.

Biliary Pancreatitis in Pregnancy

Acute pancreatitis during pregnancy is rare with an incidence of approximately 1 per 1000–3000 pregnancies [40, 41]. It appears more prevalent in multiparous women who account for approximately 75 % of the acute pancreatitis attacks during pregnancy, and is rare in the first and second trimester of pregnancies, but more common in the third trimester and the postpartum period. Over half the episodes of acute pancreatitis in pregnancy occur in the third trimester with 38 % postpartum [42].

Acute pancreatitis during pregnancy carries significant morbidity, but maternal-fetal mortality is low (approximately 3 %) [40]. The most common etiology of acute pancreatitis in pregnancy is from gallstones (65–100 %), alcohol (5–10 %), and hypertriglyceridemia (5 %) [43]. As there may be significant morbidity with the risk of fetal loss, it is important to establish a diagnosis early to allow proper counseling and treatment.

Diagnosing acute pancreatitis during pregnancy may be difficult. Alkaline phosphatase is produced from the placenta so elevated levels are not specific to the biliary system. Alkaline phosphatase can reach up to three times the upper limit of normal in pregnancy, thus this enzyme will not help in determining the diagnosis of gallstone pancreatitis during pregnancy. Elevated ALT greater than three times the upper limit of normal is a very sensitive marker for gallstone pancreatitis. Amylase and lipase elevations greater than

three times the upper limit of normal should carry the same concern for acute pancreatitis as in a nonpregnant patient.

The workup of a pregnant patient with acute pancreatitis is similar to the nonpregnant patient during the initial stages. A proper history and physical examination should be performed. Laboratory studies including a complete blood count, comprehensive metabolic panel including liver function tests, amylase, and lipase should be assessed.

The radiological investigations for a pregnant patient should be safe for the mother and fetus. The initial radiological examination performed for acute pancreatitis in pregnancy is a transabdominal ultrasound. Abdominal ultrasound is safe with a higher sensitivity than CT in detecting gallstones. Limitations of ultrasound include its poor sensitivity (22–55%) for choledocholithiasis and difficulty evaluating the distal extrahepatic bile duct due to overlying bowel gas, which may lead to retained stones being missed. MRCP is as accurate as ultrasound for cholelithiasis with superior ability to assess the entire extrahepatic bile duct. Although not necessary for MRCP, gadolinium does not cause fetal toxicity while iodinated contrast medium for CT scan could cause fetal hypothyroidism [44]. These radiology tests are all noninvasive. A more accurate but invasive test for the evaluation of gallstones is EUS. Since EUS is a more invasive test requiring sedation, this is not a first-line examination to assess the biliary system in pregnant patients.

Acute biliary pancreatitis during pregnancy has a high recurrence rate (70%) compared to the general population (20–30%) [45]. Management should consider risks to both the mother and fetus. There is a high risk of fetal loss with recurrent pancreatitis or severe acute pancreatitis. The benefits of performing a procedure should outweigh the risks of maternal harm or fetal loss. Options in management include conservative management and observation, ERCP, or surgery.

There are no published standardized guidelines regarding the most effective management for biliary pancreatitis in pregnancy to reduce maternal and fetal morbidity and mortality. The high risk of recurrent acute pancreatitis with conservative treatment may drive the treatment algorithm to ERCP or surgery rather than waiting for the postpartum period if the patient presents in the first or second trimester. One proposed algorithm depends on the trimester of presentation [45]. In the first trimester, conservative management followed by laparoscopic cholecystectomy in the second trimester is recommended while in the second trimester, surgery can occur. The third trimester may allow for ERCP or conservative management if at term with cholecystectomy in the early postpartum period. ERCP appears safe in expert hands during pregnancy (Chap. 19).

Case 5

A 26-year-old obese pregnant female presents with increasing epigastric pain for the past 24 h at 8 weeks gestation. The patient is G2P1 and had an uncomplicated first pregnancy 2 years ago. She reports having had intermittent episodes of right upper quadrant abdominal pain over the past year that typically lasted a few hours and would then resolve. She related the symptoms to the consumption of fatty meals. The patient is in slight distress and tachycardic at 110 beats/min. IV fluids are given and labs are drawn. Her lipase is 2500 with total bilirubin 1.0, ALT 250, AST 275, and ALP 300. WBC is 9000. An abdominal ultrasound is obtained which reveals cholelithiasis, no gallbladder wall thickening or pericholecystic fluid, and a dilated bile duct to 6 mm without evidence of choledocholithiasis.

Questions:

1. What is the probability of choledocholithiasis?
2. What is the role for ERCP at this time?
3. Should other imaging be obtained at this time?
4. What is the risk of recurrent acute pancreatitis?

Weighing the Risks and Benefits of Acute Pancreatitis, Its Potential Recurrence, and Therapies in Pregnancy

The patient has a high probability of choledocholithiasis due to the persistent abdominal pain, elevated LFTs, and dilated bile duct in the setting

of cholelithiasis. The patient may spontaneously pass the gallstone, the stone may "ball-valve" into the distal extrahepatic bile duct, or remain lodged at the ampulla. She is currently in her first trimester when the risk of fetal malformation is the greatest (medication exposure, radiation exposure). Also, the patient is at high risk of miscarriage if the biliary pancreatitis persists, recurs, worsens, or if she develops post-ERCP pancreatitis. The data would suggest that there is a high rate of recurrent pancreatitis following conservative management. This patient needs specific counseling regarding risks to the fetus if conservative management is chosen (risk of fetal loss) versus performing ERCP (risk of radiation exposure during the first trimester and fetal malformations, post-ERCP pancreatitis with morbidity and possible fetal loss). Because the patient is in the first trimester during a period where the fetus is susceptible to greatest risk of fetal malformation, EUS may be the safest test to evaluate for small retained stones that may be missed by ultrasound or MRCP. If there is evidence of retained stone on EUS, then proceeding with ERCP carries more chances of benefit than risk to the mother and fetus. ERCP in the pregnant patient should emphasize limiting fluoroscopy time, shielding the maternal pelvis and fetus with lead apron, and minimizing procedure time [46].

Case Follow-Up

After a long discussion with the patient and obstetrics and gynecology (OB/GYN) service, it was decided to proceed with EUS evaluation of the extrahepatic bile duct. An EUS was performed with monitored anesthesia care sedation. There was no evidence of retained stone or sludge within the extrahepatic bile duct. Since the EUS was negative for choledocholithiasis, an ERCP was not performed. The patient subsequently underwent a laparoscopic cholecystectomy in the second trimester without complications.

Figure 11.5 is an algorithm for managing patients with suspected choledocholithiasis

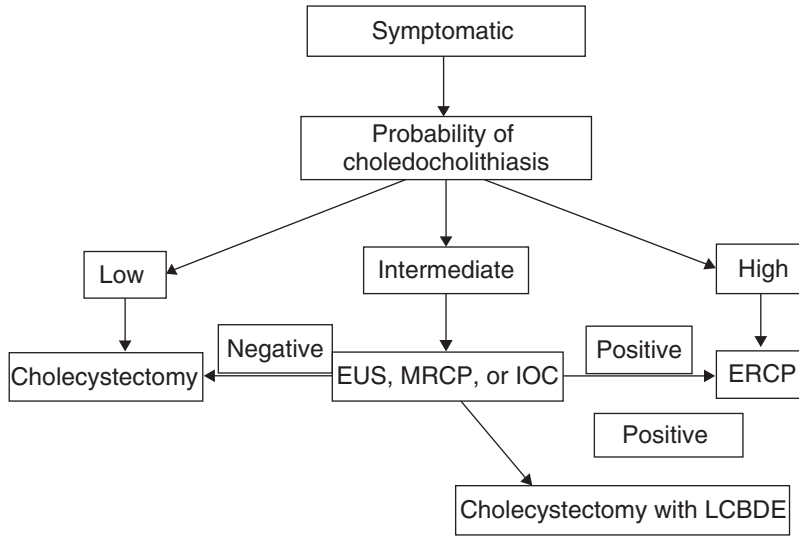

Fig. 11.5 Algorithm for managing patients with suspected choledocholithiasis. *EUS*: endoscopic ultrasound; *MRCP*: magnetic resonance cholangiopancreatography; *ERCP*: endoscopic retrograde cholangiopancreatography; *IOC*: intraoperative cholangiography; *LCBDE*: laparoscopic common bile duct exploration. (Adapted from [2])

Key Points

- Evaluation of patient with suspected biliary pancreatitis relies on clinical presentation, biochemical markers, and radiological imaging.
- No single parameter accurately predicts the presence of choledocholithiasis.
- Multiple imaging modalities (transabdominal ultrasound, CT, MRCP, EUS) are utilized to assess for choledocholithiasis with each modality having advantages and disadvantages.
- A risk-stratification scheme is recommended in the management of patients with suspected biliary pancreatitis to determine who needs ERCP for high suspicion of choledocholithiasis.
- Patients with intermediate probability of choledocholithiasis may undergo EUS, MRCP, or cholecystectomy with intraoperative cholangiography depending on availability and local expertise.
- Biliary pancreatitis in patients with RYGB anatomy may pose particular challenges if choledocholithiasis or cholangitis is suspected, and intraoperative cholangiography with laparoscopic CBD exploration are alternatives to ERCP.
- Acute biliary pancreatitis in pregnant patients poses potential morbidity not only for the mother, but also for the fetus with high rates of recurrence, and one approach relies on the trimester of presentation to guide management towards conservative, ERCP, or surgery.

Video Caption

Video 11.1 This video demonstrates a native major papilla. Selective biliary cannulation is achieved with a sphincterotome and guidewire. The cholangiogram demonstrates filling defects in the distal extrahepatic bile duct. A biliary sphincterotomy is performed. Multiple balloon sweeps initially yield stone fragments. Eventually, a large 10 × 12 mm gallstone is extracted from the extrahepatic bile duct

References

1. van Geenen EJ, van Santvoort HC, Besselink MG, van der Peet DL, van Erpecum KJ, Fockens P, et al. Lack of consensus on the role of endoscopic retrograde cholangiography in acute biliary pancreatitis in published meta-analyses and guidelines: a systematic review. Pancreas. 2013;42(5):774–80.
2. Maple JT, Ben-Menachem T, Anderson MA, Appalaneni V, Banerjee S, Cash BD, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. Gastrointest Endosc. 2010;71(1):1–9.
3. Petrov MS. ERCP versus conservative treatment in acute pancreatitis: meta-analysis or meta-confusion? Dig Liver Dis. 2008;40(9):800–1; author reply 1–2.
4. Folsch UR, Nitsche R, Ludtke R, Hilgers RA, Creutzfeldt W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on acute biliary pancreatitis. N Engl J Med. 1997;336(4):237–42.
5. Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. Cochrane Database Syst Rev. 2012;5:CD009779.
6. Yang MH, Chen TH, Wang SE, Tsai YF, Su CH, Wu CW, et al. Biochemical predictors for absence of common bile duct stones in patients undergoing laparoscopic cholecystectomy. Surg Endosc. 2008;22(7):1620–4.
7. Canto MI, Chak A, Stellato T, Sivak MV, Jr. Endoscopic ultrasonography versus cholangiography for the diagnosis of choledocholithiasis. Gastrointest Endosc. 1998;47(6):439–48.
8. Chak A, Hawes RH, Cooper GS, Hoffman B, Catalano MF, Wong RC, et al. Prospective assessment of the utility of EUS in the evaluation of gallstone pancreatitis. Gastrointest Endosc. 1999;49(5):599–604.
9. Petrov MS, Savides TJ. Systematic review of endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis. Br J Surg. 2009;96(9):967–74.
10. Garrow D, Miller S, Sinha D, Conway J, Hoffman BJ, Hawes RH, et al. Endoscopic ultrasound: a meta-analysis of test performance in suspected biliary obstruction. Clin Gastroenterol Hepatol. 2007;5(5):616–23.
11. Tse F, Liu L, Barkun AN, Armstrong D, Moayyedi P. EUS: a meta-analysis of test performance in suspected choledocholithiasis. Gastrointest Endosc. 2008;67(2):235–44.
12. Verma D, Kapadia A, Eisen GM, Adler DG. EUS vs MRCP for detection of choledocholithiasis. Gastrointest Endosc. 2006;64(2):248–54.
13. Palmucci S, Mauro LA, La Scola S, Incarbone S, Bonanno G, Milone P, et al. Magnetic resonance cholangiopancreatography and contrast-enhanced magnetic resonance cholangiopancreatography versus endoscopic ultrasonography in the diagnosis of extrahepatic biliary pathology. Radiol Med. 2010;115(5):732–46.

14. Moon JH, Cho YD, Cha SW, Cheon YK, Ahn HC, Kim YS, et al. The detection of bile duct stones in suspected biliary pancreatitis: comparison of MRCP, ERCP, and intraductal US. Am J Gastroenterol. 2005;100(5):1051–7.
15. Varghese JC, Liddell RP, Farrell MA, Murray FE, Osborne DH, Lee MJ. Diagnostic accuracy of magnetic resonance cholangiopancreatography and ultrasound compared with direct cholangiography in the detection of choledocholithiasis. Clin Radiol. 2000;55(1):25–35.
16. Iranmanesh P, Frossard JL, Mugnier-Konrad B, Morel P, Majno P, Nguyen-Tang T, et al. Initial cholecystectomy vs sequential common duct endoscopic assessment and subsequent cholecystectomy for suspected gallstone migration: a randomized clinical trial. JAMA. 2014;312(2):137–44.
17. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, et al. IAP Guidelines for the surgical management of acute pancreatitis. Pancreatology. 2002;2(6):565–73.
18. Banks PA, Freeman ML, Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101(10):2379–400.
19. Overby DW, Apelgren KN, Richardson W, Fanelli R, Society of American Gastrointestinal and Endoscopic Surgeons. SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. Surg Endosc. 2010;24(10):2368–86.
20. Ito K, Ito H, Whang EE. Timing of cholecystectomy for biliary pancreatitis: do the data support current guidelines? J Gastrointest Surg. 2008;12(12):2164–70.
21. Hernandez V, Pascual I, Almela P, Anon R, Herreros B, Sanchiz V, et al. Recurrence of acute gallstone pancreatitis and relationship with cholecystectomy or endoscopic sphincterotomy. Am J Gastroenterol. 2004;99(12):2417–23.
22. van Baal MC, Besselink MG, Bakker OJ, van Santvoort HC, Schaapherder AF, Nieuwenhuijs VB, et al. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. Ann Surg. 2012;255(5):860–6.
23. Kaw M, Al-Antably Y, Kaw P. Management of gallstone pancreatitis: cholecystectomy or ERCP and endoscopic sphincterotomy. Gastrointest Endosc. 2002;56(1):61–5.
24. Davidson BR, Neoptolemos JP, Carr-Locke DL. Endoscopic sphincterotomy for common bile duct calculi in patients with gall bladder in situ considered unfit for surgery. Gut. 1988;29(1):114–20.
25. Hill J, Martin DF, Tweedle DE. Risks of leaving the gallbladder in situ after endoscopic sphincterotomy for bile duct stones. Br J Surg. 1991;78(5):554–7.
26. Working Party of the British Society of G, Association of Surgeons of Great B, Ireland, Pancreatic Society of Great B, Ireland, Association of Upper GISoGB. UK guidelines for the management of acute pancreatitis. Gut. 2005;54(Suppl 3):1–9.
27. Nagem RG, Lazaro-da-Silva A, de Oliveira RM, Morato VG. Gallstone-related complications after Roux-en-Y gastric bypass: a prospective study. Hepatobiliary Pancreat Dis Int. 2012;11(6):630–5.
28. Nagem R, Lazaro-da-Silva A. Cholecystolithiasis after gastric bypass: a clinical, biochemical, and ultrasonographic 3-year follow-up study. Obes Surg. 2012;22(10):1594–9.
29. Warschkow R, Tarantino I, Ukegjini K, Beutner U, Guller U, Schmied BM, et al. Concomitant cholecystectomy during laparoscopic Roux-en-Y gastric bypass in obese patients is not justified: a meta-analysis. Obes Surg. 2013;23(3):397–407.
30. Kohn GP, Galanko JA, Overby DW, Farrell TM. Recent trends in bariatric surgery case volume in the United States. Surgery. 2009;146(2):375–80.
31. Choi EK, Chiorean MV, Cote GA, El Hajj I, Ballard D, Fogel EL, et al. ERCP via gastrostomy vs. double balloon enteroscopy in patients with prior bariatric Roux-en-Y gastric bypass surgery. Surg Endosc. 2013;27(8):2894–9.
32. Shah RJ, Smolkin M, Yen R, Ross A, Kozarek RA, Howell DA, et al. A multicenter, U.S. experience of single-balloon, double-balloon, and rotational overtube-assisted enteroscopy ERCP in patients with surgically altered pancreaticobiliary anatomy (with video). Gastrointest Endosc. 2013;77(4):593–600.
33. Schreiner MA, Chang L, Gluck M, Irani S, Gan SI, Brandabur JJ, et al. Laparoscopy-assisted versus balloon enteroscopy-assisted ERCP in bariatric post-Roux-en-Y gastric bypass patients. Gastrointest Endosc. 2012;75(4):748–56.
34. Bennion RS, Wyatt LE, Thompson JE, Jr. Effect of intraoperative cholangiography during cholecystectomy on outcome after gallstone pancreatitis. J Gastrointest Surg. 2002;6(4):575–81.
35. Sheffield KM, Han Y, Kuo YF, Townsend CM, Jr, Goodwin JS, Riall TS. Variation in the use of intraoperative cholangiography during cholecystectomy. J Am Coll Surg. 2012;214(4):668–79; discussion 679–81.
36. Ford JA, Soop M, Du J, Loveday BP, Rodgers M. Systematic review of intraoperative cholangiography in cholecystectomy. Br J Surg. 2012;99(2):160–7.
37. Horwood J, Akbar F, Davis K, Morgan R. Prospective evaluation of a selective approach to cholangiography for suspected common bile duct stones. Ann R Coll Surg Engl. 2010;92(3):206–10.
38. Lu J, Cheng Y, Xiong XZ, Lin YX, Wu SJ, Cheng NS. Two-stage vs single-stage management for concomitant gallstones and common bile duct stones. World J Gastroenterol. 2012;18(24):3156–66.
39. Rogers SJ, Cello JP, Horn JK, Siperstein AE, Schecter WP, Campbell AR, et al. Prospective randomized trial of LC + LCBDE vs ERCP/S + LC for common bile duct stone disease. Arch Surg. 2010;145(1):28–33.
40. Eddy JJ, Gideonsen MD, Song JY, Grobman WA, O'Halloran P. Pancreatitis in pregnancy. Obstet Gynecol. 2008;112(5):1075–81.

41. Pandey R, Jacob A, Brooks H. Acute pancreatitis in pregnancy: review of three cases and anaesthetic management. Int J Obstet Anesth. 2012;21(4):360–3.
42. Ramin KD, Ramin SM, Richey SD, Cunningham FG. Acute pancreatitis in pregnancy. Am J Obstet Gynecol. 1995;173(1):187–91.
43. Papadakis EP, Sarigianni M, Mikhailidis DP, Mamopoulos A, Karagiannis V. Acute pancreatitis in pregnancy: an overview. Eur J Obstet Gynecol Reprod Biol. 2011;159(2):261–6.
44. Webb JA, Thomsen HS, Morcos SK, Members of Contrast Media Safety Committee of European Society of Urogenital Radiology. The use of iodinated and gadolinium contrast media during pregnancy and lactation. Eur Radiol. 2005;15(6):1234–40.
45. Ducarme G, Maire F, Chatel P, Luton D, Hammel P. Acute pancreatitis during pregnancy: a review. J Perinatol. 2014;34(2):87–94.
46. Tham TC, Vandervoort J, Wong RC, Montes H, Roston AD, Slivka A, et al. Safety of ERCP during pregnancy. Am J Gastroenterol. 2003;98(2):308–11.

Endoscopic Management of Complications in Acute Pancreatitis

12

Wasif M. Abidi and Christopher C. Thompson

Introduction

Pancreatitis is currently the most common gastrointestinal diagnosis for hospital admissions, accounting for over 270,000 admissions in 2009 [1]. A common complication of acute pancreatitis is the presence of a pancreatic or peripancreatic collection, previously commonly referred to as a "pseudocyst." Recently, these collections have been better described and classified into four different types of collections (Fig. 12.1): acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection, and walled-off pancreatic necrosis (WOPN) [2]. As their names would suggest, acute peripancreatic fluid collections (APFC) and acute necrotic collections occur early (usually < 4weeks) and are differentiated from each other by the presence of necrosis—APFC contain only liquid or fluid around the pancreas, while acute necrotic collections contain necrosis of either the pancreas or peripancreatic tissue. Pseudocysts and WOPN are more mature collections that have developed a well-defined wall, usually after about 4 weeks. Pseudocysts are peripancreatic collections that contain only fluid, while WOPN contain both liquid components and necrotic tissue. Infections can occur with any of these collections. Additionally, an often contributory process to the development of a collection is a pancreatic duct (PD) disruption. In acute pancreatitis, this is thought to be related to local necrosis of the PD and resultant disruption. As will be discussed in this chapter, recognition of a PD disruption can have a significant impact on a patient's management and outcome [3, 4].

Pancreatic and peripancreatic collections manifest as a variety of symptoms and complications based on the location and extent of the fluid collection. The presence of a collection is often associated with abdominal pain of variable intensity, distention, and anorexia. These symptoms are not relieved as the other manifestations of pancreatitis resolve. In addition, based on the location of the collection, local duodenal or biliary obstruction may be seen and may need to be addressed separately. A fistula can also develop to surrounding structures, which can present as drainage from a pancreaticocutaneous fistula, ascites from a pancreaticoperitoneal fistula [5] or shortness of breath from a pancreaticopleural fistula [6].

Distention from a fluid collection can be severe and may lead to more diffuse abdominal compartment syndrome [7]. Abdominal compartment syndrome (ACS) is a sustained elevation of the intra-abdominal pressure (IAP) that is

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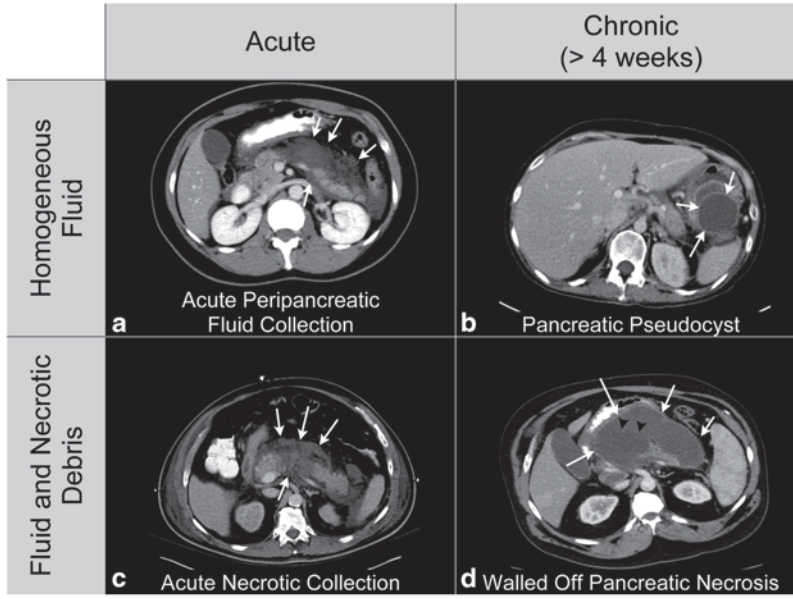

Fig. 12.1 Types of pancreatic and peripancreatic collections based on the revised Atlanta classification system of acute pancreatitis with representative contrast-enhanced CT images. Collections are differentiated by the presence or absence of necrotic debris, and their chronicity (greater than or less than 4 weeks). **a** Acute peripancreatic fluid collection (APFC; *white arrows* show border of APFC). **b** Pancreatic pseudocyst (*white arrows* show border of pseudocyst). **c** Acute necrotic collection after an episode of severe acute necrotizing pancreatitis (*white arrows* show border of collection). **d** Same patient as *C,* now a few weeks later with walled-off pancreatic necrosis (WOPN; *white arrows* show border of WOPN, *black arrowheads* show areas of debris)

associated with new onset organ failure or acute worsening of existing organ failure. It typically presents as a tensely dilated abdomen, oliguria, and increased peak airway pressures. In necrotizing pancreatitis, it appears early and is thought to be related to a combination of mass effect from a necrotic collection, acute inflammation, edema of surrounding tissue, and possibly over resuscitation. The diagnosis is made by measuring bladder pressure with a transurethral probe [8]. Normal bladder pressures in hospitalized patients are 5–7 mmHg, with decreased perfusions developing at 12 mmHg or more. Organ failure and thus ACS begins to develop at bladder pressures > 20 mmHg. Identification of ACS is critical as it can be associated with up to 50% mortality and 90% morbidity [7]. Initial management consists of sedation, neuromuscular blockade, nasogastric decompression, and correction of a positive cumulative fluid balance that may be contributing to increased IAP. If these fail, percutaneous catheter drainage of an acute fluid collection or peritoneal fluid may be necessary. Finally, if these fail, surgical decompression can be performed and an open abdomen maintained.

Peripancreatic collections can also result in vascular pathology. Erosion of pancreatic fluid into surrounding vasculature may result in a pseudoaneurysm. If bleeding occurs from a pseudoaneurysm into a collection, it will likely present as worsening or severe abdominal pain. If bleeding occurs into the pancreatic duct, it will manifest as hemosuccus pancreaticus (Chap. 16) with intermittent melena and potentially abdominal pain. Imaging with either contrast-enhanced computed tomography angiography (CTA), magnetic resonance angiography (MRA), or sometimes with MRCP alone is used to identify pseudoaneurysms. These should be managed separately by interventional radiologists [9], and by surgery in the setting of chronic pancreatitis. If there is pancreatic necrosis, vascular involvement may also

present as thrombosis of the splenic, portal, or superior mesenteric veins. These can result in development of collateral veins and varices, which may be seen during endoscopic evaluation (see walled-off pancreatic necrosis below). Direct complications from such a thrombosis are rare and treatment is rarely required [10] unless there are significant varices, extensions to the inferior vena cava or impending renal compromise.

Case 1

A 37-year-old male with a prior history of diabetes and high cholesterol presented with severe acute abdominal pain radiating to his back. On initial examination, he was hypotensive and tachycardic. He was alert, but slightly tachypneic and had a distended abdomen with diminished bowel sounds. On initial workup, his lipase was 1840 U/L (normal 13–60 U/L). Immediate fluid resuscitation with Lactated Ringer's (LR) was begun. Further workup showed that his liver function tests and right upper quadrant ultrasound were normal, and per his family, there was no history of heavy alcohol use. Further laboratory tests showed a triglycerides level of 2000 mg/dL. He was admitted to the ICU, continued on 300 mL/h LR to maintain his urine output at 0.5 mL/kg/h, and started on appropriate insulin therapy. Bladder pressures remained 10–12 mmHg and slowly his hemodynamics and laboratory studies normalized over the next few days. Unfortunately, he continued to be in pain and his abdomen remained distended. A contrast-enhanced computed tomography (CT) of his abdomen and pelvis showed an edematous pancreas without definitive necrosis and a large 17 cm × 12 cm × 18 cm homogeneous cystic collection with minimal rim enhancement anterior to the pancreas (Fig. 12.2). No significant debris was seen within the collection. Surgery and gastroenterology were consulted for the management of the fluid collection and continued abdominal pain.

What Are Our Initial Diagnostic and Therapeutic Options?

The patient in the case illustrated has a large collection that has not been fully characterized. Once a pancreatic or peripancreatic fluid collection is suspected, imaging to better classify its location and the type of collection is important. In particular, the identification of necrotic debris in a collection can be crucial in clinical management, as this would require endoscopic debridement instead of endoscopic drainage alone. The

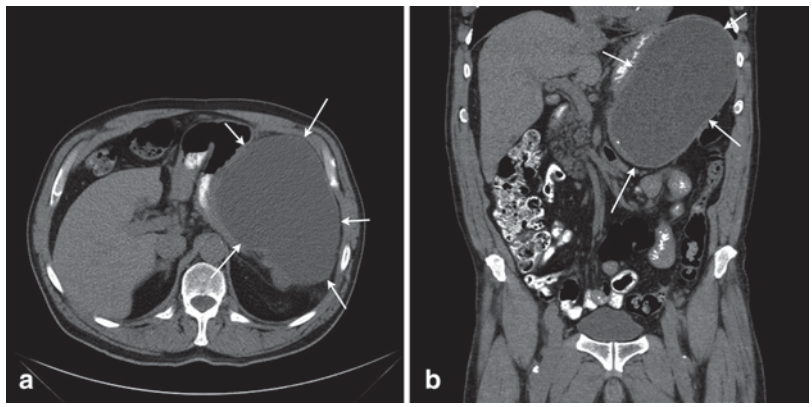

Fig. 12.2 Contrast-enhanced CT scan of the abdomen from Case 1—a 37-year-old male with acute pancreatitis thought secondary to hypertriglyceridemia. A large acute peripancreatic collection was found as shown on **a** axial and **b** coronal CT. *Arrows* show border of collection

Table 12.1 Morphological features of the four types of pancreatic and peripancreatic collections typically seen on radiological imaging

	Associated type of pancreatitis	Density on CT	Encapsulated	Location
APFC	Interstitial edematous	Liquid	No	Extrapancreatic
Pseudocyst	Interstitial edematous	Liquid	Yes	Extrapancreatic
ANC	Necrotizing	Liquid and non-liquid	No	Extra- and/or intrapancreatic
WOPN	Necrotizing	Liquid and non-liquid	Yes	Extra- and/or intrapancreatic

APFC acute peripancreatic fluid collection, *ANC* acute necrotic fluid collection, *WOPN* walled-off pancreatic necrosis

modality most commonly used is a contrast-enhanced CT (Table 12.1) [2]. CT can identify the extent of the collection and the presence of necrosis, although the sensitivity and specificity can be low [11]. Studies have shown that magnetic resonance imaging (MRI) can have higher sensitivity and specificity in evaluating necrotic debris and may be more helpful than CT in indeterminate cases [12, 13]. MRI has the advantage of avoiding exposure to harmful radiation, which can be significant in a younger patient requiring multiple imaging studies [14].

Cholangiopancreatography protocol with MRCP can be used to detect pancreatic ductal disruptions and pancreatic fistulae. MRCP can be further enhanced with the administration of secretin, a hormone that induces pancreatic ductal secretion resulting in better visualization of the pancreatic duct morphology and any fistulae. Recent data have shown that the sensitivity of detecting pancreatic ductal anomalies can be increased from 47 to 66% by performing MRCP with the administration of secretin [15, 16]. However, secretin-MRCP is not currently widely adopted.

It should be noted that pancreatic cystic neoplasm is an important differential diagnosis that must be excluded. The management strategy will change significantly if the fluid collection is a cystic neoplasm as the patient may need to undergo surgery. Clinical history, as well as comparison with any available abdominal radiology before the pancreatitis attack, is fairly reliable in making this distinction. In rare cases, if there is confusion regarding the etiology of the collection, endoscopic ultrasound (EUS) or percutaneous sampling may be necessary.

Initial Management of a Collection

Initial steps in the management of acute pancreatitis consist of aggressive supportive care including IV hydration with lactated ringer's, pain management, and efficient steps to identify the cause of pancreatitis. Once a collection has been characterized, the complications of the collection may need to be addressed separately (see Introduction). If after the management of the acute pancreatitis and these complications, no or minimal symptoms remain, conservative management of the collection with watchful waiting can be attempted. Data on pancreatic collections show that in patients that can be managed without intervention, spontaneous resolution can occur in 30–60% of patients [17–19]. More specific data on the different types of acute fluid collections are sparse, although based on a few studies, we know that fluid collections associated with non-necrotizing pancreatitis resolve faster, often within 2 weeks in about 70% of patients [20] compared to spontaneous resolution in about 30% by month 6 in patients with necrotizing pancreatitis [17].

Back to the Case…

The patient's pain and symptoms were managed for the next 2 weeks as he improved, although he continued to have baseline abdominal pain, distention, and anorexia. Therefore, MRI of the pancreas with MRCP was obtained, which showed the large abdominal fluid collection had grown slightly, again without any evidence of necrotic debris. In addition, the fluid collection was likely

communicating with the main pancreatic duct in the mid-body, which probably represented a pancreatic duct disruption.

Transpapillary Pancreatic Duct Stenting

Timing and Approach

In the case detailed above, a pancreatic duct disruption has occurred, which is likely resulting in the development of an acute peripancreatic fluid collection. Duct disruption regardless of etiology (acute pancreatitis, pancreatic surgery, or trauma) can be treated using a similar endoscopic approach. Initial conservative therapy for ductal disruptions can include nasojejunal feeding, somatostatin analogues, and pancreatic enzyme replacement. Nasojejunal feeding is associated with significantly higher spontaneous closure rate for post-surgical pancreatic duct fistulae, presumably by reducing pancreatic stimulation [21]. Somatostatin analogues are routinely used perioperatively for pancreatic surgeries [22, 23] although there are only a few studies describing its use for pseudocysts and the practice remains controversial [24].

If conservative management has not resulted in any improvement, either clinically or on imaging (as with our patient), ERCP with transpapillary pancreatic duct stent placement should be attempted [3, 5, 25, 26]. One scenario where transpapillary stenting is of unclear utility is the disconnected duct syndrome [5, 27]. This involves full transection of the pancreatic duct, and the proximal (tail) portion of the pancreas freely secretes pancreatic juices. On pancreatogram, there is either blowout of the duct or a complete cutoff with no duct opacified upstream from this area (Fig. 12.3). Given the full transection, a bridging stent cannot be placed and management focuses on creating a cystgastrostomy to allow a fistulous connection back to the lumen of the stomach or bowel. If this approach fails, combined percutaneous and endoscopic rendezvous procedures may succeed [27], and surgical options include pancreaticojejunostomy and distal pancreatectomy. Percutaneous drainage is not an appealing option as the rate of persistent external pancreatic fistula from the drains is high [27].

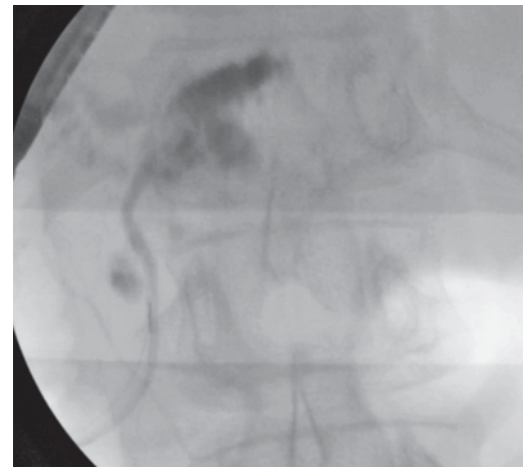

Fig. 12.3 ERCP fluoroscopy images of disconnected duct syndrome after acute pancreatitis. The pancreatogram demonstrates a complete pancreatic duct disruption with contrast leaking out in area of the neck and no contrast filling the upstream pancreatic duct. Bridging stent placement is not possible and treatment focuses on creation of a cystgastrostomy

Timing for ERCP can vary significantly based on the clinical scenario, from immediately on recognition of the ductal leak to > 4 weeks after the episode of acute pancreatitis. On the basis of the literature, we generally try to wait 4–6 weeks for patients with pancreatitis-related duct disruption, although patient's discomfort or more acute symptoms may lead us to intervene sooner. ERCP is performed in a standard fashion, and the site of disruption is identified during pancreatography. In addition, the location of any stricture or stones should be noted. Most often, a 5Fr or 7Fr stent is utilized, although the exact size will depend on the clinical scenario and has not been shown to be related to successful closure of the PD leak. Any strictures or stones that may have contributed to the leak should be traversed and managed. In addition, the stent should ideally bridge the disruption to maximize chances of success (see next section). The stent should be left in place at least 6 weeks, although time to closure can vary significantly with studies reporting a median closure time as high as 4 months

[3, 26]. Prophylactic antibiotics should be administered with all these procedures since ERCP introduces non-sterile contrast into an otherwise sterile fluid collection.

It should be noted that depending on the clinical scenario (including the degree of symptoms from the fluid collection and maturity of wall around the pseudocyst), many investigators have reported performing a cystgastrostomy in the same endoscopic session as the ERCP, particularly for large encapsulated fluid collections. Hookey at al [28] in a retrospective chart review and prospective follow-up, reported on the resolution of pancreatic fluid collections in 15 patients with transpapillary stent alone, 60 patients with transmural drainage alone, and a combined approach in 41 patients. Overall clinical success (resolution of symptoms and collection) was 88 % and was not dependent on the drainage technique performed. However, patient characteristics differed significantly among the different groups. For example, the 15 patients with transpapillary stenting alone typically had a smaller fluid collection (< 7 cm) with evidence of pancreatic duct obstruction and communication between the pancreatic duct and the pseudocyst. A combined approach was used for larger cysts communicating with the pancreatic duct or when the transpapillary approach was unable to bridge the leak. These data contrast with a small study from Singh's group in India, who employed a pure transpapillary approach for larger cysts (> 7 cm) in the tail of the pancreas and found resolution in only 33 % of patients, while the other 67 % were complicated by infection requiring further percutaneous drainage. Overall, transpapillary stenting alone is not recommended for large mature fluid collections where transmural drainage or combined transmural drainage and transpapillary stenting likely has the best outcome. Immature fluid collections cannot be drained transmurally, and would require transpapillary stenting if drainage is necessary.

Outcomes and Alternative Treatment of Failures

ERCP with transpapillary stenting is fairly effective for the treatment of pancreatic duct leaks [3, 26, 29, 30]. Review of literature shows resolution of pancreatic duct leaks in 58–100 % of patients, although the etiology of the pancreatic duct leak in these studies included cases from chronic pancreatitis, trauma, and post-surgical leaks in addition to acute pancreatitis. In addition, the technique varied substantially and may explain the variability of the outcomes. Success was positively associated with findings of a partial duct disruption, location of the disruption in the body of the pancreas, maintaining the stents for at least 6 weeks, and placement of stent that bridges the duct leak. Data from our institution [3] showed that a stent that bridged a disruption was associated with successful resolution of a leak in 92 % of patients. Patients in whom the stent was placed only across the papilla or up to the disruption, by comparison, were associated with only a 44–50 % success rate (Fig. 12.4), stressing the importance of bridging a disruption.

Mortality of this procedure is rare and complications (7–9 %) are mainly associated with performance of the ERCP. More specific complications include fevers and infection following stent placement, stent occlusion, or transpapillary stenting alone of large pseudocysts. Recurrence in the setting of stent failure or stent dislodgement can be treated with repeat ERCP and restenting for another 6–8 weeks. With unsuccessful procedures occurring from either failure to place the pancreatic duct stent or failure to resolve the leak, a trial of draining the fluid collection alone can be attempted (see below, Endoscopic Ultrasound and Transmural Drainage of a Pseudocyst). About 4 % ultimately require surgery; surgical options include a pancreaticojejunostomy and a distal pancreatic resection for ductal disruption in the body and tail. Overall success of the surgical approach is high at 90–92 %, although with a mortality of 6–9 % [31].

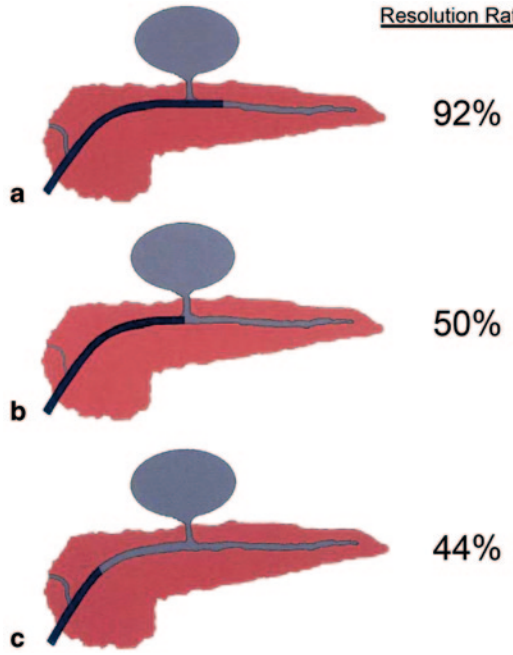

Fig. 12.4 **a** A stent bridging a pancreatic duct (PD) disruption is associated with a 92% resolution rate, versus **b** 50% for a stent that ends at the leak and **c** 44% for a stent that only crosses the papilla. (*Adapted from* [3])

Case Continued

The patient was taken to the endoscopy suite and the site of the leak was readily identified during pancreatography. A 7Fr x 9 cm plastic stent was placed in the patient's pancreatic duct, bridging the pancreatic duct leak (Fig. 12.5). Cystgastrostomy could not be performed as the wall around the pseudocyst had not matured yet. The patient did well immediately post-procedure with gradual decline in his abdominal pain. However, the pain did not resolve and he continued to endorse anorexia and gradual weight loss. Repeat contrast-enhanced CT four weeks after the ERCP and stent placement showed an 8 cm x 10 cm fluid collection adjacent to body of the stomach, now with a well-formed wall.

Endoscopic Ultrasound and Transmural Drainage of Pseudocysts

Technique of Endoscopic Cystgastrostomy

Later sequelae of a pancreatic duct leak can include pancreatic ascites, pancreaticopleural fistula, and pseudocyst. The patient in our case has

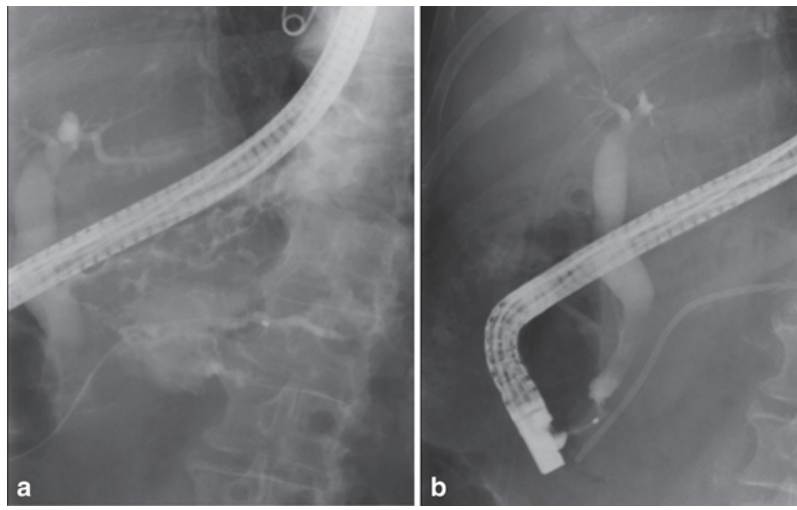

Fig. 12.5 ERCP representative of Case 1. **a** Pancreatic duct leak noted on ERCP with pancreatogram showing partial disruption in the body of the pancreas with contrast leaking out around the duct. **b** Plastic stent placed bridging the leak

developed a pseudocyst with a well-defined wall. Management of a pseudocyst can include watchful waiting for asymptomatic lesions; for symptomatic collections, percutaneous, surgical, or endoscopic strategies are available, and the choice should be made in a multidisciplinary fashion with the expertise of the particular institution in mind. Endoscopic drainage of a pseudocyst was first described by Gerald Rogers et al. in 1975 [32] with subsequent improvement by creating a fistula into the stomach by Richard Korazek in 1985 [33]. The methodology has since undergone several modifications.

Prior to starting a cystgastrostomy, consultation with a radiologist is often necessary, and at the minimum, careful review of abdominal CT and/or MRI should be done to ensure there is a mature wall around the fluid collection (Fig. 12.1b) and direct apposition of the stomach wall and the pseudocyst [34]. Of note, the radiology imaging should be a recent study obtained within 1–2 weeks of the planned procedure. A mature wall often develops in 4–6 weeks, although we have seen mature walls as early as 3 weeks [2]. An appropriate wall for a cystgastrostomy (and necrosectomy) is considered to be >3 mm. While some centers consider the upper limit of wall thickness to be 1 cm since thicker walls are thought to increase the risk of complications [34], we do not limit our interventions to capsules less than 1 cm and have had technical success with much thicker walls.

Patients are given antibiotics prior to the procedure (usually intravenous ciprofloxacin and metronidazole). We use general anesthesia rather than conscious sedation to reduce the risk of aspiration when draining large amounts of fluid into the stomach and to allow maximal sedation if complications arise that require a longer duration of the procedure. We use CO_2 insufflation as it is rapidly absorbed by the body at the end of the procedure. The initial step is identification of the location of the pseudocyst and finding an appropriate puncture site. While traditionally direct endoscopic visualization of a bulge into the gastric or duodenal lumen was used as a marker, currently most centers use EUS guidance [35–39]. EUS is important for better localization of the fluid collections when there is no large extra-luminal compression, identification, and avoidance of blood vessels at the access site, and confirmation of the lack of necrotic tissue. The best data supporting the use of EUS was a randomized controlled trial by Varadarajulu et al. [35] comparing EGD to EUS-guided cystgastrostomy of pseudocysts, where the use of ultrasound was associated with greater success (100% versus 33%, $P<0.001$) and trend toward decreased complications. EGD-related complications included one death from massive hemorrhage of gastric varices at the puncture site not visualized during the EGD.

Once a site has been identified using a therapeutic linear echoendoscope, we use a 19-gauge needle to puncture into the pseudocyst (Fig. 12.6). We try to puncture at an angle that ideally allows the endoscope to be kept straight in the body of the patient, allowing forces to be transmitted directly to the wall of the pseudocyst. Fluid can be aspirated for bacteriological and culture studies. In addition, contrast is instilled into the pseudocyst to identify borders of the pseudocyst and to maintain distention. We over-inject contrast to expand the pseudocyst by 5–10 mm to keep the pseudocyst distended and obviate the need for electrocautery when trying to traverse the wall of the pseudocyst (In press data). A 0.035-inch guidewire is then coiled numerous times into the cavity, and the access site is dilated using hydrostatic balloons. We start with a 6-mm biliary-dilating balloon (typically the Hurricane Biliary Balloon Dilation Catheter, Boston Scientific, Marlborough, MA) and serially dilate to 15 mm. Alternative strategies for tract creation include brief use of cautery with a needle-knife sphincterotome or cystotome. These strategies, however, likely pose increased risk of bleeding due to inadvertent cutting of a gastric vessel. Double pigtail stents are then placed through the tract to allow adequate drainage. We generally use three 10Fr double pigtails for drainage, with length depending on the depth necessary to adequately drain the pseudocyst.

On follow-up (Fig. 12.7), we reimage our patients in 4–6 weeks with a CT scan or MRI to evaluate for continued contraction or resolution

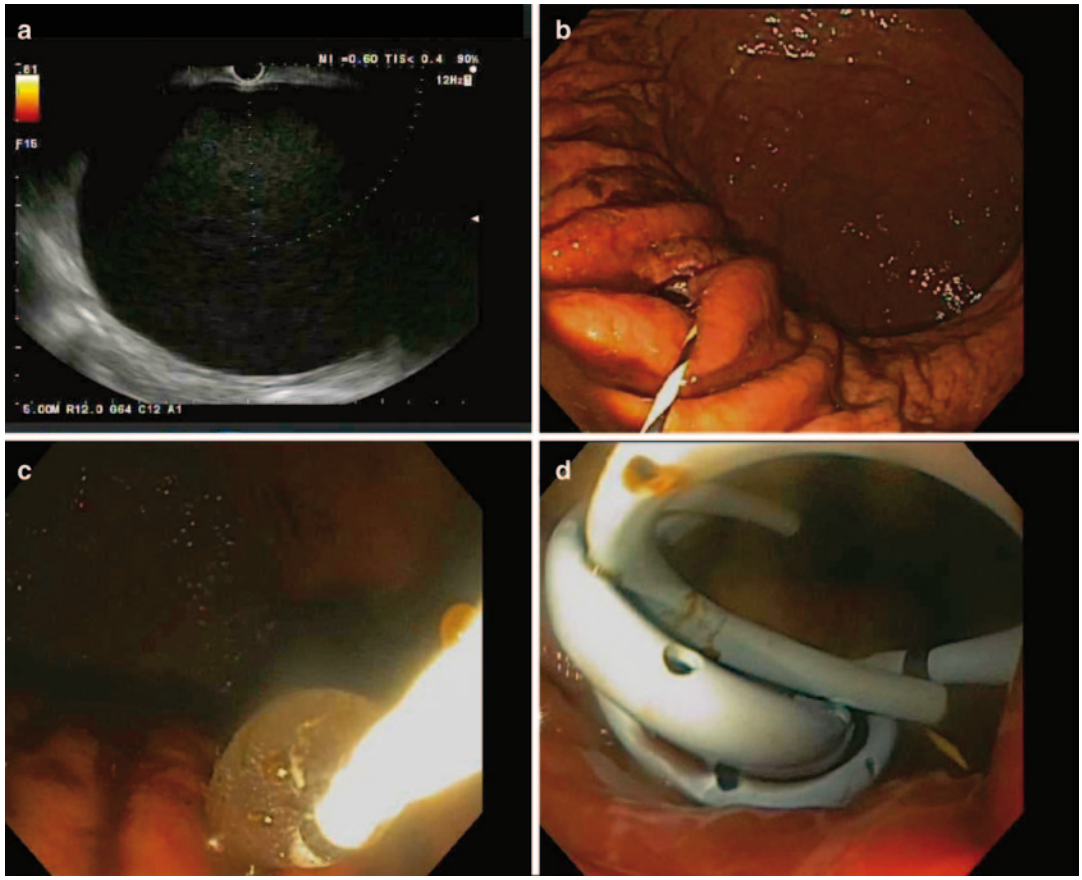

Fig. 12.6 Cystgastrostomy of patient in Case 1. **a** An appropriate path was found using EUS, devoid of any intervening vasculature. In addition, the purely liquid nature of the collection was confirmed. **b** A long guidewire was then placed in the collection and **c** the tract was dilated with a hydrostatic balloon. **d** One 10Fr × 7 cm and one 10Fr × 4 cm pigtail stents were placed into the pseudocyst to allow drainage

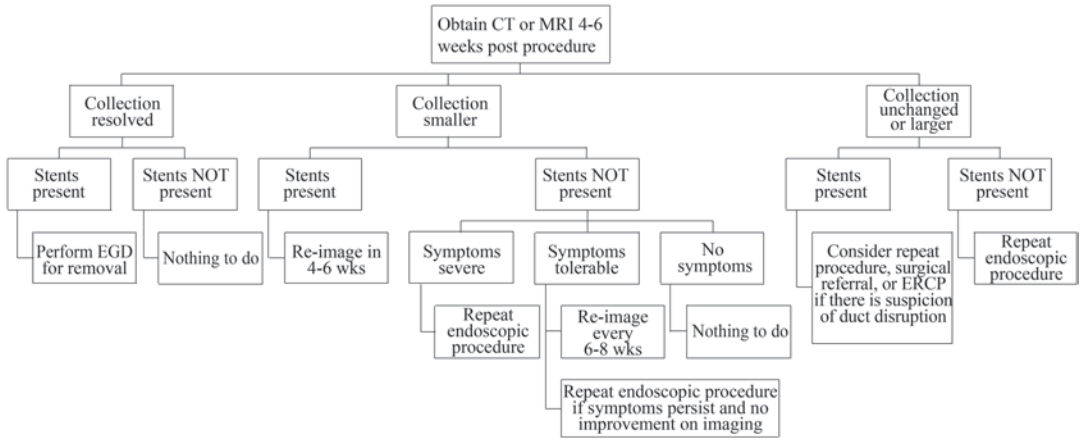

Fig. 12.7 Sample algorithm for follow-up after cystgastrostomy of a pseudocyst or endoscopic necrosectomy of a walled-off pancreatic necrotic collection. Actual protocol should be tailored to the clinical presentation of each patient

of the pseudocyst and the presence of the stents. If the pseudocyst has resolved and the stents remain in place, we perform an EGD to remove the stents, although a small randomized controlled study has shown that leaving stents in place even after resolution of pseudocyst may decrease recurrence of the collection [40]. In this small study, patients either had their stents removed at a median of 2 months following cystgastrostomy or 12 months later with 38 % (5/13 patients) recurring in the former group compared to no recurrences with long-term stent patients. If the stents have fallen out by themselves, no further procedure is needed. If the pseudocyst is resolving, more time is allowed for drainage and involution. If the stents have fallen out and the patient remains symptomatic with an ongoing pseudocyst, a further cystgastrostomy may be needed to adequately drain the pseudocyst. Finally, if there is no change or increase in size of the pseudocyst, we reevaluate for pancreatic duct disruption and possible stent blockage. Surgical referral may also be appropriate as discussed below.

Outcomes, Complications, and Alternative Treatment for Failures

When performed in the setting of an experienced multidisciplinary team, the initial success rate in creation of the cystgastrostomy is high, up to 94–95 %, with a pseudocyst resolution rate of 90–100 % [41–43]. Complications can occur in 0–20 % of patients and include bleeding sometimes requiring surgery usually due to the use of electrocautery without EUS guidance to enter the pseudocyst, inadequate drainage, and pseudocyst infection. There is minimal mortality (< 1 %) with at least one death related to electrocautery used to access the pseudocyst without EUS. Recurrences can range from 0 to 16 %, and at least one recent paper shows resolution of the pseudocyst in all patients and no recurrence over at least 24-month follow-up [41]. Of note, in this paper, patients undergoing endoscopic cystgastrostomy had stents routinely removed 2 months following the procedure if imaging demonstrated resolution of the pseudocyst. Success is significantly lower if there is necrotic debris in the collection, underscoring the importance of preprocedural evaluation with imaging and EUS and ensuring the collection is a pseudocyst. Hookey et al. [28] showed that success of cystgastrostomy with or without transpapillary stenting of a pseudocyst was over 88 %, compared to only 25 % if necrotic debris is present.

If the endoscopic approach fails, either because of initial failure, failure to resolve, or a major complication, percutaneous or surgical approaches can be pursued. Percutaneous drainage may be indicated if an acute fluid collection is causing significant symptoms and has not matured to allow safe cystgastrotomy, or if the endoscopic approach is unable to identify a clear tract to the collection. Drainage is usually performed with CT guidance, and either a direct route or transhepatic route may be taken [44]. A drainage catheter should be placed as simple aspiration rarely results in resolution of the fluid collection. Unfortunately, the outcomes of percutaneous drainage are not yet well reported, with success ranging from 32 to 90 % [44]. Surgical options include anastomosis of the pancreatic duct to small bowel if a leak is present, or surgical drainage of a fluid collection [45, 31]. More specifically, surgery may involve a pancreaticojejunostomy, distal pancreatic resection for ductal disruption in the body or tail, cystgastrostomy, cystjejunostomy, or fistulojejunostomy. Overall success of the surgical approach is 90–92 % with a mortality of 6–9 % [31]. Recurrence rates can be similar to endoscopic management. In addition, endoscopy and surgery do not have significantly different clinical outcomes with similar initial success and resolution including the results from a randomized trial. Surgery however has a significantly longer length of stay and associated costs [41, 43].

Case Continued

Our patient underwent an EUS-guided cystgastrostomy with drainage of the pseudocyst (Fig. 12.6) and placement of one 10Fr × 7 cm and two 10Fr × 4 cm double pigtail stents. He did well

post-procedure with immediate resolution of his distention and increased appetite. At follow-up in 4 weeks, the pseudocyst had diminished in size to 18 mm in maximum dimension with one of the stents still in place. An EGD was performed at week 8, and the stent was removed without complications. The pseudocyst did not recur on 6- and 12-month follow-up.

Case 2

A 42-year-old obese female presented with severe acute abdominal pain radiating to her back. She was noted to have elevated liver function tests and elevated lipase to 1200 U/L. In addition to the standard initial management for acute pancreatitis, an ERCP was performed with sphincterotomy and removal of 2 biliary stones. The elevated liver enzymes resolved over the course of the next few days; however, the patient remained in pain, febrile, and complained of a distended abdomen. On day 7, given lack of improvement, contrast-enhanced CT of the abdomen and pelvis was obtained, which showed necrosis in 40 % of her pancreas and a 16.4 cm × 8.3 cm × 8.9 cm pancreatic fluid collection (Fig. 12.8a). Interventional radiology was consulted and fluid was aspirated under CT guidance. The culture failed to grow any pathogens, and despite her continued fevers, antibiotics were not administered. Fevers resolved by the second week but she continued to complain of pain. Acute kidney failure developed despite adequate urine output (presumed acute tubular necrosis). By week 3, her kidney function was slowly improving, her pain was controlled with opiates, and she tolerated soft foods. Given the improvement, she was discharged and arranged for follow-up imaging. CT scan 1 month after the initial pancreatitis showed a smaller but persistent 9.8 cm × 4.5 cm peripancreatic fluid collection with solid debris, now with a mature appearing solid rim around the collection (Fig. 12.8b). The diagnosis of WOPN was made, and given she had continued abdominal pain, an elective endoscopic necrosectomy was scheduled in 2 weeks.

Initial Management of Walled-off Pancreatic Necrosis

Case 2 illustrates another collection that can be managed endoscopically. As discussed above, WOPN is a mature collection surrounded by a well-defined wall that contains necrotic debris. Similar to a pseudocyst, a pancreatic duct disruption can contribute to the emergence of WOPN. Initial workup is the same as for pancreatic

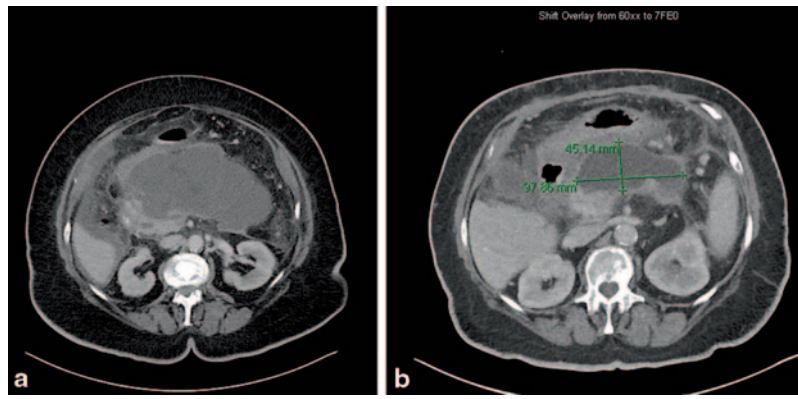

Fig. 12.8 CT imaging of the patient in Case 2—a 42-year-old obese female presenting with necrotizing gallstone pancreatitis. **a** CT on day 7 of hospitalization showed a 16.4 cm × 8.3 cm × 8.9 cm acute necrotic collection. **b** By 5 weeks later, the collection was reduced in size and developed a mature wall. Imaging 2 weeks later showed no change in the walled-off pancreatic necrosis (not shown)

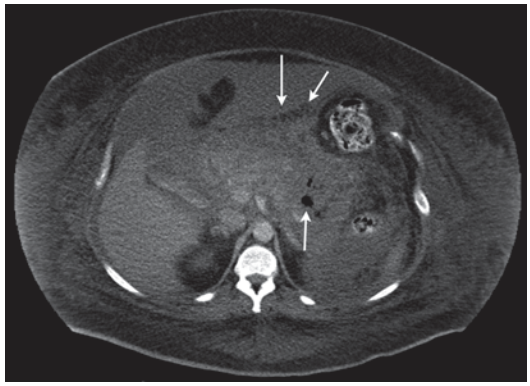

Fig. 12.9 Abdominal CT scan showing acute necrotic fluid collection with air pockets (*white arrows*) within the necrosis

pseudocyst; assessment with an MRI of the pancreas with MRCP may be important to identify necrotic debris and a pancreatic duct disruption. Imaging with a contrast-enhanced CT or MR angiogram can be important in excluding a pseudoaneurysm if there is enough clinical suspicion.

Similar to pseudocysts, initial management focuses on supportive medical care, which can result in resolution of 30–60% of patients with pancreatic necrotic fluid collections [17]. Medical management will include the decision to use antibiotics if there are signs of infection such as fevers, SIRS, and the presence air or gas in a collection on imaging (Fig. 12.9) [2]. Fever and SIRS symptoms can cause confusion as they can be a manifestation of the pancreatitis itself or may result from an infected necrotic fluid collection. Generally, infection should be considered after the first 7–10 days of acute presentation. Antibiotics should be administered if definitive infection is documented via a CT-guided fine needle aspiration (FNA), although there is a 4–10% false-negative rate [46–48]. As such, if clinical signs point to infection despite a sterile FNA, antibiotics can be used.

Antibiotic prophylaxis has been discussed in the setting of necrotizing pancreatitis and an acute necrotic fluid collection, however this is controversial. The American Gastroenterological Association currently makes no firm recommendation, but restricts antibiotic prophylaxis to patients with > 30% necrosis of their pancreas, while the American College of Gastroenterology does not recommend antibiotic prophylaxis [46, 47]. We do not routinely provide antibiotic prophylaxis to our patients.

Endoscopic Drainage and Debridement of WOPN

Technique of Endoscopic Necrosectomy

If there is no resolution and continued symptoms, definitive management can be pursued; options include surgical, endoscopic, and percutaneous drainage and debridement. The presence of necrotic debris in a "pseudocyst" was traditionally considered a contraindication for endoscopic therapy as presence of necrotic debris increased the risk of complications such as infection. These patients would be taken for surgical necrosectomy. However, in 1996, Baron and colleagues described the first case of endoscopic treatment of a pancreatic necrotic fluid collection, initially with placement of a nasobilliary drain into the collection and irrigation every 4 h [49]. This has been further modified over the years. We now do not routinely place nasocystic drains and instead enter the collection and directly debride necrotic material [50, 51].

The initial steps of endoscopic necrosectomy are similar to pseudocyst drainage. After giving the patient antibiotics, sedating under general anesthesia, and using carbon dioxide insufflation, the first step is identification and puncture of the wall of the WOPN (Video 12.1 and Fig. 12.10). EUS is used to identify the location of the WOPN and confirm debris within the collection. Doppler interrogation is important to find a suitable location for entry that does not have any intervening large vessels or gastric varices. We try to approach the wall of the WOPN at an angle that will keep the endoscope in a straight configuration; we believe this maximizes our ability to transmit forces to the wall during puncture and ease of the procedure during debridement. The collection is accessed with a 19-gauge needle and samples aspirated for diagnostic studies including culture.

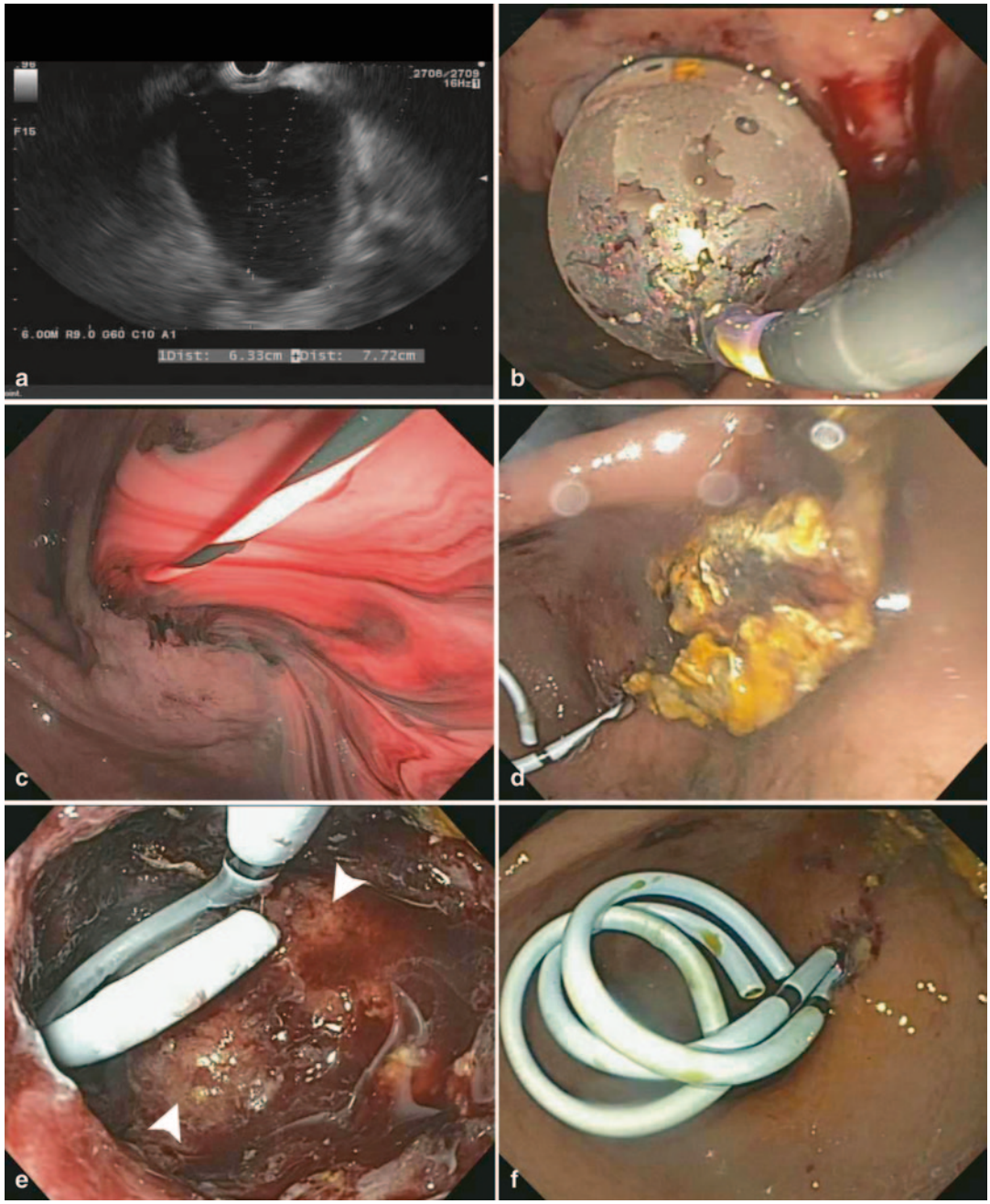

Fig. 12.10 Endoscopic necrosectomy of a WOPN of the patient in Case 2. **a** As in Fig. 12.6, an appropriate path was found using EUS and after the placement of a guidewire, **b** the tract was dilated. **c** Purulent and bloody fluid drained after dilation of the tract. **d** The WOPN was entered and necrotic material was removed into the stomach lumen. **e** View of the inside of the WOPN after debridement (*white arrowheads* point to wall of WOPN). **f** Finally, three pigtail stents were placed through the cyst-gastrostomy site to allow continued drainage

Contrast is then instilled into the cavity under fluoroscopic guidance to outline the WOPN. The collection is over-injected to expand the collection by 5−10 mm, thereby creating tension on the wall and easing the completion of the rest of the procedure. A long 0.035" guidewire is coiled into the collection. The tract is serially dilated first with a 6-mm biliary balloon catheter and then with an 18-to 20-mm hydrostatic balloon to a final diameter of 20 mm. We usually use the Hurricane biliary balloon dilation catheter (Boston Scientific, Marlborough, MA). The linear echoendoscope is then replaced with a wide-channel therapeutic gastroscope over the guidewire, allowing entry into the necrotic collection and direct debridement using a combination of accessories including snare, rat-toothed forceps, and baskets. We attempt to debride all necrotic tissue in a timely fashion, completing the debridement in under an hour if possible. We debride all necrotic tissue as we do not plan to bring patients back for a second procedure unless symptoms recur or the clinical course dictates a repeat procedure (Fig. 12.7). The cavity is also lavaged with warmed antibiotic solution throughout the procedure. The antibiotic rinse is aspirated after the debridement is complete. At the end of the procedure, double pigtail stents, usually three 10Fr, are placed across the gastrostomy. These stents are thought to allow autodigestion and further drainage of the cavity.

Antibiotics are continued for 4 weeks since the necrotic space is now open to pathogens. A liquid diet is recommended for at least 2 weeks. Similar to pseudocysts, follow-up (Fig. 12.7) starts with reimaging our patients after 4–6 weeks with a CT scan or MRI to evaluate for continued contraction or resolution of the WOPN and the presence of the stents. We alternate CT and MRI to reduce the total dosage of radiation. For the same reason, we may opt for MRI in younger patients. If the WOPN has resolved, we perform an EGD to remove stents as needed (they may fall out spontaneously). If the WOPN is decreasing in size, more time is allowed for drainage and involution. If however, there is no change or increase in size of the pseudocyst, we reevaluate for pancreatic duct disruption and possible stent blockage. Surgical referral may also be appropriate.

Alternative Techniques to Endoscopic Necrosectomy

Other centers have reported various alternative techniques and strategies for endoscopic treatment of WOPN. Although as previously discussed, endoscopic drainage alone without debridement is not recommended for WOPN, a combined percutaneous and endoscopic drainage strategy has been advocated recently as a way to avoid debridement altogether [52]. While this has been shown to be superior compared to percutaneous drainage alone and long-term data are promising [53], a comparison to necrosectomy has not been performed. Furthermore, this strategy has the disadvantage of sending patients home with at least one percutaneous catheter for a median of 2 months with its associated decrease in quality of life and the associated performance of a mean of 7 CT scans and 6 interventional radiology procedures on the percutaneous drains during the treatment period.

Another approach used by several centers is to perform an initial procedure to access the WOPN and place stents, followed by repeat procedures for transluminal necrosectomy [54]. No clear comparison has been made between this strategy and our approach of performing drainage and full debridement in one procedure, although we have had excellent technical success and no mortality [55]. Varadarajulu et al. [56] published a variation with creating and stenting more than one transluminal entry site ("multiple gateways"). This may provide more effective drainage. Another variation on the technique is the placement of a fully covered esophageal metal stent with a pigtail stent through it to keep the tract open without performing debridement, and a small case series of 5 patients demonstrated clinical success without needing debridement [57]. However, the safety, cost-effectiveness, long-term results of this strategy compared to plastic stents has not been explored and further data are needed.

Several new devices are also being developed to aid with necrosectomy. A newer short (30 mm) and wide (16 mm) fully covered self-expanding metal stent with an antimigration system has been designed specifically for necrosectomy (Nagi stent, Taewoong-Medical Co, Gyeonggi-do, Korea) with promising initial data; however, further studies are needed and it is not currently available in the United States [58]. A Clutch Cutter (Fujifilm, Tokyo, Japan), newly developed for endoscopic submucosal dissection, has been used to assist with dissecting necrotic tissue [59]. This device is a scissor-type grasping forceps that can grasp tissue and cut using electrosurgical current, thus providing hemostasis as well. Again, further studies are needed to show efficacy and cost-effectiveness.

Outcomes, Complications, and Alternative Treatment for Failures

Based mostly on retrospective cohorts, successful treatment of WOPN can be high, with average success rate of 81% [60–62]. It should be noted that the average number of endoscopic sessions is 4, although in our experience with debridement during the initial session, most patients have resolution of the necrotic collection in 1–2 sessions. Complications occurred in 36% of patients on average, with bleeding, perforation, and air embolisms the most common, although several series reported much lower complications rates (5%). Overall mortality remains low, on average 6%. Using our methods, we have seen no mortality in over 60 patients and we attribute this to the use of EUS, avoiding electrocautery, and antibiotic lavage (data in press).

Recently, the Dutch Pancreatitis Study Group [63] published the results of their PENGIUN trial, a randomized controlled trial of 22 patients with infected necrotizing pancreatitis randomized to either surgical or endoscopic necrosectomy. While their primary outcome was not a clinical outcome (post-procedural IL-6 was measured), their secondary outcomes were mortality and a predefined composite endpoint of major complications that included new onset multi-organ failure, enterocutaneous fistulae, pancreatic fistula, and bleeding. Endoscopic necrosectomy resulted in a reduced post-procedural IL-6 level 24 h post-procedure with a lower composite clinical endpoint of major complications (20% vs 80%, $P=0.03$) and a trend toward a lower number of deaths as well (10% vs 40%, $P=0.30$). Other long-term complications included occurred about equally in both groups, including new onset diabetes (20% vs 30%), requirement for pancreas enzymes (0% vs 30%), and recurrence of collection (20% vs 30%). As such, an endoscopic approach to debridement is the initial procedure of choice.

Endoscopy may fail if the collection is not accessible by EUS, does not resolve with treatment, or if major complications such as bleeding or infection occur. Should endoscopic treatment fail, alternative strategies include surgical necrosectomy (open or minimally invasive) and percutaneous drainage. The traditional surgical approach is an open necrosectomy although minimally invasive techniques have been described. The surgical approach is typically associated with high rates of complications, mortality, and long-term pancreatic insufficiency. More recently, a step-up approach (SUA) has been advocated to reduce complications. In this method, endoscopic or percutaneous drainage is performed first, and if clinical resolution does not occur, patients undergo minimally invasive retroperitoneal necrosectomy [64]. In the PANTER trial, 88 patients were randomly assigned to either primary open necrosectomy versus the SUA. Although mortality did not differ (16% vs 19% for SUA), the step-up approach significantly reduced a composite score of major complications (69% vs 40%, $p=0.006$) and new-onset diabetes (38% vs 16%, $p=0.02$). Thus, when needed, a step-up approach may be efficacious and safer than open necrosectomy. However, directly proceeding with endoscopic necrosectomy (DEN) as the initial procedure of choice is preferred to the SUA when feasible. In our study of patients with suspected or confirmed infected WOPN, we compared the SUA to DEN. We found decreased antibiotic use, pulmonary failure, endocrine insufficiency, length of stay, and health care utilization in the patients who un-

derwent DEN [55]. Clinical resolution remained equivalent. These data provide evidence that endoscopic necrosectomy and debridement may be the procedure of choice for WOPN with percutaneous drains used in endoscopically inaccessible or immature collections.

Case Continued

The patient presented to the ED 1 week after her CT scan with fever and increased abdominal pain. There was no evidence of recurrence of her pancreatitis with normal amylase and lipase. MRI of the pancreas with MRCP was obtained and did not show evidence of a pancreatic duct leak or acute pancreatitis. The necrotic collection remained with an enhancing rim. She underwent endoscopic necrosectomy on hospital day 2 after starting broad-spectrum antibiotics (Fig. 12.10). A transgastric approach was deemed most feasible, and the initial puncture was made with EUS guidance; 50 mL of fluid was sent for culture. The puncture site was then serially dilated to 20 mm with hydrostatic balloon dilatation. About 500 mL of purulent fluid drained from the site of the cystgastrostomy. A therapeutic endoscope was then introduced into the walled-off collection, and multiple passes were made to debride the necrotic tissue using a rat-toothed forceps. The WOPN collection was irrigated with warmed bacitracin solution throughout the procedure. Three double-pigtail 10Fr stents of varying lengths were placed into the cavity. The patient was maintained on 4 weeks of ciprofloxacin and metronidazole after the procedure and 2 weeks of liquid diet. She did well post-procedure with immediate resolution of fevers, pain, and abdominal distention. Her post-procedure course was complicated by new onset diabetes. Follow-up imaging at 3, 6, and 12 months did not show recurrence of the WOPN.

Key Points

- Acute pancreatitis can result in several complications that can be addressed endoscopically, including pancreatic duct disruption, pseudocyst, and walled-off pancreatic necrosis.
- Pancreatic duct disruptions are initially worked up and managed with appropriate imaging (CT or MRCP), nasojejunal feeding, somatostatin analogues, and pancreatic enzyme replacement.
- Pancreatic duct disruption that does not respond to initial medical management can be addressed with ERCP and placement of a stent that relieves any distal strictures and bridges the disruption.
- Accurate imaging to classify a collection is important as the presence of necrosis that develops into walled-off pancreatic necrosis will require debridement, if possible via endoscopic necrosectomy.
- Pseudocysts that do not resolve spontaneously and are symptomatic can be successfully managed with endoscopic cystgastrostomy and placement of pigtail catheters.

Video Caption

Video 12.1 The initial steps of endoscopic necrosectomy are similar to pseudocyst drainage. After giving the patient antibiotics, sedating under general anesthesia, and using carbon dioxide insufflation, the first step is identification and puncture of the wall of the WOPN. EUS is used to identify the location of the WOPN and confirm debris within the collection

References

1. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology.2012;143(5):1179–87. e1–3. doi:10.1053/j.gastro.2012.08.002.
2. 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(1):102–11. doi:10.1136/gutjnl-2012-302779.
3. 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(1):18–24
4. Nealon WH, Walser E. Main pancreatic ductal anatomy can direct choice of modality for treating pancreatic pseudocysts (surgery versus percutaneous drainage). Ann Surg. 2002;235(6):751–8.
5. Larsen M, Kozarek RA. Management of pancreatic ductal leaks and fistulae. J Gastroenterol Hepatol. 2014;29:1360–70. doi:10.1111/jgh.12574.
6. Tay CM, Chang SK. Diagnosis and management of pancreaticopleural fistula. Singapore Med J. 2013;54(4):190–4.
7. van Brunschot S, Schut AJ, Bouwense SA, Besselink MG, Bakker OJ, van Goor H, Hofker S, Gooszen HG, Boermeester MA, van Santvoort HC, Dutch Pancreatitis Study Group. Abdominal compartment syndrome in acute pancreatitis: a systematic review. Pancreas. 2014;43(5):665–74. doi:10.1097/MPA.0000000000000108.
8. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C, Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med. 2013;39(7):1190–206. doi:10.1007/s00134-013-2906-z.
9. Pang TC, Maher R, Gananadha S, Hugh TJ, Samra JS. Peripancreatic pseudoaneurysms: a management-based classification system. Surg Endosc. 2014;28(7):2027–38. doi:10.1007/s00464-014-3434-9.
10. Easler J, Muddana V, Furlan A, Dasyam A, Vipperla K, Slivka A, Whitcomb DC, Papachristou GI, Yadav D. Portosplenomesenteric venous thrombosis in patients with acute pancreatitis is associated with pancreatic necrosis and usually has a benign course. Clin Gastroenterol Hepatol. 2014;12(5):854–62. doi:10.1016/j.cgh.2013.09.068.
11. Kumar N, Sahni VA, Thompson CC. Differentiation of walled-off pancreatic necrosis from other peripancreatic fluid collections: a comparison of CT and EUS. Gastroenterology. 2012;142(5, Supplement 1):S-23. (Digestive Diseases Week; 2012; San Diego, California).
12. Sheu Y, Furlan A, Almusa O, Papachristou G, Bae KT. The revised Atlanta classification for acute pancreatitis: a CT imaging guide for radiologists. Emerg Radiol. 2012;19(3):237–43. doi:10.1007/s10140-011-1001-4 (Epub 2011 Dec 13).
13. Morgan DE, Baron TH, Smith JK, Robbin ML, Kenney PJ. Pancreatic fluid collections prior to intervention: evaluation with MR imaging compared with CT and US. Radiology. 1997;203(3):773–8.
14. Thai TC, Riherd DM, Rust KR. MRI manifestations of pancreatic disease, especially pancreatitis, in the pediatric population. AJR Am J Roentgenol. 2013;201(6):W877–92. doi:10.2214/AJR.13.10834.
15. Sherman S, Freeman ML, Tarnasky PR, Wilcox CM, Kulkarni A, Aisen AM, Jacoby D, Kozarek RA. Secretin (RG1068) administration increases sensitivity of detection of duct abnormalities by magnetic resonance cholangiopancreatography in patients with pancreatitis. Gastroenterology. 2014;147(3):646–54. doi:10.1053/j.gastro.2014.05.035 (2014 Jun 3. pii: S0016-5085(14)00724–0).
16. Cappeliez O, Delhaye M, Devière J, Le Moine O, Metens T, Nicaise N, Cremer M, Stryuven J, Matos C. Chronic pancreatitis: evaluation of pancreatic exocrine function with MR pancreatography after secretin stimulation. Radiology. 2000;215(2):358–64.
17. Rana SS, Bhasin DK, Reddy YR, Sharma V, Rao C, Sharma RK, Gupta R. Morphological features of fluid collections on endoscopic ultrasound in acute necrotizing pancreatitis: do they change over time? Ann Gastroenterol. 2014;27(3):258–61.
18. Vitas GJ, Sarr MG. Selected management of pancreatic pseudocysts: operative versus expectant management. Surgery. 1992;111(2):123–30.
19. Yeo CJ, Bastidas JA, Lynch-Nyhan A, Fishman EK, Zinner MJ, Cameron JL. The natural history of pancreatic pseudocysts documented by computed tomography. Surg Gynecol Obstet. 1990;170(5):411–7.
20. Lenhart DK, Balthazar EJ. MDCT of acute mild (non-necrotizing) pancreatitis: abdominal complications and fate of fluid collections. AJR Am J Roentgenol. 2008;190(3):643–9. doi:10.2214/AJR.07.2761.
21. Klek S, Sierzega M, Turczynowski L, Szybinski P, Szczepanek K, Kulig J. Enteral and parenteral nutrition in the conservative treatment of pancreatic fistula: a randomized clinical trial. Gastroenterology. 2011;141(1):157–63, 163.e1. doi:10.1053/j.gastro.2011.03.040.
22. Allen PJ, Gönen M, Brennan MF, Bucknor AA, Robinson LM, Pappas MM, Carlucci KE, D'Angelica MI, DeMatteo RP, Kingham TP, Fong Y, Jarnagin WR. Pasireotide for postoperative pancreatic fistula. N Engl J Med. 2014;370(21):2014–22. doi:10.1056/NEJMoa1313688.
23. Gurusamy KS, Koti R, Fusai G, Davidson BR. Somatostatin analogues for pancreatic surgery. Cochrane Database Syst Rev. 2013;4:CD008370. doi:10.1002/14651858.CD008370.pub3.
24. Wensil AM, Balasubramanian SA, Bell TL. Resolution of a posttraumatic pancreatic pseudocyst with octreotide acetate in a pediatric patient. Pharmacotherapy. 2011;31(9):924. doi:10.1592/phco.31.9.924.
25. Tanaka T, Kuroki T, Kitasato A, Adachi T, Ono S, Hirabaru M, Matsushima H, Takatsuki M, Eguchi S. Endoscopic transpapillary pancreatic stenting

for internal pancreatic fistula with the disruption of the pancreatic ductal system. Pancreatology. 2013;13(6):621–4. doi:10.1016/j.pan.2013.08.006.
26. Bakker OJ, van Baal MC, van Santvoort HC, Besselink MG, Poley JW, Heisterkamp J, Bollen TL, Gooszen HG, van Eijck CH, Dutch Pancreatitis Study Group. Endoscopic transpapillary stenting or conservative treatment for pancreatic fistulas in necrotizing pancreatitis: multicenter series and literature review. Ann Surg. 2011;253(5):961–7. doi:10.1097/SLA.0b013e318212e901.
27. Irani S, Gluck M, Ross A, Gan SI, Crane R, Brandabur JJ, Hauptmann E, Fotoohi M, Kozarek RA. Resolving external pancreatic fistulas in patients with disconnected pancreatic duct syndrome: using rendezvous techniques to avoid surgery (with video). Gastrointest Endosc. 2012;76(3):586–93.e1–3. doi:10.1016/j.gie.2012.05.006.
28. Hookey LC, Debroux S, Delhaye M, Arvanitakis M, Le Moine O, Devière J. Endoscopic drainage of pancreatic-fluid collections in 116 patients: a comparison of etiologies, drainage techniques, and outcomes. Gastrointest Endosc. 2006;63(4):635–43.
29. Bhasin DK, Rana SS, Nanda M, Chandail VS, Gupta R, Kang M, Nagi B, Sinha SK, Singh K. Comparative evaluation of transpapillary drainage with nasopancreatic drain and stent in patients with large pseudocysts located near tail of pancreas. J Gastrointest Surg. 2011;15(5):772–6. doi:10.1007/s11605-011-1466-1.
30. Varadarajulu S, Noone TC, Tutuian R, Hawes RH, Cotton PB. Predictors of outcome in pancreatic duct disruption managed by endoscopic transpapillary stent placement. Gastrointest Endosc. 2005;61(4):568–75
31. Alexakis N, Sutton R, Neoptolemos JP. Surgical treatment of pancreatic fistula. Dig Surg. 2004;21(4):262–74. (Epub 2004 Aug 11).
32. Rogers BH, Cicurel NJ, Seed RW. Transgastric needle aspiration of pancreaticpseudocyst through an endoscope. Gastrointest Endosc. 1975;21(3):133–4.
33. Kozarek RA, Brayko CM, Harlan J, Sanowski RA, Cintora I, Kovac A. Endoscopic drainage of pancreatic pseudocysts. Gastrointest Endosc. 1985;31(5):322–7.
34. Aghdassi AA, Mayerle J, Kraft M, Sielenkämper AW, Heidecke CD, Lerch MM. Pancreatic pseudocysts—when and how to treat? HPB (Oxford). 2006;8(6):432–41.doi:10.1080/13651820600748012.
35. Varadarajulu S, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). Gastrointest Endosc. 2008;68(6):1102–11. doi: 10.1016/j.gie.2008.04.028
36. Lee LS, Conwell DL. Update on advanced endoscopic techniques for the pancreas: endoscopic retrograde cholangiopancreatography, drainage and biopsy, and endoscopic ultrasound. Radiol Clin North Am. 2012;50(3):547–61. doi:10.1016/j.rcl.2012.03.002.
37. Chahal P. EUS-guided double cystgastrostomy of 2 infected pseudocysts in series: a novel case of endoscopic cystocystgastrostomy. Gastrointest Endosc. 2011;74(2):448. doi:10.1016/j.gie.2011.01.048.
38. Giovannini M, Pesenti C, Rolland AL, Moutardier V, Delpero JR. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope. Endoscopy. 2001;33(6):473–7.
39. Binmoeller KF, Seifert H, Soehendra N. Endoscopic pseudocyst drainage: a new instrument for simplified cystoenterostomy. Gastrointest Endosc. 1994;40(1):112.
40. Arvanitakis M, Delhaye M, Bali MA, Matos C, De Maertelaer V, Le Moine O, Devière J. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. Gastrointest Endosc. 2007;65(4):609–19. (Epub 2007 Feb 26).
41. Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. Gastroenterology. 2013;145(3):583–90.e1. doi:10.1053/j.gastro.2013.05.046.
42. Sharma SS, Bhargawa N, Govil A. Endoscopic management of pancreatic pseudocyst: a long-term follow-up. Endoscopy. 2002 ;34(3):203–7.
43. Lo SK, Rowe A. Endoscopic management of pancreatic pseudocysts. Gastroenterologist. 1997;5(1):10–25 (Review. PubMed PMID: 9074916).
44. Lee MJ, Wittich GR, Mueller PR. Percutaneous intervention in acute pancreatitis. Radiographics. 1998;18(3):711–24 (1998 Sep-Oct;18(5):1336. discussion 728. Review. Erratum in: Radiographics)
45. Voss M, Ali A, Eubanks WS, Pappas TN. Surgical management of pancreaticocutaneous fistula. J Gastrointest Surg. 2003;7(4):542–6.
46. Baillie J, American Gastroenterological Association (AGA) Institute on "Management of Acute Pancreatits" Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA Institute medical position statement on acute pancreatitis. Gastroenterology. 2007;132(5):2019–21.
47. Tenner S, Baillie J, DeWitt J, Vege SS; American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400-15; 1416. doi:10.1038/ajg.2013.218 (Epub 2013 Jul 30. Erratum in: Am J Gastroenterol. 2014;109(2):302).
48. Stiles GM, Berne TV, Thommen VD, Molgaard CP, Boswell WD. Fine needle aspiration of pancreatic fluid collections. Am Surg. 1990;56(12):764–8.
49. Baron TH, Thaggard WG, Morgan DE, Stanley RJ. Endoscopic therapy for organized pancreatic necrosis. Gastroenterology. 1996;111(3):755–64.
50. Seewald S, Groth S, Omar S, Imazu H, Seitz U, de Weerth A, Soetikno R, Zhong Y, Sriram PV, Ponnudurai R, Sikka S, Thonke F, Soehendra N. Aggressive endoscopic therapy for pancreatic necrosis and pancreatic abscess: a new safe and effective

treatment algorithm (videos). Gastrointest Endosc. 2005;62(1):92–100.
51. Ryou MK, Thompson CC. Translumenal access for endoscopic pancreatic necrosectomy: the safe entrance for necrosectomy sans electrocautery (SENSE) technique. Gastrointest Endosc. 2011;73(4, Supplement):AB182 (Digestive Disease Week; 2011; Chicago, Illinois).
52. Gluck M, Ross A, Irani S, Lin O, Gan SI, Fotoohi M, Hauptmann E, Crane R, Siegal J, Robinson DH, Traverso LW, Kozarek RA. Dual modality drainage for symptomatic walled-off pancreatic necrosis reduces length of hospitalization, radiological procedures, and number of endoscopies compared to standard percutaneous drainage. J Gastrointest Surg. 2012;16(2):248–56. doi:10.1007/s11605-011-1759-4
53. Ross AS, Irani S, Gan SI, Rocha F, Siegal J, Fotoohi M, Hauptmann E, Robinson D, Crane R, Kozarek R, Gluck M. Dual-modality drainage of infected and symptomatic walled-off pancreatic necrosis: long-term clinical outcomes. Gastrointest Endosc. 2014;79(6):929–35. doi:10.1016/j.gie.2013.10.014.
54. Trikudanathan G, Attam R, Arain MA, Mallery S, Freeman ML. Endoscopic interventions for necrotizing pancreatitis. Am J Gastroenterol. 2014;109(7):969–81. doi:10.1038/ajg.2014.130.
55. 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 use. Pancreas. 2014;43(7):1334–9.
56. Varadarajulu S, Phadnis MA, Christein JD, Wilcox CM. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic walled-off pancreatic necrosis. Gastrointest Endosc. 2011;74(1):74–80. doi:10.1016/j.gie.2011.03.1122.
57. Saxena P, Singh VK, Messallam A, Kamal A, Zaheer A, Kumbhari V, Lennon AM, Canto MI, Kalloo AN, Baron TH, Khashab MA. 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(2):319–24. doi:10.1016/j.gie.2014.04.041.
58. Yamamoto N, Isayama H, Kawakami H, Sasahira N, Hamada T, Ito Y, Takahara N, Uchino R, Miyabayashi K, Mizuno S, Kogure H, Sasaki T, Nakai Y, Kuwatani M, Hirano K, Tada M, Koike K. Preliminary report on a new, fully covered, metal stent designed for the treatment of pancreatic fluid collections. Gastrointest Endosc. 2013;77(5):809–14. doi:10.1016/j.gie.2013.01.009.
59. Aso A, Igarashi H, Matsui N, Ihara E, Takaoka T, Osoegawa T, Niina Y, Oono T, Akahoshi K, Nakamura K, Ito T, Takayanagi R. Large area of walled-off pancreatic necrosis successfully treated by endoscopic necrosectomy using a grasping-type scissors forceps. Dig Endosc. 2014;26(3):474–7. doi:10.1111/den.12134
60. van Brunschot S Fockens P Bakker OJ Besselink MG Voermans RP Poley JW Gooszen HG Bruno M van Santvoort HC. Endoscopic transluminal necrosectomy in necrotising pancreatitis: a systematic review. Surg Endosc. 2014;28(5):1425–38. doi:10.1007/s00464-013-3382-9
61. Papachristou GI, Takahashi N, Chahal P, Sarr MG, Baron TH. Peroral endoscopic drainage/debridement of walled-off pancreatic necrosis. Ann Surg. 2007;245(6):943–51.
62. Spofford IS, Wu BU, Conwell D, Banks PA, Mortele KJ, Korasani R, Yu S, Thompson CC. Endoscopic versus surgical necrosectomy for patients with symptomatic pancreatic necrotic collections: a retrospective cohort study. Gastroenterology. 2011;140(5, Supplement 1):S-11–2 (Digestive Disease Week; 2011; Chicago, IL).
63. Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, Poley JW, van Ramshorst B, Vleggaar FP, Boermeester MA, Gooszen HG, Weusten BL, Timmer R, Dutch Pancreatitis Study Group. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. JAMA. 2012;307(10):1053–61. doi:10.1001/jama.2012.276.
64. van Santvoort HC Besselink MG Bakker OJ Hofker HS Boermeester MA Dejong CH van Goor H Schaapherder AF van Eijck CH Bollen TL van Ramshorst B Nieuwenhuijs VB Timmer R Laméris JS Kruyt PM Manusama ER van der Harst E van der Schelling GP Karsten T Hesselink EJ van Laarhoven CJ Rosman C Bosscha K de Wit RJ Houdijk AP van Leeuwen MS Buskens E Gooszen HG, Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362(16):1491–502. doi:10.1056/NEJMoa0908821.

ERCP in Chronic Pancreatitis

13

Amit Maydeo, Suryaprakash R. Bhandari and Mukta R. Bapat

Introduction

Chronic pancreatitis (CP) is a morbid disease found commonly in the Indian subcontinent and across the world. Predominant pathologies observed in CP are pancreatic stones with or without pancreatic duct strictures which may be dominant or multiple. Pseudocyst formation and ascites with or without pleural effusion may be seen with pancreatic duct disruptions (see Chap. 12). Some patients may have an essentially small duct disease with parenchymal atrophy without stones or significant strictures. Patients with chronic pancreatitis most commonly manifest with abdominal pain, steatorrhoea, diabetes mellitus, and weight loss. Jaundice is seen with associated bile duct stenosis (see Chap. 8). The exact etiology and pathogenesis of CP remain unknown and various environmental, nutritional, and genetic factors are considered responsible. Treatment strategies for chronic pancreatitis are medical, endoscopic, or surgical. Short- and long-term outcomes of these procedures are well studied in various studies [1–5].

Endoscopic treatment for chronic calcific pancreatitis has now become an established mode of treatment for a select subset of patients. It essentially aims at decompression of the obstructed pancreatic duct. Success of endoscopic interventions depends upon the patho-morphology and cause of obstruction; i.e., number of stones, consistency of the stones (radio-opaque or radiolucent), location of the stones, and presence or absence of associated pancreatic ductal strictures. Unlike bile duct stones, pancreatic duct stones are usually radio-opaque, hard, spiculated as well as impacted and thus need pulverization prior to an attempt at endoscopic extraction. Hence, some form of lithotripsy becomes mandatory to pulverize these stones. Extracorporeal shock wave lithotripsy (ESWL) is now considered an integral part of the treatment in patients with radio-opaque calcific pancreatitis along with ERCP and has also been described as a single modality therapy in few studies [6–13].

This chapter emphasizes the technique of treating pancreatic stones using a combination of ESWL and ERCP pancreatic endotherapy for efficient clearance of pancreatic duct stones and endoscopic therapy of pancreatic duct strictures. The management of pancreatic duct leaks, pseudocysts, and biliary strictures resulting from CP are discussed in Chaps. 8 and 12.

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Case

A 38-year-old male presented with long standing upper abdominal pain and diabetes mellitus. He experienced multiple episodes of abdominal pain which was intermittent, severe, and radiating to the back. These episodes of pain led to repeated hospitalization for treatment with injectable analgesics. He had sustained weight loss and recently developed diabetes mellitus. He had no steatorrhoea, jaundice, gastrointestinal bleeding, or abdominal distention. Clinical examination was normal. Abdominal ultrasound showed pancreatic duct calcifications in a dilated pancreatic duct with no associated gallbladder stones or mass in the pancreas. His biochemical parameters revealed a normal hemogram and liver biochemistry, low serum calcium, and vitamin D 3 levels. His CA 19-9 levels were normal. His pre- and postlunch sugar levels were 180 and 330 mgs, respectively.

As a protocol for treating these radio-opaque pancreatic duct stones, we first performed fluoroscopic screening of the patient using a C-arm (dynamic fluoroscopy) machine to assess the number, location, and density of stones. Fluoroscopy showed dense radio-opaque stones in the head, body and tail of the pancreas (Fig. 13.1).

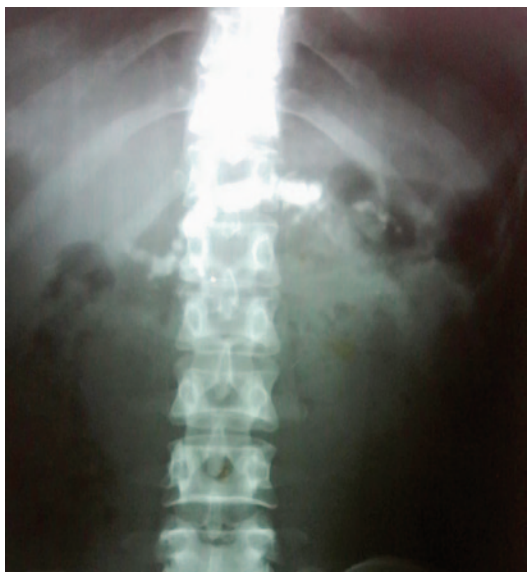

Fig. 13.1 Pre-ESWL plain abdominal x-ray image showing multiple small to large stones along the pancreatic duct in the head and body region

A magnetic resonance cholangiopancreatography (MRCP) was then obtained to assess the pancreatic ductal morphology looking for associated pancreatic ductal strictures, biliary strictures, pseudocysts, and presence of pancreas divisum. It revealed uniformly dilated duct through the tail with multiple filling defects (Fig. 13.2). There was no evidence of pancreas divisum on MRCP. The patient was offered endoscopic therapy as the first line of treatment for which he consented.

Pancreatic Endotherapy: Who is Eligible?

Patients with symptomatic pancreatic stones and suitable ductal morphology (uniformly dilated duct through the tail) on MRCP are the best candidates for endotherapy. Patients having radio-opaque stones confirmed on fluoroscopy are subjected to ESWL prior to ERCP in our unit. We do not routinely recommend ERCP prior to ESWL in patients with radio-opaque stones (>5 mm in size) as pancreatic stones are hard, impacted within the duct and at times do not even allow guidewires to be negotiated around the stones. Placing a pancreatic stent prior to ESWL is not mandatory as radio-opaque pancreatic stones can easily be targeted under X-ray guidance with the ESWL machine. On the other hand, patients with radio-lucent calculi can undergo ERCP directly as these stones are soft and amenable to endoscopic basket/balloon extraction, provided they are small in size. Patients with large radiolucent calculi require additional methods like balloon sphincteroplasty of the pancreatic orifice (Video 13.1) or insertion of a nasopancreatic tube (NPT) followed by ESWL under C-arm guidance.

Pretreatment Assessment of Patients Prior to Endotherapy

A thorough pre-procedure history and clinical examination are done for all patients before planning pancreatic endotherapy in the form of ESWL and ERCP. Characteristics of abdominal pain, weight loss, steatorrhoea, diabetes, alcohol/

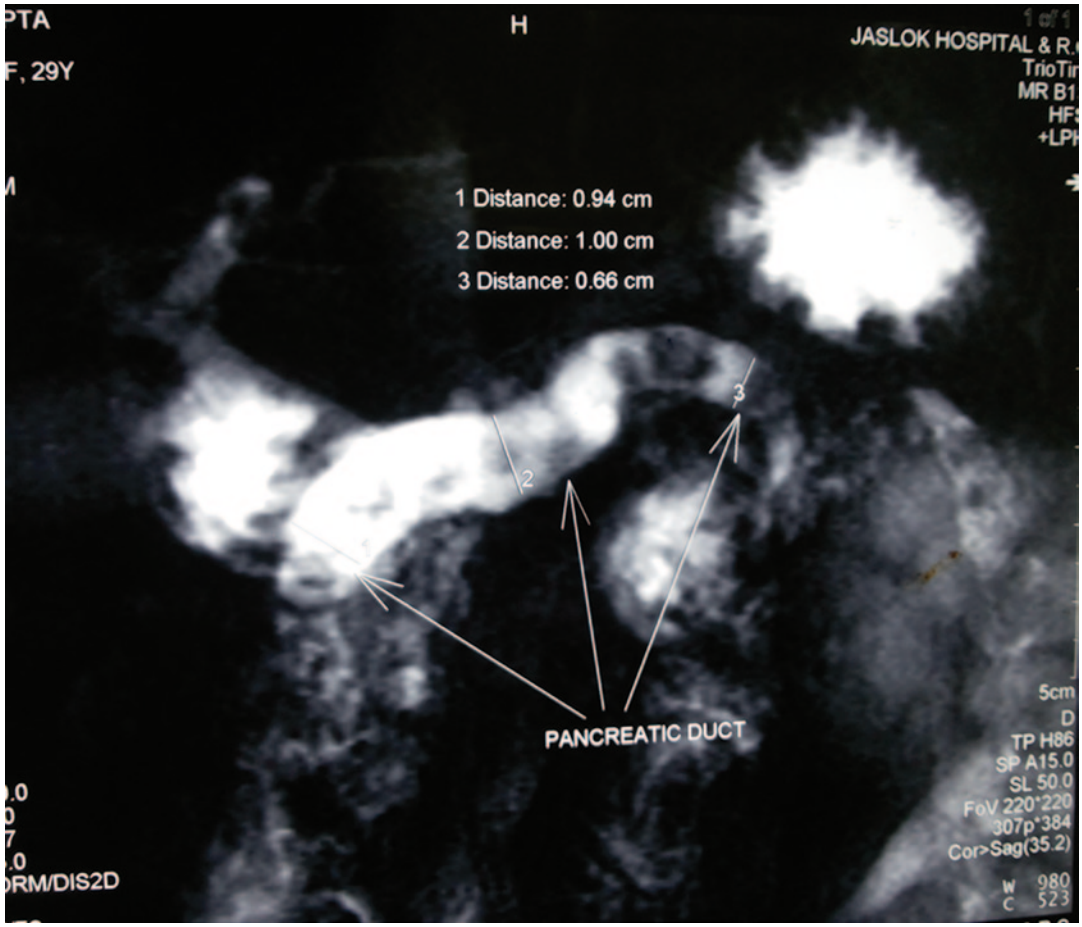

Fig. 13.2 MRCP showing diffusely dilated pancreatic duct containing multiple calculi

smoking habits, and details of prior therapy and surgery are noted in detail. Routine biochemistry is done which includes fasting and postprandial sugars, renal parameters, CA 19- 9, calcium, vitamin A/B12/D3 levels, and if needed parathyroid hormone. A dynamic fluoroscopic examination is performed preferably on a rotatable C-arm to assess the stones for consistency, number, and location. This is necessary to decide the approximate number of shock waves required to pulverize the stones. An MRCP is then obtained to accurately assess the pancreatic ductal morphology and look for associated pancreatic ductal strictures, bile duct strictures, pseudocyst, pancreas divisum, ductal disruption, or pancreatic mass. If a mass is suspected, a contrast-enhanced CT scan and EUS-FNA should be routinely performed. An altered anatomy, significant duodenal narrowing, and portal hypertension are considered relative contraindications for pancreatic endotherapy and alternative therapy is offered to these patients.

How Is ESWL Performed?

ESWL is performed in our unit by a trained radiology technician under the guidance of a gastroenterologist although urologists may offer this service as well. We use the Dornier Compact Delta II lithotripter (Dornier Med Tech, Wessling, Germany) with an integrated C-arm system that facilitates accurate localization of

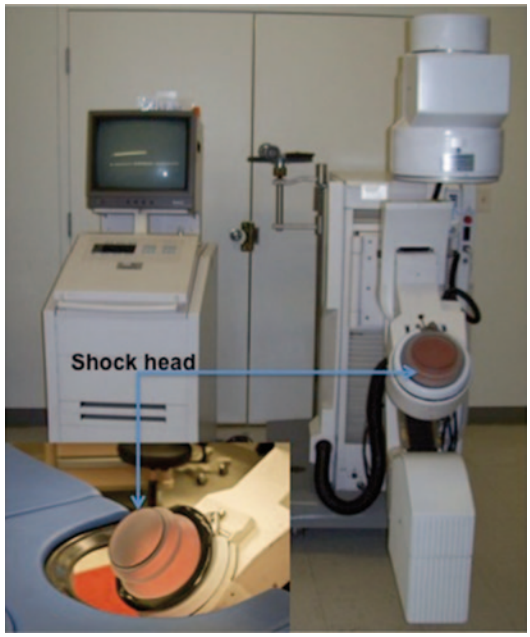

Fig. 13.3 ESWL machine with arrows pointing to shock head

the shock waves on the radio-opaque pancreatic stones. The ideal extracorporeal shock wave lithotripter should have an isocentric shock head allowing for a small focal point of less than 5 mm (Fig. 13.3). This prevents scattering of the shock waves and damage to the surrounding pancreatic parenchyma or the kidney. The focal point energy usually ranges from 0.1 to 0.6 mJ/mm^2. The Dornier machine energy level can be adjusted from Level 1 (10 kV) to Level 6 (16 kV). ESWL is usually performed under intravenous sedation/analgesia or epidural analgesia because the therapy can be painful. Oxygen saturation and cardiac tracings are continuously monitored during the procedure. The procedure is usually performed with the patient in the supine position, and the shock head touching the abdomen from above. The patient is sometimes tilted to one side by placing a bolster below the back in order to achieve effective contact with the shock head. The stones are then localized in two axes perpendicular to one another and shock wave therapy is commenced. It is best to start with low-intensity shock energy at Level 1 or Level 2 and to slowly increase it. Averages of 3000–8000 shocks are delivered in one session of ESWL. This can be completed in around 120 min. Depending upon the stone load, single or multiple sessions of shock wave therapy are administered on alternate days until effective pulverization of the stones is achieved. For patients with multiple stones, on average 2–3 sessions are necessary. The end point of ESWL therapy should be complete pulverization of the stones into powder and not just fragmentation. Pulverized stones should be less than 3 mm in size and usually lose their density, shape, and spread in the duct along the longitudinal axis.

Case Continued

The patient then underwent ESWL to pulverize the stones. Two sessions of ESWL were given on alternate days for a total of 15,000 shocks administered (7000 & 8000). This procedure was performed with intravenous sedation, and he tolerated the procedure well. Post-ESWL, repeat fluoroscopy examination revealed nicely pulverized stones spread along the entire duct (Fig. 13.4).

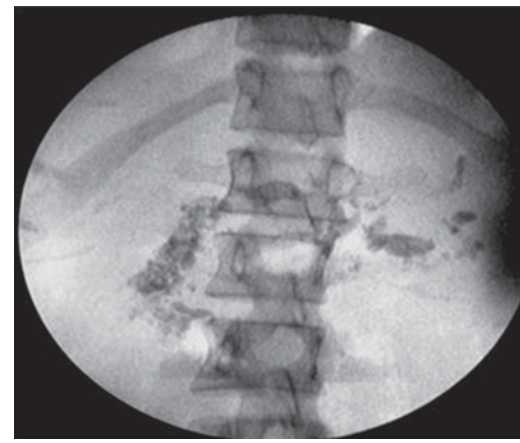

Fig. 13.4 Post-ESWL fluoroscopy image showing fragmented, pulverized calculi scattered along the pancreatic duct

When and How Is ERCP Performed?

We prefer to perform ERP at least 48 h after the last session of ESWL in order to allow the ESWL induced edema to settle. ERP completed less than 2 days after ESWL were associated with higher rates of failure (84%) compared to ERP performed more than 2 days after ESWL (18%) [14, 15]. It is done under total intravenous anesthesia with the patient in the supine or prone position to give proper anatomical orientation of the pancreatic morphology on fluoroscopy. A therapeutic duodenoscope with a working channel of 4.2 mm (e.g., TJF−160 or 180 Olympus, Tokyo, Japan; ED-3490TK, Pentax Medical, Montvale, NJ) should be used. The goal of ERCP should be complete ductal clearance of all stone material.

Initial cannulation of the pancreatic duct is best achieved using a tapered tip ERCP cannula, such as the Contour cannula (Boston Scientific, Marlborough, Massachusetts, USA). However, a tapered tip cannula from any other manufacturer can be used for this purpose. A double/triple lumen sphincterotome can also be used as this is a planned therapeutic procedure.

After performing a pancreatogram to assess the ductal morphology, a fully hydrophilic glidewire is passed through the cannula and negotiated past the pulverized stones in the pancreatic duct to the tail. The most useful wire to achieve this is a 0.035, 0.021, or 0.018 in. J tipped Terumo Glide wire (Terumo Corp., Tokyo, Japan), but other wires with a hydrophilic tip, such as the Boston Scientific Dream wire or the Cook Endoscopy Metro Tracer (Cook Medical, Bloomington, IN, USA) are also good alternatives. In patients with complete pancreas divisum, the minor papilla can be cannulated using the same accessories.

In rare instances, if direct access to the pancreatic duct (major or accessory) is not possible through the normal papillary orifice due to edema or retropapillary narrowing, and the pancreatic duct is dilated, an EUS-guided rendezvous technique can be used to enter the pancreatic duct transgastrically and then the guidewire negotiated across the papilla and coiled in the duodenum. The procedure can then be completed with the echoendoscope exchanged to a duodenoscope.

Sphincterotomes

A wire guided sphincterotome, such as the Olympus Clever Cut, Boston Scientific Ultratome Excel, or Cook Medical Dome Tip sphincterotome, is used for pancreatic sphincterotomy. It is important that the sphincterotome have a short monofilament wire and a short, rounded/atraumatic tip. In cases where the minor papilla needs to be cannulated and the opening is tiny, an ultra-tapered sphincterotome is required which accepts a thinner guide wire (0.018 or 0.021 in.). For cutting the pancreatic sphincter, we usually use a blended endocut current. The sphincterotomy is usually performed between the 12 and 2 o'clock positions. The size of the sphincterotomy should always be tailored according to the size of ampulla, stone load and proposed plan of endotherapy.

Stone Extraction Techniques/ Accessories

Once deep access is achieved into the pancreatic duct, the pulverized stones can usually be removed using a 1.0 or 1.5 cm stone extraction balloon (available from several manufacturers, including Boston Scientific, Cook Medical, or MediGlobe). However, the triple-sized balloon from Olympus is sometimes preferred for pancreatic stone extraction because it is sturdier and with its three different expandable diameters, its size can be adjusted according to the duct size. As the pulverized stones can be hard and spiculated, balloons may rupture easily. In these situations, a wire-guided basket should be used to extract the stones. The ideal basket for pancreatic stone extraction is small, easy to advance to the tail of the pancreas, and can be passed over a guidewire. The Olympus Tetra V wire guided basket is the most ideal basket for this purpose. However, the Olympus hard wire basket (FG−22Q) can also be used alongside a previously placed guide wire. Whichever basket is used, it should be suitable for emergency lithotripsy in case of impaction. In some special situations, small, spiral baskets such as the Segura basket (Cook Medical, Bloomington, IN, USA) can be used. The stones nearest

to the ampulla should be removed first and the remaining with subsequent passes progressing from the head to the tail. Lithotripsy compatible baskets like trapezoid basket from Boston Scientific are rarely used primarily (without ESWL) in centers having an aggressive ESWL protocol for crushing pancreatic stones. Negotiating this stiff basket across hard and impacted pancreatic stones is very difficult and we do not recommend this.

Case Continued

ERCP was done 48 h after effective pulverization of the stones was achieved by ESWL (Video 13.2). A diclofenac suppository (100 mg) was administered as per our routine immediately before ERCP. Pancreatogram obtained from the major papilla showed a uniformly dilated duct through the tail with filling defects in the head region. Pancreatic sphincterotomy was performed using a blended current and a standard sphincterotome (Clevercut, Olympus, Japan or Ultratome XL, Boston Scientific). Large chunks of pulverized stone fragments were then extracted using a wire guided Dormia basket (Olympus Tetra V, Japan), and partial ductal clearance was achieved. At the end of the procedure, a temporary 7 Fr single pigtail stent was placed in the pancreatic duct to ensure an unobstructed flow of pancreatic juice and allow for passage of the residual pulverized stone powder (Fig. 13.5). The patient was observed in the hospital for 2 days and then discharged. He had mild epigastric pain for a day post-ERCP which resolved with non-opioid analgesics.

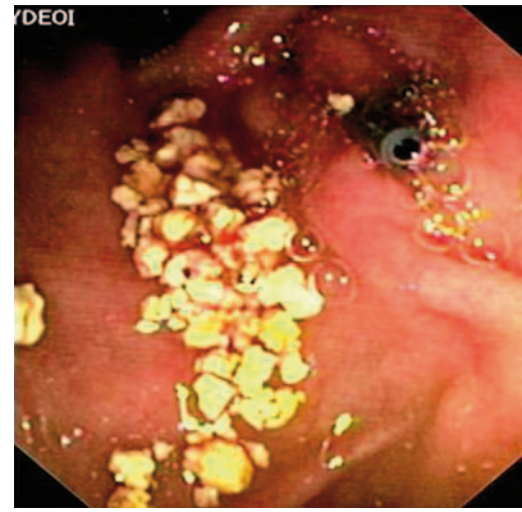

Fig. 13.5 Endoscopy image of extracted pancreatic duct calculi. Temporary 7 Fr stent placed in the pancreatic duct

How to Deal with Impacted Pulverized Stones

If the pulverized stones are still impacted or conglomerated together tightly and it is not possible to negotiate a stone extraction balloon or a basket across, one can create a pathway through the stones using a 10 Fr over the wire Soehendra stent retriever (Cook Medical). With this instrument, a passage through the impacted stones can be drilled. Using this technique, not only is a passage established for stent placement but the pulverized stones become loose and can then be extracted. This facilitates removal of chunks of pulverized stones from the duct and allows better ductal clearance in a single setting.

Pancreatic Stents

During pancreatic stone extraction, temporary stents are usually used until the next session of stone extraction is performed and the duct is completely cleared. The most commonly used stents for this purpose are either 5 or 7 Fr single pigtail stents available from Cook Medical or Olympus. The length of the stents can be decided according to the ductal morphology and presence and length of any strictures. Management of pancreatic duct strictures is discussed in more detail later in this chapter.

Difficult Pancreatic Endotherapy and Rescue Technique

Adequacy of ESWL and complete stone pulverization should always be judged prior to subjecting the patient to ERCP. As a protocol, we routinely do a fluoroscopic examination to evaluate the adequacy of stone pulverization with ESWL.

Pulverized pancreatic stones appear less dense, lose their character, and usually spread along the duct length. Pancreatic stones are usually hard and despite pulverization with ESWL, some fragments can be hard and difficult to extract with simple techniques. Therefore, when using a basket to retrieve stones, care must be taken to open the basket only partially and to catch very few stones at one time to prevent basket impaction. In rare instances if the basket becomes impacted, every attempt should be made to disimpact the basket by quick jiggling movements and flushing the basket with normal saline. Despite repeated attempts, if the basket does not get disimpacted, then repeat rescue ESWL can be performed with the scope in situ. This is an effective way to disimpact the basket, and the ERCP can be completed later once adequate pulverization of the stones has been achieved.

Selective cannulation of the pancreatic duct (major or minor) can be difficult at times. In patients with a dilated pancreatic duct, EUS-guided rendezvous can be performed for pancreatic duct cannulation. In patients of incomplete pancreas divisum, a major to minor papilla rendezvous can be done under fluoroscopic guidance. The guidewire is passed from the major papilla, negotiated across the minor papilla, and out into the duodenal lumen. The wire is then captured with a snare or forceps, pulled through the channel of the duodenoscope, and the procedure can be completed.

In patients with a uniformly dilated pancreatic duct and persistent larger stone fragments despite adequate ESWL, pancreatoscopy can be performed in order to pulverize the pancreatic stone fragments under direct visualization using a Holmium Laser or electrohydraulic lithotripsy. The stone fragments are then extracted using routine techniques.

How Should Patients Be Followed After Initial Endotherapy?

Patients should be assessed immediately post-procedure for any complications, which have been reported in about 6% of patients and consists mainly of mild pancreatitis [16]. Other less common post-ERCP complications include bleeding post-sphincterotomy, stent migration or occlusion, duct leak, and pancreatic abscess [17]. Injury to the duct usually occurs with the use of hard, stiff accessories especially in the tail of the pancreas. ESWL-related complications are minimal and include 1% hemosuccus pancreaticus (Chap. 16) and skin or duodenal wall erythema.

In most cases, the pulverized stones cannot be completely cleared in one procedure. Thus a temporary pancreatic stent is placed to ensure continuous flow of pancreatic juice before the next session. In 3 months, a fluoroscopic examination is done to look for any residual radio-opaque stones. If radio-opaque stones are found, then a repeat session(s) of ESWL occurs before repeating the ERCP to attempt complete ductal clearance. In patients with ductal strictures and upstream stones, if the stricture has not yet resolved multiple large diameter stents (10 Fr) are placed during each subsequent ERCP until the stricture resolves and the stones can be cleared. During each follow-up, the patients are also assessed for pain relief, weight gain, and control of any exocrine and endocrine deficiencies. Pancreatic enzyme supplementation and strict control of blood sugars are advised when necessary. Abstinence from alcohol and smoking are mandatory once pancreatic endotherapy is performed.

Case Follow-Up

At the first follow-up 3 months later, the patient reported significant reduction in his abdominal pain and a weight gain of 3 kg. During ERCP, the previously stent was removed and a repeat pancreatogram was done. It showed a mildly dilated pancreatic duct containing a few residual filling defects. Residual stone fragments were extracted using a basket, and complete duct clearance was achieved. The duct was flushed and irrigated with normal saline, and the patient was given a stent free trial. During subsequent visits at 3 month intervals, the patient remained pain free and had a total 8 kg weight gain. His diabetes was well controlled. At the end of 1 year following stent removal, he remained pain free.

What Are the Long-Term Results of ESWL and ERCP?

A large amount of data including randomized trials is now available supporting the use of ESWL prior to endoscopic management of pancreatic stones. Success rates of pulverization of pancreatic stones using ESWL range between 38 and 100%, [18], and ESWL alone can provide significant pain relief [19–21]. However, ESWL followed by ERCP has been shown to achieve the most satisfactory pain relief in patients with chronic calcific pancreatitis. The combination of ESWL with ERCP yields a stone fragmentation rate of 54–100% and complete or partial pain relief ranging from 48 to 85% [22–27]. Table 13.1 summarizes seven studies published to date on long-term follow-up (≥23 months) of patients undergoing ESWL and ERCP for patients with chronic calcific pancreatitis. The largest study by Tandan et al. [28] included 636 patients of whom 364 were followed for 2–5 years and 272 for over 5 years for nonalcoholic chronic calcific pancreatitis. Clinical outcomes were similar for both groups of patients; they experienced significant improvement in pain scores with 60–69% remaining pain-free compared to 0% pre-procedure and 4–6% having severe pain compared to 25–36% pre-procedure. Complete duct clearance occurred in 76–78% of all patients. Weight remained stable or increased in 94–99% of patients and quality of life improved in 93%. The two differences between the intermediate (2–5 year) follow-up and long-term (>5 year) follow-up patients were increased need for repeat procedure (47 vs. 29%, $p=0.007$) and rate of diabetes (51 vs. 24%, $p=0.0001$) in the long-term group.

The US experience, which consists mainly of alcohol-induced chronic pancreatitis, is similar although perhaps with slightly lower efficacy with 50% of patients remaining pain-free at mean 4 year follow-up [22]. Quality of life improved in 77% while rate of diabetes increased from 18 to 35% comparing pre-ESWL to last follow-up. Interestingly, when patients with at least 4 year follow-up after ESWL+ERCP were compared with postsurgical patients, the former group had significantly more patients reporting complete pain relief (61 vs. 21%, $p=0.009$) although they also required more ERCPs as well.

Few prospective and retrospective studies have evaluated factors predicting successful outcomes of pancreatic endotherapy in calcific pancreatitis [8, 10, 12, 13, 25]. These factors include age, sex, etiology of CP, number, location and maximum diameter of stones, completeness of stone removal, presence of a main pancreatic duct stricture, duration of disease, and timing of ERCP in the course of illness. However, the results have significant variations. Brand et al. [8] in their prospective evaluation of early outcome of endotherapy in 48 patients with chronic pancreatitis identified nonalcoholic etiology and a decrease in pancreatic duct diameter as factors associated with significant pain relief. Smits et al. [13] in their retrospective analysis of 53 patients reported no significant difference in treatment success (pain relief) between alcoholic vs. nonalcoholic pancreatitis, presentation with pain vs. pancreatitis, single vs. multiple stones, location of stones in pancreatic head alone vs. head/body/tail, and the presence of a stricture vs. no stricture.

A potential alternative to ESWL is ERCP with pancreatoscopy and electrohydraulic lithotripsy or laser lithotripsy. In a study of 46 patients, ini-

Table 13.1 Stone fragmentation and pain relief in long-term studies

Authors	Year	No of patients	Fragmentation (%)	Complete or partial pain relief (%)	Mean follow – up (months)
Seven et al. [22]	2012	120	–	85	28
Dumonceau et al. [16]	2007	29	100	55	51
Kozarek et al. [24]	2002	40	100	80	30
Farnbacher et al. [25]	2002	125	85	48	29
Adamek et al. [26]	1999	80	54	76	40
Costamagna et al. [35]	1997	72	100	72	27

tial attempt at passing the pancreatoscope failed in 17% although ultimately after repeat effort, 91% technical success was achieved. A median of four ERCPs were performed per patient with 70% complete ductal clearance of stones and 74% clinical success, which was defined as at least 50% reduction in pain score or opiate use following final ERCP over median 18 month follow-up. Complications occurred in 10% of patients mainly related to pancreatitis. While further studies and long-term follow-up are necessary, this may offer an alternative to combined ESWL and ERCP management [29].

In our experience, ESWL is currently the cornerstone in endotherapy of pancreatic stones as it helps in pulverizing hard, spiculated, and even impacted pancreatic ductal stones thereby facilitating their extraction with ERCP. Nearly 90% of patients with a favorable ductal morphology (uniform ductal dilation without strictures), as commonly seen in idiopathic chronic pancreatitis, achieve complete clearance of these stones. While the amount of stone burden suitable for ESWL therapy is debatable, we have found that the number or location of the stones are not a contraindication to ESWL, provided the stones are targeted accurately [17]. However, in the presence of a downstream stricture or complex ductal disease as often encountered in patients with alcoholic CP, stone extraction and clearance can be difficult despite using an aggressive ESWL protocol and ERCP technique with success rates as low as 40%. In this subset of patients, stone clearance may be incomplete, and these patients can have persistent pain and eventually require surgery.

Briefly, the following surgical options are available for patients with chronic pancreatitis [30]. The Partington–Rochelle (modified Puestow) procedure creates a lateral pancreaticojejunostomy (anastomosis between the longitudinally incised main pancreatic duct and Roux-Y jejunal loop). This is the most commonly performed drainage procedure in patients with CP. In the Beger procedure, the pancreatic head is resected while preserving the duodenum. The pancreas is transected at the border between the pancreatic head and body with a thin pancreatic disc left between the common bile duct and duodenum. The pancreatic body is drained by an end-to-end pancreaticojejunostomy and the pancreatic head disc is drained by a side-to-side pancreaticojejunostomy. The Frey procedure combines the Puestow with coring out the diseased pancreatic head. Finally, the Whipple surgery involves pancreaticoduodenectomy with reconstruction by pancreaticojejunostomy, hepaticojejunostomy, and gastrojejunostomy.

Two randomized studies [31, 32] compared the results of surgical and endoscopic therapy for pain in chronic pancreatitis with a follow-up of 2–5 years and reported apparently better results with surgery. One study randomized 72 patients to endoscopic therapy consisting of pancreatic sphincterotomy, stenting for mean 16 months, and/or stone removal or surgery which mainly consisted of resection with a few drainage (pancreaticojejunostomy) procedures in 20%. Immediate pain relief or improvement occurred in about 90% for both groups, however, at 5 year follow-up, rates of complete pain relief were higher following surgery (34 vs. 15%, $p=0.002$). The second trial randomized 39 patients to endoscopic treatment (sphincterotomy, stenting with or without dilation, ESWL followed by ERCP) or surgery which was mainly pancreaticojejunostomy. Although stones were completely removed in 89% of patients, only 50% experienced resolution of strictures to produce overall 53% technical success with endoscopy. Stents were in place for a median 27 months (range 6–67 months) with 10 Fr stents ultimately placed and 56% having multiple stents inserted. After median follow-up of 2 years, complete or partial pain relief was significantly higher after surgery than endoscopy (75 vs. 32%, $p=0.007$). Both trials have major biases due to the lack of availability of ESWL in the former and the low rate of endoscopic success in dilating dominant pancreatic strictures with some patients having a very short period of stenting in the other.

Managing Pancreatic Duct Stricture

Patients with chronic pancreatitis can have a single dominant or multiple strictures, and about half of patients with CP undergoing endoscopic therapy have a pancreatic stricture. As patients

with chronic pancreatitis are at increased risk for pancreatic cancer, malignancy must always be excluded in the setting of strictures [16]. Evaluation should include radiologic imaging (CT scan, MRI, and/or EUS), and if ERCP is performed, tissue should be obtained from the stricture by brushing for cytology and pancreatic fluid may also be sent for cytology.

A dominant pancreatic stricture is defined by a stricture with one of the following: at least 6 mm upstream duct dilation, no contrast outflow from a 6 Fr catheter advanced upstream from the stricture, abdominal pain during 1 L saline infusion for 12–24 h through a nasopancreatic tube [16]. Tight strictures are negotiated using a glidewire as described above. However in patients who have very tight fibrotic strictures, an over the wire 10 Fr Soehendra stent retriever may be used to core through the stricture. Pancreatic sphincterotomy should be performed. Short tight strictures are dilated using a 6 or 8 mm Boston Scientific Hurricane Balloon. These strictures are then further dilated chronically using single or multiple plastic pancreatic stents of increasing diameters (7 or 10 Fr) at 3-month intervals followed by attempts to clear the duct of the stones after partial or complete stricture resolution. If using a single plastic stent as treatment, 10 Fr stents are recommended as they were associated with decreased hospitalization compared to smaller stents [33]. Regularly scheduled stent exchanges is recommended due to high rates of stent occlusion (20%) [34]. The stricture is considered to be adequately dilated when a 6 Fr catheter easily passes across the stricture with good flow of saline or contrast through the stricture and no significant hold up of contrast upstream. Typically this process takes at least 12 months. If symptoms recur following stent removal, management options include another trial of stent therapy or surgery.

Pancreatic stenting is technically successful in 85–98% of pancreatic duct strictures. Immediate pain relief occurs in 65–95% of patients while during longer follow up (14–58 months), 32–68% of patients report ongoing pain relief [18]. After prolonged pancreatic duct stenting with definitive stent removal following stricture resolution, relapsing pain occurred in 36–48% of patients, repeat stenting was required in 22–30% of patients, and 4–26% patients were subjected to pancreatic surgery [18]. Complications related to pancreatic stenting occurred in about 6–39% of patients and include mild acute pancreatitis, stent occlusion, stent migration, bleeding, and rarely pancreatic abscesses requiring surgery [16].

Similar to treatment of benign biliary strictures with multiple plastic stents, the same Italian group applied this concept to pancreatic duct strictures in the head of the pancreas of patients with symptomatic severe chronic pancreatitis [35]. These patients had all failed two previous single stent placements ($\geq$8.5 Fr) for at least 3 months each. The technique involved stricture dilation to mean 7.8 mm followed by median three stents inserted for average 7 months. During mean 38 month follow-up following final stent removal, 84% remained asymptomatic and 11% developed symptomatic recurrent stricture, which responded to repeat stenting. Also analogous to management of benign biliary strictures, interest has blossomed in the use of fully covered self-expandable metallic stents (SEMS) for these pancreatic strictures. A recent review of the currently published case series found that the technical success of SEMS was 100%, similar to that of multiple plastic stenting, with only 8% migration rate, and 85% patients reported pain relief [36]. Some case series did report the presence of new focal strictures following stent removal. Further studies are necessary to evaluate the efficacy, safety, long-term results of covered SEMS and compare with plastic stenting.

European Society of Gastrointestinal Endoscopy (ESGE) guidelines state that dominant pancreatic duct strictures be treated with placement of a single 10 Fr stent with stent exchange planned for up to 1 year. Multiple plastic stents should be inserted in strictures that persist after 1 year of single stent placement or even sooner. Uncovered SEMS should not be placed in the pancreatic duct. Finally, ESGE guidelines also state that temporary placement of fully covered SEMS should only be performed in the setting of trials [18].

Conclusions

Management of pancreatic ductal stones in CP can be performed effectively with endotherapy. Aggressive pancreatic endotherapy with judicious application of ESWL has high technical success rates in terms of ductal clearance and yields excellent short and long-term results with pain relief in chronic calcific pancreatitis. Treatment is more challenging in the presence of pancreatic ductal strictures which should be treated with sphincterotomy, dilation, and long-term single or multiple pancreatic duct stenting. Whether patients with idiopathic chronic pancreatitis respond better than alcoholic disease is the subject of our ongoing research protocol.

Key Points

- Chronic pancreatitis can lead to sequelae including pancreatic duct stones with or without pancreatic duct strictures, biliary stricture, and pseudocyst.
- Endoscopic management of both pancreatic duct stones and pancreatic duct strictures is successful in select patients with low morbidity.
- The type, number, and size of pancreatic duct stones will dictate treatment. Small radiolucent stones may be removed by ERCP with sphincterotomy while large radiolucent stones may require balloon sphincteroplasty as well or ESWL.
- Large radiopaque stones respond to combination of ESWL followed by ERCP removal of pulverized stone debris using a variety of accessories.
- Surgery is an alternative for patients who fail endoscopic management. Typically surgery involves either a drainage procedure of the duct like a lateral pancreaticojejunostomy, pancreatic resection like a Whipple procedure, or a combination of drainage and resection.
- Malignancy must be excluded in chronic pancreatitis-related pancreatic duct strictures.
- Pancreatic duct strictures from chronic pancreatitis usually require long-term stenting for at least 1 year and possibly multiple plastic stents.

Video Captions

Video 13.1 Endotherapy for radio-lucent pancreatic duct calculi

Pancreatogram showing hugely dilated (sigmoid type) pancreatic duct through the tail containing multiple large radio-lucent calculi. Pancreatic sphincterotomy done. The pancreatic duct orifice was further dilated using a CRE balloon (Boston Scientific, Marlborough, MA) up to 12 mm. Multiple radiolucent calculi extracted using a stone extraction balloon. Temporary 7 Fr stent placed in the pancreatic duct.

Video 13.2 Endotherapy for radio-opaque pancreatic duct stones

Pancreatogram showing dilated irregular duct through the tail containing multiple pulverized calculi following ESWL. Pancreatic sphincterotomy done. Pulverized calculi were then extracted using a stone extraction balloon. Temporary stent placed in the pancreatic duct (not shown), and patient was asked to follow up 3 months later for repeat ERCP.

References

1. Gourgiotis S, Germanos S, Rodolfini PM. Surgical treatment of chronic pancreatitis. Hepatobiliary Pancreat Dis Int. 2007;6:121–33.
2. Cunha JEM, Penteado S, Jukemura J, Machado MCC, Bacchella T. Surgical and interventional treatment of chronic pancreatitis. Pancreatology. 2004;4:540–50.
3. Warshaw AL, Banks PA, Fernández-Del Castillo C. AGA technical review: treatment of pain in chronic pancreatitis. Gastroenterology. 1998;115:765–76.
4. Witt H, Apte MV, Keim V, Wilson JS. Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis and therapy. Gastroenterology. 2007;132:1557–73.
5. ASGE Guideline. Endoscopic therapy of chronic pancreatitis. Gastrointest Endosc. 2000;52(6):843–47.
6. Choi KS, Kim MH. Extracorporeal shock wave lithotripsy for the treatment of pancreatic duct stones. J Hepatobiliary Pancreat Surg. 2006;13:86–93.
7. Triangali A, Boskoski I, Costamagna G. The role of endoscopy in the therapy of chronic pancreatitis. Best Pract Res Clin Gastroenterol. 2008;22:145–65.
8. Brand B, Kahl M, Sidhu S, et al. Prospective evaluation of morphology, function, and quality of life after extracorporeal shockwave lithotripsy and endoscopic treatment of chronic pancreatitis. Am J Gastroenterol. 2000;95:3428–38.

9. Rosch T, Daniel S, Scholz M, et al. Endoscopic treatment of chronic pancreatitis: a multicenter study of 1000 patients with long term follow up. Endoscopy. 2002;34(10):765–71.
10. Tadenuma H, Ishihara T, Yamaguchi T, et al. Long term results of extracorporeal shockwave lithotripsy and endoscopic therapy for pancreatic stones. Clin Gastroenterol Hepatol. 2005;3:1128–35.
11. Tandan M, Reddy DN, Darisetty S, et al. Extracorporeal shock wave lithotripsy and endotherapy for pancreatic calculi—a large single centre experience. Indian J Gastroenterol. 2010;29:143–8.
12. Dumonceau JM, Deviere J, Moine OL, et al. Endoscopic pancreatic drainage in chronic pancreatitis associated with ductal stones: long-term results. Gastrointest Endosc. 1996;43:547–55.
13. Smits M, Rauws E, Tytgat G, Huibregtse K. Endoscopic treatment of pancreatic stones in patients with chronic pancreatitis. Gastrointest Endosc. 1996;43:556–60.
14. Maydeo A, Bhandari S, Bapat M. Endoscopic balloon sphincteroplasty for extraction of large radiolucent pancreatic duct stones (with videos). Gastrointest Endosc. 2007;70(4):798–802.
15. Merill JT, Mullady DK, Early DS, et al. Timing of endoscopy after extracorporeal shock wave lithotripsy for chronic pancreatitis. Pancreas. 2011;40(7):1087–90.
16. Dumonceau JM1, Delhaye M, Tringali A, Dominguez-Munoz JE, Poley JW, Arvanitaki M, Costamagna G, Costea F, Devière J, Eisendrath P, Lakhtakia S, Reddy N, Fockens P, Ponchon T, Bruno M. Endoscopic treatment of chronic pancreatitis: European Society Of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2012;44(8):784–800.
17. Maydeo A, Soehendra N, Reddy N, Bhandari S. Endotherapy for chronic pancreatitis with intracanalar stones. Endoscopy. 2007;39:653–58.
18. Guda NM, Partington S, Freeman ML. Extracorporeal shock wave lithotripsy in the management of chronic calcific pancreatitis: a meta analysis. JOP. 2005;6:6–12.
19. Choi KS, Kim MH. Extracorporeal shock wave lithotripsy for the treatment of pancreatic duct stones. J Hepatobiliary Pancreat Surg. 2006;13:86–93.
20. 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.
21. Karasawa Y, Kawa A, Aoki Y, et al. Extracorporeal shock wave lithotripsy of pancreatic duct stones and patient factors related to stone disintegration. J Gastroenterol. 2002;37:369–75.
22. 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.
23. Dumonceau JM, Costamagna G, Tringali A, et al. Treatment of painful calcified chronic pancreatitis: extracorporeal shock wave lithotripsy versus endoscopic approach treatment: a randomized controlled trial. Gut. 2007;56:545–52.
24. Kozarek RA, Brandabur JJ, Ball TJ, et al. Clinical outcomes in patients who undergo extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc. 2002;56:496–500.
25. Farnbacher MJ, Shoen C, Rabenstein T, Benninger J, Hahn E, Schneider T. Pancreatic duct stones in chronic pancreatitis: criteria for treatment intensity and success. Gastrointest Endosc. 2002;56:501–6.
26. Adamek HE, Jakobs R, Buttman A, Adamek MU, Schneider ARJ, Reimann JF. Long term follow up of patients with chronic pancreatitis and pancreatic stones treated with extracorporeal shock wave lithotripsy. Gut. 1999;45:402–5.
27. Costamagna G, Gabbrielli A, Mutigani M, et al. Extracorporeal shock wave lithotripsy of pancreatic stones in chronic pancreatitis: immediate and medium term results. Gastrointest Endosc. 1997;46:231–6.
28. Tandan M, Reddy DN, Talukdar R, et al. Long term clinical outcomes of extracorporeal shockwave lithotripsy in painful chronic pancreatitis. Gastrointest Endosc. 2013;78(5):726–33.
29. Attwell AR, Brauer BC, Chen YK, et al. Endoscopic retrograde cholangiopancreatograpy with per oral pancreatoscopy for calcific chronic pancreatitis using endoscope and catheter based pancreatoscopes: a 10-year single-center experience. Pancreas. 2014;43(2)268–74.
30. Jablonska B. Is endoscopic therapy the treatment of choice in all patients with chronic pancreatitis? World J of Gastroenterol. 2013;19(1):12–6.
31. Dite P, Ruzicka M, Zboril V, Nonotny IA. Prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy. 2003;35:553–8.
32. Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancretitis: a prospective randomized trial. N Eng J Med. 2007;356:676–84.
33. Sauer BG, Gurka MJ, Ellen K, et al. Effect of pancreatic duct stent diatmeter on hospitalization in chronic pancreatitis: does size matter? Pancreas. 2009;38:728–31.
34. Kasmin FE1, Siegel JH. Endoscopic therapy for chronic pancreatitis. Surg Clin North Am. 2001;81(2):421–30.
35. Costamagna G, Bulajic M, Tringali A, et al. Multiple stenting of refractory pancreatic duct strictures in severe chronic pancreatitis: long-term results. Endoscopy. 2006;38:254–9.
36. Shen Y, Liu M, Chen M, et al. Covered metal stent or multiple plastic stents for refractory pancreatic ductal strictures in chronic pancreatitis: a systemic review. Pancreatology. 2014;14:87–90.

14 Idiopathic Acute Pancreatitis and Sphincter of Oddi Dysfunction: Diagnostic and Therapeutic Role of ERCP and Sphincter of Oddi Manometry

Ji Young Bang and Gregory A. Coté

Case Presentation

A 44-year-old female presents to the office 1 month following an episode of acute pancreatitis (AP). She denies a history of alcohol use and smoking, has no family history of pancreatitis, and takes no medications. At the time of her presentation, serum liver chemistries, calcium, and triglyceride levels were normal; serum lipase was more than three times the upper limit of normal. At the time of admission, a transabdominal ultrasound (US) showed changes of prior cholecystectomy; this had been performed for intermittent abdominal pain and suspected chronic cholecystitis 5 years ago. The common bile duct was poorly visualized but felt to be normal in diameter. During her admission, a contrast-enhanced abdominal computed tomography (CT) revealed peripancreatic stranding consistent with interstitial AP. There was no evidence of chronic pancreatitis or other structural abnormalities.

She has fully recovered from this recent episode of AP, but now reports intermittent episodes of transient, mild epigastric pain, each lasting 15–60 min. She is asymptomatic in the office, but concerned for her risk of permanent damage to her pancreas, and fears recurrence of the severe abdominal pain that prompted admission with AP. She is diagnosed with idiopathic AP. What is your diagnostic and therapeutic approach?

Introduction

AP is an acute inflammatory process of the pancreas that may arise from a multitude of etiologies. Its short and long-term morbidity is highly variable, and the mortality rate is at least 1 % [1–5]. Pancreatitis (acute and chronic) is the most common inpatient gastrointestinal disease, accounting for more than 250,000 hospitalizations annually in the USA [1, 6, 7].

Diagnosis and Initial Evaluation

Patients with AP usually present with abrupt onset of epigastric pain, often radiating to the back, and associated with nausea/vomiting. Symptoms may be present for minutes to days before patients present for medical attention; in some cases, particularly in individuals who have

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suffered previous episodes, patients will manage AP at home without ever seeking medical attention. This poses a unique challenge in defining a patient with recurrent AP (RAP), if only one episode was worked up in a medical facility. In addition to symptoms suggestive of AP, a definitive diagnosis requires a substantial (> 3 × upper limit of normal) elevation of serum lipase or amylase, with or without radiologic confirmation [8].

The most common (~ 70 % in the USA) causes of AP are gallstones and alcohol. While there is no clear threshold above which alcohol may cause AP, alcohol-induced pancreatitis is often self-evident following a thorough history. Gallstone pancreatitis should be suspected in the setting of an intact gallbladder or when alanine aminotransferase (ALT) is elevated to > 3 × upper limit of normal, which has a positive predictive value of 95 % [9]. However, AP of any etiology may cause extrinsic compression of the extrahepatic biliary tree, leading to mild elevation in liver chemistries or even common bile duct dilation. Thus, mild elevation in liver chemistries is not pathognomonic for gallstone pancreatitis.

Other etiologies should be considered when neither gallstones nor alcohol is probable. These may include medications, hypertriglyceridemia, hypercalcemia, infections (viral, bacterial, fungal), autoimmune/inflammatory diseases such as autoimmune pancreatitis or systemic lupus erythematosus, ischemia, and postoperative or other trauma (Table 14.1) [8, 10–19]. Consequently, for patients presenting with their first episode of AP, the initial management strategy must encompass a thorough history and physical examination, basic laboratories including liver chemistries, serum calcium and triglyceride levels, as well as an US and/or contrast-enhanced CT of the abdomen (Fig. 14.1) [1, 14, 20].

Transabdominal US is a low-cost and widely available test that has reasonable sensitivity for detecting gallbladder stones. However, its sensitivity for detecting choledocholithiasis and common bile duct dilation is limited, particularly in obese individuals. Transabdominal US is also limited during episodes of AP when patients are less compliant with deep probing of the upper abdomen using the US transducer [8, 21–24]. CT is usually not necessary or helpful during the initial 72 h of AP. Iodinated contrast may precipitate renal failure, and it is inaccurate in gauging the severity of AP at this early stage, particularly the presence of local complications. On the other hand, contrast-enhanced abdominal CT is useful when the diagnosis is unclear after history and routine laboratory tests. CT may identify occult pancreatic tumors and local complications of AP such as peripancreatic fluid collections and pancreatic necrosis, and thus is also helpful if the patient is not improving after the initial 48–72 h of hospitalization [21].

What is the Role of Endoscopic Retrograde Cholangiopancreatography (ERCP) Following a Single Episode of Acute Pancreatitis?

Given the risks of iatrogenic pancreatitis, among others, endoscopic retrograde cholangiopancreatography (ERCP) is typically reserved for patients with a high suspicion of gallstone-induced AP with ongoing biliary obstruction or cholangitis [25]. Other reasonable indications for ERCP following a single episode of AP include radiographic demonstration of a main pancreatic duct stricture with upstream dilation, suspicion of main duct intraductal papillary mucinous neoplasm (IPMN), main pancreatic duct stones, or a suspected ampullary tumor. ERCP is rarely performed outside of these indications (Table 14.2) given ERCP-specific risks, the availability of less invasive imaging such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS), and the knowledge that the majority of individuals with a single episode of idiopathic AP will not progress to a second episode.

An empiric biliary sphincterotomy may be appropriate when gallstone pancreatitis is highly suspected. In patients with an intact gallbladder, the prevalence of occult biliary sludge (suspension of crystals and other material in bile) or microlithiasis (small stones < 3 mm in diameter) may be as high as 75 % [26, 27]. The probability of microlithiasis as a cause for pancreatitis is

Table 14.1 Etiologies of acute pancreatitis

Cause	Relative Frequency (% of all AP unless stated otherwise)
Gallstones	40–70 %
Alcohol	25–35 %
Genetic mutations	
PRSS1 (Cationic trypsinogen encoding gene; "hereditary pancreatitis")	
Cystic fibrosis (CFTR)	
SPINK1 (Serine peptidase inhibitor Kazal type 1)	
CTRC (Chymotrypsin C)	
Alpha-1 antitrypsin deficiency	
Metabolic	
Hypertriglyceridemia	1–4 %
Hypercalcemia	< 1 %
Drugs	0.2–6 %
Azathioprine	
6-Mercaptopurine	
Proton pump inhibitors	
Loop diuretics	
Trimethoprim-Sulfamethoxazole	
Mesalamine	
ACE inhibitors	
Statins	
GLP-1 inhibitors	
Infection/Toxin	4 %
Bacterial: *Mycoplasma, Legionella*	
Viral: Mumps, Hepatitis B, VZV, Coxsackie	
Parasites: Ascaris	
Scorpion bite	
Organophosphate insecticides	
Autoimmune/inflammatory disorders	
Celiac disease	HR 2.85
SLE	1/1000[a]
Autoimmune pancreatitis	5 %
Obstructive	2–3 %
Neoplasm (pancreas, ampullary, bile duct)	
Intraductal papillary mucinous neoplasm (main duct or side branch)	
Pancreas divisum	
Annular pancreas	
Anomalous pancreatobiliary junction	
Sphincter of Oddi dysfunction[b]	
Trauma/Iatrogenic (postoperative, post-ERCP)	3 %
Tropical	
Smoking	RR 2.29

VZV varicella zoster virus, *HR* Hazard ratio, *RR* Relative Risk

[a] Annual incidence of AP was 1 in 1000 in patients with SLE

[b] The clinical significance and implications of sphincter of Oddi dysfunction are discussed at length later in this chapter

increased when microcrystals are identified from bile or duodenal aspirate; although these studies were primarily completed in an era when MRCP and EUS were in their nascence [20, 28, 29]. We recommend empiric cholecystectomy or empiric biliary sphincterotomy in patients who are post-

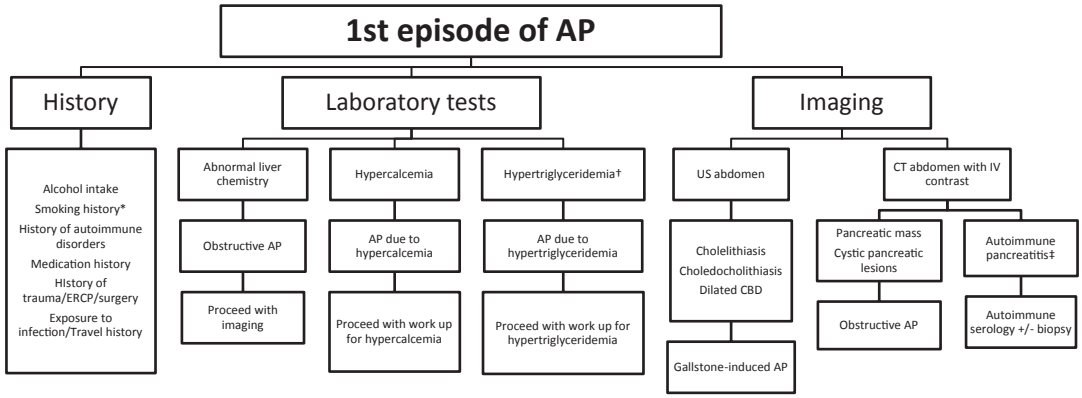

Fig. 14.1 A flow diagram showing the initial investigations that should be performed for acute pancreatitis. * Smoking is an independent risk factor for AP; † A specific threshold for serum triglycerides precipitating AP is unknown, but typically considered in cases of serum triglycerides ≥ 1000 mg/dl; ‡ CT imaging may be suggestive of autoimmune pancreatitis

Table 14.2 Indications for ERCP following the first episode of acute pancreatitis

High suspicion for gallstone-induced acute pancreatitis
Elevation in total bilirubin > 4 mg/dL in association with acute episode
Common bile duct stone visualized on other imaging
Common bile duct dilation, particularly in the setting of an intact gallbladder, with elevated total bilirubin
Cholangitis
Suspicion of obstructive etiology for acute pancreatitis
Concomitant chronic pancreatitis with obstructing pancreatic duct stone or stricture visualized on other imaging
Periampullary tumor identified or suspected on other imaging
Otherwise unexplained main pancreatic duct dilation, such as suspected main duct intraductal papillary mucinous neoplasm (IPMN)

cholecystectomy when gallstone pancreatitis is likely after the initial presentation (transient elevation in liver chemistries with or without bile duct dilation) or when CT, US, MRCP, or EUS imaging suggests gallbladder or biliary sludge.

Case Continued

After the initial consultation, no additional diagnostic testing or intervention is recommended. The patient is readmitted with a second episode of AP 6 months later, again having normal serum liver chemistries, calcium and triglycerides during the admission. A contrast-enhanced CT scan confirms interstitial pancreatitis, but no other abnormalities. Her symptoms resolve within 2 weeks. Now what do you recommend?

Recurrent Acute Pancreatitis

Up to 20–30% of patients following a single episode of AP suffer one or more recurrent episodes, which is termed recurrent AP (RAP), and even develop full-blown chronic pancreatitis in 10–25% of cases (Fig. 14.2) [26, 30, 31]. Additionally, when an etiological factor cannot be elucidated despite performing all the initial routine investigations stated above, this is defined as idiopathic RAP (iRAP). RAP is idiopathic in approximately 20% of cases [14, 32] and since patients with iRAP have a high risk of suffering additional episodes, more advanced diagnostic testing is warranted. Issues with the literature about iRAP abound mainly from lack of consensus regarding the exact definition of idiopathic, evolving notions of what studies should

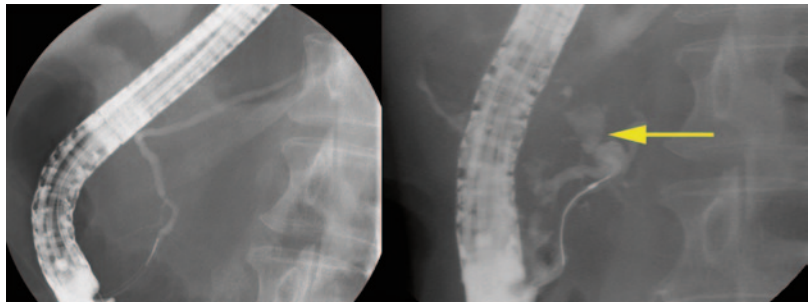

Fig. 14.2 Progression from recurrent acute to chronic pancreatitis. A 53-year-old woman underwent ERCP with sphincter of Oddi manometry after three documented episodes of unexplained acute pancreatitis. At the time of her initial ERCP (*left image*), pancreatography was unremarkable. She underwent dual sphincterotomies for the treatment of pancreatic sphincter of Oddi dysfunction, and recovered uneventfully. She developed two additional episodes in the ensuing 16 months, and a follow-up CT scan and ERCP (*right image*) demonstrated severe chronic pancreatitis with obstructing pancreatic duct stone (*arrow*)

be performed before deeming the etiology of RAP as idiopathic, lack of consensus regarding the threshold of alcohol intake and triglyceride level that should be considered as etiologic for RAP, and unclear appreciation for whether some findings are incidental or truly etiologic (e.g., pancreas divisum, sphincter of Oddi dysfunction (SOD)) [33].

In the remainder of this chapter, we will frame the discussion of ERCP in the setting of iRAP around two fundamental questions: first, what is the diagnostic and prognostic significance of diagnostic ERCP and sphincter of Oddi manometry (SOM) in identifying a cause for iRAP? Second, what is the therapeutic impact of endoscopic sphincterotomy (biliary, pancreatic, or both) in preventing episodes of AP? Additionally, we will briefly discuss both biliary and pancreatic SOD with respect to endoscopic therapy.

What Initial Diagnostic Studies Should Be Performed in Idiopathic RAP?

There is little consensus defining the "minimum" diagnostic work-up required to classify a patient with AP as idiopathic. Typically, AP is deemed idiopathic when "routine" diagnostics are negative. Most would agree this includes a thorough history and physical examination including a focused social history for exposure to alcohol and smoking, review of medications, and laboratories to rule out hypertriglyceridemia and hypercalcemia. With the advent of more sophisticated tests such as secretin-enhanced MRCP (S-MRCP), EUS, and testing for less common causes such as autoimmune pancreatitis and genetic mutations, an etiology can be found in 38–76 % of those initially deemed idiopathic [20, 34]. Therefore, one or more of these tests should be strongly considered in a patient having two or more unexplained episodes [14, 20]. The most common etiologies in patients initially diagnosed with idiopathic AP include microlithiasis/occult choledocholithiasis [34, 35], congenital anomalies of the pancreas such as pancreas divisum and annular pancreas [36], choledochocele [37], anomalous pancreatobiliary junction [38], chronic pancreatitis with main pancreatic duct stricture [39], genetic abnormalities [40], and SOD (Fig. 14.3) [41]. The role of SOD as a cause or consequence of RAP is complex with a recent trial demonstrating no incremental benefit of pancreatic sphincterotomy over biliary sphincterotomy in patients with RAP and pancreatic SOD [42]. Prior to performing ERCP with or without SOM, we advocate the use of one or more of the following less invasive diagnostic modalities to further characterize patients with iRAP.

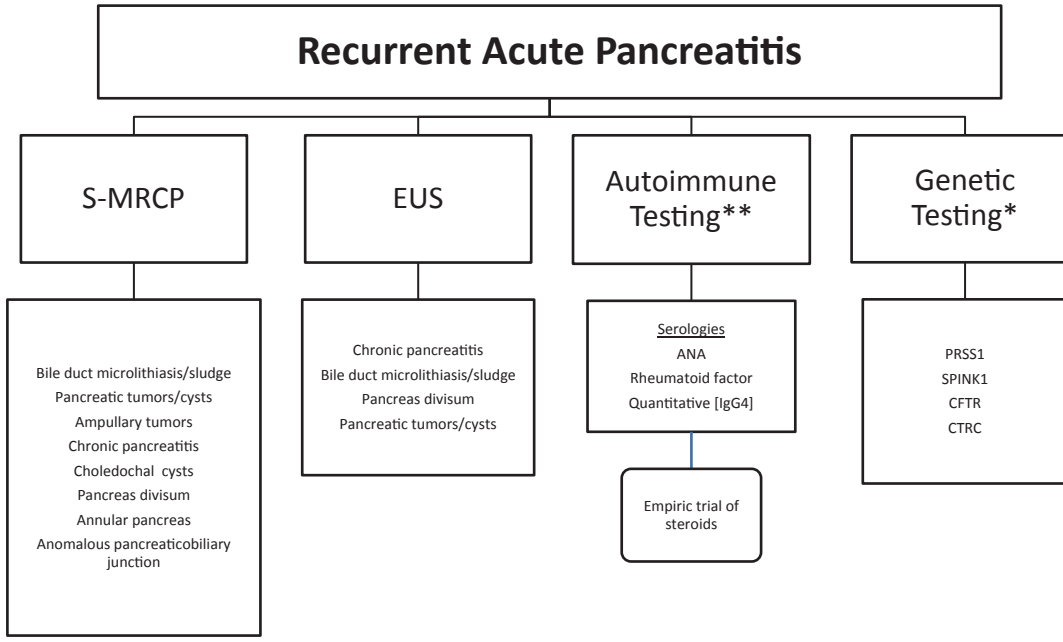

Fig. 14.3 Second tier investigations indicated in patients with recurrent acute pancreatitis
* Consider genetic testing in patients < 40 years of age with family history of acute pancreatitis, after negative autoimmune serologies and ruling out structural abnormalities with S-MRCP or EUS
** Radiographic features such as mass-like lesions or a sausage-shaped pancreas often seen in this male-predominant disease

Magnetic Resonance Cholangiopancreatography with Secretin (S-MRCP)

MRCP has a very high sensitivity (95%) and specificity (97%) for detecting pancreatobiliary abnormalities [43]. The concomitant administration of supraphysiologic secretin promotes juice secretion and bicarbonate production from centroacinar and pancreatic ductal cells, thereby improving visualization of the main pancreatic duct and side branches [44]. In studies comparing the diagnostic yield of S-MRCP with ERCP for detecting pancreatobiliary abnormalities in patients with iRAP, no significant differences were found (66% for S-MRCP, 64% for ERCP) [44]. Also, S-MRCP has 100% specificity (although low sensitivity of 57%) for detecting obstructing lesions in the pancreatobiliary tree [45] and is associated with minimal risk of pancreatitis as opposed to ERCP [42, 45]. MRCP with magnetic resonance imaging may additionally identify occult pancreatic tumors, pancreas divisum, biliary sludge, or IPMN as a potential cause of pancreatitis, and some of these abnormalities would obviate the need for ERCP and prompt alternative interventions such as surgery. The incremental benefit of S-MRCP over MRCP was recently confirmed in a study of 252 patients with acute or acute recurrent pancreatitis who all underwent MRCP, S-MRCP, and ERCP within 30 days of each other with images reviewed by blinded experts [46]. Sensitivity of MRCP increased from 47 to 66% ($p < 0.0001$), while specificity decreased insignificantly from 90 to 85% following secretin administration. Complete visualization of the pancreatic duct was possible in more patients using secretin (55% versus 26%, $p < 0.0001$). S-MRCP facilitates the diagnosis of mild chronic pancreatitis and pancreas divisum by highlighting ductal anatomy [47–49] and may also be useful for diagnosing SOD, although additional studies are needed [44, 50, 51].

Endoscopic Ultrasound (EUS)

Compared to ERCP, EUS is a less invasive endoscopic modality that provides excellent imaging of the pancreatic parenchyma, pancreatic duct, and extrahepatic biliary tree, with no risk of AP in the absence of pancreatic fine needle aspiration or biopsy. EUS may identify a definitive etiology in 68–88% of patients with idiopathic AP [20, 52–56], and is particularly useful for the detection of occult stones in the gallbladder or common bile duct [52]. Additionally, in patients with idiopathic AP who had previously undergone a cholecystectomy, EUS identified chronic pancreatitis (39%) and pancreas divisum (10%) in these patients [56]. EUS has high sensitivity for detecting pancreatic cancers not visualized on CT [18, 45] as well as early chronic pancreatitis [57]. Therefore, similar to S-MRCP, EUS may identify an etiology for AP that obviates the need for ERCP or SOM.

Genetic Testing

Even in the absence of a family history of pancreatitis or pancreatic cancer, several genetic abnormalities should be considered in adult individuals with iRAP or chronic pancreatitis. These include *PRSS1* (cationic trypsinogen encoding gene), SPINK1 (serine peptidase inhibitor Kazal type 1), *CTRC* (chymotrypsin C gene), and CFTR (cystic fibrosis transmembrane conductance regulator protein) mutations [58]. There is emerging evidence highlighting the importance of newly discovered mutations in *CLDN2* (claudin) and *PRSS1-PRSS2* genes [59]. Patients with genetic abnormalities are more likely to present with AP at a younger age (although not necessarily during childhood), have pancreas divisum, and progress to chronic pancreatitis [49]. The long-term risk of pancreatic cancer requires further study, although mutations in *PRSS1* probably confer a lifetime risk of 40% [58].

In an adult population with iRAP, the timing and need for genetic testing are unclear. Since many patients with genetic abnormalities do not have a family history, this should not be considered a *sine qua non*. The treating physician must also consider the implications on patient anxiety and future insurability, should a mutation be confirmed. Furthermore, complete gene sequencing is now available, and may identify mutations of unknown significance, further confusing the picture [48]. We typically perform genetic testing in the following patients: age < 40 and iRAP after structural abnormalities and autoimmune disease have been excluded, a family history of AP, a recurrent episode of AP after ERCP and cholecystectomy, and also on a case-by-case basis.

Case Continued

Since our patient already suffered two unexplained episodes of AP, she underwent an EUS that showed no evidence of pancreatobiliary malignancy, chronic pancreatitis, pancreas divisum, or occult choledocholithiasis/sludge. Autoimmune serologies (ANA, rheumatoid factor, quantitative IgG4 levels) and ampullary biopsies for IgG4 staining were also normal. Genetic testing was not performed. The treating physician decided to proceed with ERCP and SOM.

What is the Role of ERCP in Idiopathic Acute Pancreatitis?

ERCP has three potential roles in patients with idiopathic AP: (1) identifying a clear etiology via cholangiopancreatography with or without tissue sampling; (2) evaluating for elevation in basal biliary and pancreatic sphincter pressures (i.e., SOD via SOM); (3) therapy via sphincterotomy, stone extraction, stricture dilation, stent placement, or some combination of the above [20].

ERCP as a Diagnostic Test for Idiopathic RAP

With improvements in cross-sectional imaging and EUS, the diagnostic yield of ERCP among patients with iRAP has likely decreased; however, this requires further investigation specifically

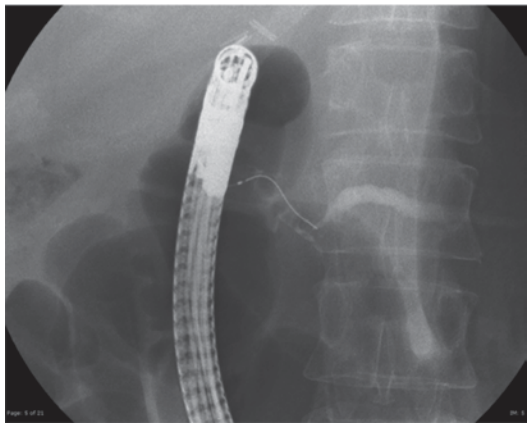

Fig. 14.4 Complete pancreas divisum. The minor papilla is cannulated while the duodenoscope is in the long position. Opacification of the dorsal pancreatic duct across the spine confirms the diagnosis of complete pancreas divisum in this patient with RAP and previously unremarkable CT scan and EUS

among iRAP patients who have undergone thorough evaluation with MRCP, EUS, and laboratories that include autoimmune serologies and genetics before ERCP. ERCP may identify the underlying etiology for iRAP in 38–79% of cases; however, this is based on older studies before the routine use of MRCP and EUS. The diagnostic yield varies widely depending on whether the gallbladder is intact [15, 20, 34, 60–64]. The likelihood of occult choledocholithiasis or microlithiasis (biliary crystals) is highest in patients with an intact gallbladder (50%) compared to nearly none in patients post-cholecystectomy [20, 64], and structural abnormalities such as obstructing tumors and pancreas divisum are more likely in older (age > 60) individuals [15]. The most common abnormalities discovered during ERCP for iRAP include SOD found in 15–65% of patients and pancreas divisum in 1–23% of patients (Fig. 14.4) [20, 34, 60, 62–64]. We recommend proceeding to ERCP with SOM in patients with iRAP only after they have undergone further laboratory testing for autoimmune disease and advanced imaging such as EUS, MRI/MRCP, or both [20, 65–67].

What is the Role of Empiric Biliary Sphincterotomy?

Studies evaluating the efficacy of biliary, pancreatic, or dual sphincterotomies for the treatment of iRAP are limited by small sample sizes and short-term follow-up. Since microlithiasis or occult choledocholithiasis is often implicated as the underlying etiology especially in patients with an intact gallbladder, empiric biliary sphincterotomy has been advocated in certain cases (Fig. 14.5). This is extrapolated from studies demonstrating the efficacy of empiric cholecystectomy for iRAP. These older studies were performed in an era of inferior cross-sectional imaging and without EUS—when false negative rates for detecting cholelithiasis were higher. The efficacy of empiric cholecystectomy is substantially reduced when the patient has normal or near-normal liver chemistries and no evidence of gallstones on

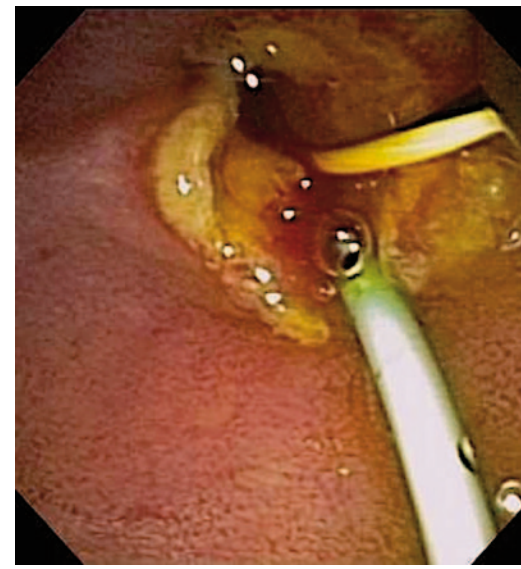

Fig. 14.5 Empiric biliary sphincterotomy. A pull-type biliary sphincterotomy has been performed in a 26-year-old woman following her second episode of acute pancreatitis. She had gallstones and elevated liver chemistries at the time of her first episode, prompting cholecystectomy. Nevertheless, a second episode occurred 5 months later during which her liver chemistries were raised and transabdominal US revealed a common bile duct of 11 mm. Biliary sphincterotomy was performed for high suspicion of sludge/microlithiasis-induced RAP. Note the presence of a prophylactic pancreatic duct stent

transabdominal US [27]. The likelihood of recurrent pancreatitis after cholecystectomy was significantly higher (61%) when neither was present compared to patients with both these abnormalities (9%). While a comparable study of biliary sphincterotomy is lacking, a small number of patients with iRAP and normal SOM who were randomized to biliary sphincterotomy ($n=11$) or sham ($n=9$) showed similar rates of recurrent pancreatitis during follow-up (50% for both groups) [42]. Other studies suggest a benefit of biliary sphincterotomy when microlithiasis is suspected [15]. We recommend empiric biliary sphincterotomy when there is a reasonable suspicion for microlithiasis. This would include transient fluctuation in liver chemistries in association with episodes of AP, or a history of gallstone pancreatitis that preceded cholecystectomy. This recommendation is indirectly supported by epidemiological data showing a reduction in repeat hospitalizations when ERCP is performed during the initial admission for gallstone pancreatitis [44]. Empiric biliary sphincterotomy should not be performed in patients with normal liver tests.

Sphincter of Oddi Dysfunction

SOD is an obstructive disorder of the sphincter of Oddi whose pathophysiology and clinical relevance are poorly understood. By definition, SOD is a functional obstruction, and patients do not present with jaundice or complete occlusion of pancreatic outflow. Dysfunction may involve the sphincter muscle overlying the pancreatic duct, common bile duct, and/or common channel [14]. Biliary and pancreatic SOD are divided clinically into types I–III. Biliary type I is defined as biliary-type pain with elevated ALT, AST, or alkaline phosphatase to greater than 1.5 times the upper limit of normal on one occasion, and bile duct >10 mm. Type II is pain with one of the other two criteria for type I. Type III is pain only. Pancreatic SOD classification is analogous with type I defined as pancreatitis with dilated pancreatic duct >6 mm in the head or 5 mm in the body [68]. Manometrically, SOD is typically defined as an elevation in basal sphincter pressure >40 mmHg, although some have argued that peak pressures and phasic wave frequency should be considered [10]. In theory, pancreatic SOD causes elevation in intraductal pressure, thereby triggering premature activation of pancreatic enzymes and AP. On the other hand, recurrent episodes of AP (or perhaps early chronic pancreatitis) may trigger a fibroinflammatory response, leading to elevation in basal sphincter pressure as a result rather than a cause of iRAP.

In both biliary and pancreatic SOD, the approximate frequency of abnormal SOM findings may vary with the type: in biliary, 75–95% for type I, 55–65% for type II, and 25–60% for type III and in pancreatic, 100% of type I, 67% of type II, and 59% of type III [68, 69]. Regardless of manometry findings, over 90% of patients with biliary type I SOD respond to biliary sphincterotomy and SOM is not necessary in these patients [70]. Manometric findings do seem to predict response to biliary sphincterotomy in biliary type II patients as 50–70% with abnormal SOM improve, while less than 30% respond to sphincterotomy with normal SOM. A recent randomized sham-controlled trial of biliary type III patients found that SOM findings did not predict response to treatment and sphincterotomy did not perform better than sham [71]. Therefore, ERCP with SOM and empiric sphincterotomy are not recommended in type III patients.

Medical therapy can be entertained before ERCP with SOM in biliary type II and III patients. Sublingual nifedipine and nitrates decrease sphincter of Oddi pressure, and several studies have demonstrated pain relief in 67–75% patients with suspected or manometrically confirmed SOD [72–74]. Despite lack of long-term data and patient's intolerance to medications, the relative safety of medical therapy certainly makes it reasonable to try before proceeding with ERCP and SOM.

What Is the Relationship Between Sphincter of Oddi Dysfunction and Acute Pancreatitis?

The most commonly implicated pathology following ERCP in patients with idiopathic AP who have undergone prior cholecystectomy is SOD,

particularly in younger (age < 60) individuals [15]. Unfortunately, despite declaring SOD as the "cause" for RAP in 15–50% of cases, the efficacy of treatment (i.e., endoscopic sphincterotomy or surgical sphincteroplasty) is poorly defined.

There is a high frequency (15–65%) of SOD among patients with iRAP, but the long-term efficacy of biliary, pancreatic, and dual sphincterotomies is debated. Multiple studies, the majority having a cohort design, suggest response to biliary sphincterotomy alone and an incremental benefit of dual over biliary sphincterotomy [18, 47, 75–78]. To date, there are two published, randomized clinical trials on this topic. Jacob et al. randomized 34 patients with iRAP to serial pancreatic duct stenting versus sham and observed a reduction in the rate of recurrent AP from 53 to 11% in the stent group during a mean follow-up time of 33 months [47]. In a larger clinical trial of 69 patients with iRAP and pancreatic SOD randomized to biliary sphincterotomy or dual sphincterotomy, there was no significant difference in recurrence rates of AP (close to 50% in each group) after a minimum follow-up of 12 months [42]. However, there was a high rate of recurrent/persistent pancreatic SOD in the subgroup who underwent repeat ERCP with SOM, including those who had undergone previous pancreatic sphincterotomy. Compared to patients with normal basal pancreatic sphincter pressures, pancreatic SOD was a significant, independent risk factor (hazard ratio 4.3, 95% confidence interval 1.3–14.5) for occurrence of AP during follow-up, regardless of treatment allocation. Therefore, while pancreatic sphincterotomy did not prevent subsequent episodes of AP, this may have resulted from inadequate separation of the pancreatic sphincter muscle, high rates of re-stenosis, or the possibility that pancreatic SOD was not the etiology of iRAP but simply a marker for more aggressive disease. All three scenarios likely apply, but additional studies are needed in this area. Whether biliary sphincterotomy alone reduces risk of RAP is unclear and should be evaluated in a sham-controlled study. At this point, we cannot endorse empiric pancreatic sphincterotomy for iRAP regardless of the manometry results.

What Is the Technique of Pancreatic Sphincterotomy and Sphincter of Oddi Manometry?

Pancreatic Sphincterotomy

There are two accepted techniques for performing pancreatic sphincterotomy. First, a needle knife sphincterotomy may be performed after a pancreatic stent is deployed. This approach uses the stent as a "backboard" and a guide to direct the cut. Alternatively, a standard pull-type sphincterotome may be used, similar to biliary sphincterotomy. The cut is typically directed in the one o'clock direction, and the top margin of the sphincterotomy is less delineated than the biliary sphincter complex (Video 14.1).

Sphincter of Oddi Manometry

Medications that could interfere with the SO pressure should be held for at least 8–12 h before SOM. These include calcium channel blockers, anticholinergics, nitrates, and glucagon which lower the pressure and narcotics and cholinergic medications that stimulate the sphincter muscle [69]. If glucagon has been administered, SOM should be postponed for 8–15 min.

The majority of SOM is performed using a triple lumen, aspiration catheter (Cook Medical, Bloomington, Indiana, United States) through a water perfused pneumohydraulic system. Aspiration during the process of perfusion manometry (specifically the pancreatic sphincter/duct) minimizes the likelihood of post-ERCP pancreatitis [57]. The aspiration catheter has three lumens: one lumen has an end port to accommodate a guidewire (0.018″ or 0.021″) or contrast injection; two lumens have side ports to accommodate water perfusion (0.25 mL/min). From the catheter tip, there is one red ring (distal side port), one black ring, a second red ring (proximal side port), and then seven

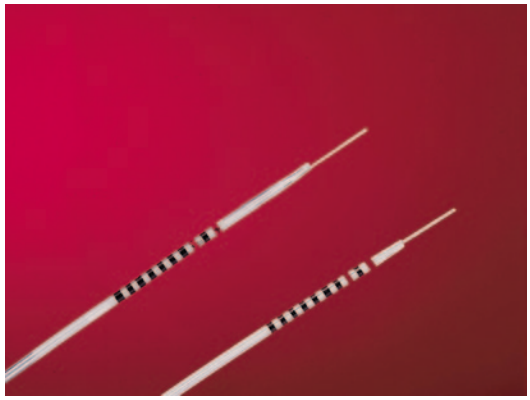

Fig. 14.6 Aspiration-type manometry catheter. The triple lumen aspiration catheter accommodates a guidewire (0.018″ or 0.021″) or contrast through the end port at the tip (*wire shown*). Each ring is separated by 1 mm, with the red rings indicating the location of the distal and proximal side ports used for water perfusion during sphincter of Oddi manometry

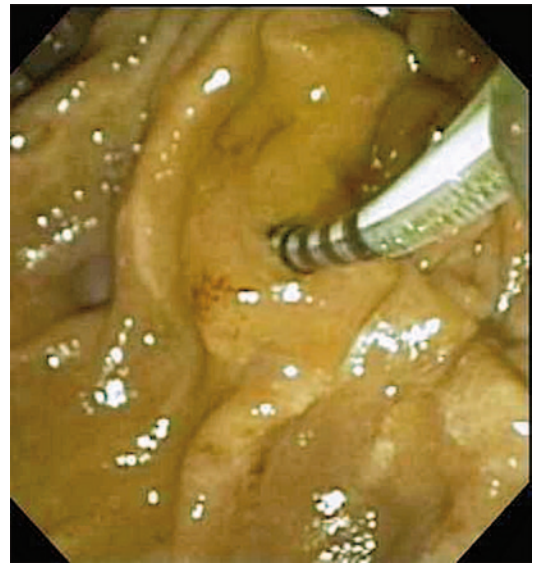

Fig. 14.7 Sphincter of Oddi manometry—endoscopy. The aspiration-type catheter is slowly pulled across the sphincter complex, using the rings to denote its depth

additional black rings (Fig. 14.6). Each ring is separated by 1 mm. A solid-state catheter provides similar results to the aspiration catheter system and with comparable risks [79]. All patients undergoing SOM should receive rectal indomethacin and placement of a prophylactic pancreatic duct stent to minimize the risk of post-ERCP pancreatitis.

Among patients with iRAP, SOM should be performed at the time of the index ERCP, assuming an alternative etiology is not identified during cholangiopancreatography. Ideally, the bile duct and pancreatic duct should be cannulated and opacified to rule out alternative etiologies for RAP. Free cannulation using the manometry catheter is preferred, and ideally manometry of both the pancreatic and biliary sphincters should be performed during the same session. A guidewire may be used to facilitate cannulation, but the impact of the guidewire on subsequent manometry tracings is poorly studied. Opacification of the pancreatic duct should be minimized although it is important to ensure that the manometry catheter is not embedded into a side branch. An adequate pancreatogram only requires opacification to the proximal body of the pancreas to rule out complete pancreas divisum, main pancreatic duct stricture, or anomalous pancreatobiliary union, realizing that a pre-procedure MRI/MRCP should rule these out with high (>80%) sensitivity [80].

The technique of SOM is fairly straightforward. For reference, a baseline pressure in the duodenum should precede cannulation of each duct. After deep cannulation and a normal cholangiogram or pancreatogram are achieved, the manometry catheter should be slowly withdrawn while the pressure tracing is observed for changes (Fig. 14.7, Video 14.1). The catheter should be pulled back in 1 mm increments, using the rings as a guide. Of particular importance is the nadir or basal sphincter pressure observed during phasic contractions of the sphincter (Fig. 14.8). If an elevation>40 mmHg is identified, the position should be held for at least 30 s to minimize the likelihood of artifact. As the catheter is withdrawn further, an elevation in the more distal transducer should be observed, and the catheter should again be maintained in position for at least 30 s. Ideally, the transducer is pulled across the sphincter complex twice to confirm the reproducibility of the tracing; in practice, a single pull-through is probably sufficient.

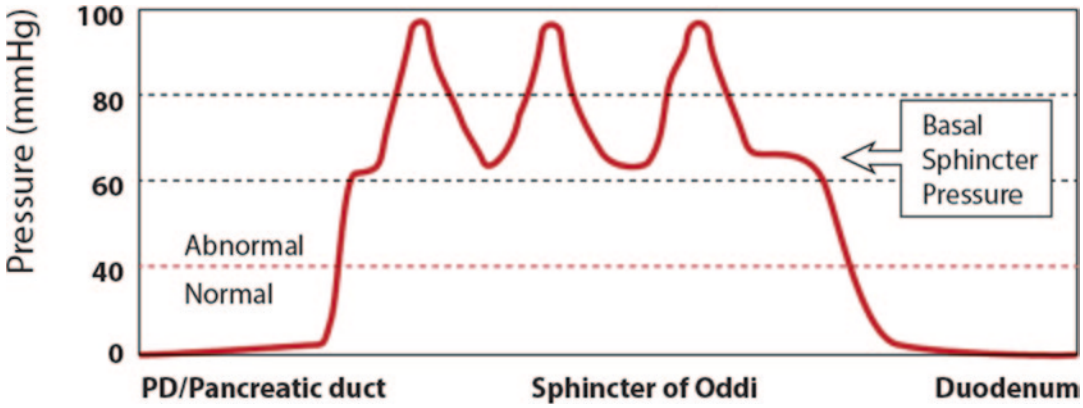

Fig. 14.8 Sphincter of Oddi manometry—tracing. An animated depiction of a typical tracing observed during sphincter of Oddi manometry. Elevation in peak pressures and wave frequency is less important than the basal sphincter pressure. A threshold of 35–40 mmHg defines sphincter of Oddi dysfunction

Case Continued

After thoroughly detailing the potential risks and reviewing the controversial evidence surrounding SOM and sphincterotomy in the setting of unexplained recurrent AP, the patient agreed to undergo the procedure. ERCP demonstrated normal pancreatic and biliary ductal anatomy. Using an aspiration manometry catheter, the basal pancreatic sphincter pressure was 120 mmHg and biliary pressure 60 mmHg. As per the preprocedure discussion, the endoscopist performed a biliary sphincterotomy and placed a temporary prophylactic pancreatic duct stent; pancreatic sphincterotomy was not performed given the weaker level of evidence supporting its benefit. The patient remains in follow-up, having had no recurrent episodes of pancreatitis during the first 6 months after ERCP.

Conclusion

The role of ERCP in the diagnosis and treatment of patients with idiopathic AP continues to evolve. ERCP remains a useful imaging modality in selected cases, but newer and lower risk tests such as MRCP and EUS often identify a clear etiology for AP without the need for ERCP. An empiric biliary sphincterotomy is effective in cases of AP or RAP when microlithiasis is highly probable. Otherwise, if ERCP is performed for iRAP, the endoscopist should be prepared to perform SOM in the same session, assuming no alternative etiology is identified during ductography. Pancreatic SOD connotes a higher risk for subsequent episodes of AP, but the incremental benefit of pancreatic sphincterotomy over biliary sphincterotomy alone in attenuating future episodes remains unproven. Biliary SOD is managed according to the subtype with SOM and biliary sphincterotomy not recommended for type III patients. Given substantial advances in pancreatic imaging and genetics, the current definition of iRAP has become more stringent. Future studies are needed to measure the diagnostic yield and efficacy of ERCP and sphincterotomy (biliary, pancreatic, or both) for patients meeting these strict criteria for iRAP. In addition, the implication of pancreatic SOD on prognosis and treatment options requires further study.

Key Points

- Up to 20% of AP cases are idiopathic.
- Patients with idiopathic AP are at risk for having recurrent episodes and the subsequent development of overt chronic pancreatitis.

- At a minimum, the diagnostic work-up for a patient with AP should include a thorough history (alcohol, smoking and medication use, recent precipitating events such as surgery, family history), physical examination (for stigmata of chronic alcohol use, hyperlipidemia, trauma), basic laboratories (serum calcium and triglycerides), and cross-sectional imaging (transabdominal ultrasound and/or contrast-enhanced CTscan).
- After a single episode of AP, ERCP with empiric biliary sphincterotomy should be reserved for patients with a high suspicion of gallstone pancreatitis, particularly those having antecedent cholecystectomy.
- After two or more episodes of idiopathic AP, additional diagnostics preceding ERCP should include MRCP and/or EUS with consideration for genetic testing even in the absence of a family history or those with adult-onset disease, and a work-up for autoimmune pancreatitis in selected cases.
- Elevation in basal pancreatic sphincter pressure (a.k.a., pancreatic SOD) is associated with a greater likelihood of having recurring episodes of AP.
- Endoscopic pancreatic sphincterotomy is ineffective in attenuating episodes of recurrent AP; this may be related to limitations of the technique in ablating the pancreatic sphincter, or because pancreatic sphincter stenosis represents the consequence as opposed to the cause of AP.
- Of the three types of biliary SOD, manometry is only recommended for type II to guide the need for biliary sphincterotomy. Type I patients should undergo biliary sphincterotomy without manometry while type III patients should not undergo sphincterotomy or manometry.

Video Caption

Video 14.1 Pancreatic sphincterotomy

References

1. Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1252–61.
2. Appelros S, Borgstrom A. Incidence, aetiology and mortality rate of acute pancreatitis over 10 years in a defined urban population in Sweden. Br J Surg 1999;86:465–70.
3. Goldacre MJ, Roberts SE. Hospital admission for acute pancreatitis in an English population, 1963–98: database study of incidence and mortality. Bmj 2004;328:1466–9.
4. Satoh K, Shimosegawa T, Masamune A, Hirota M, Kikuta K, Kihara Y, Kuriyama S, Tsuji I, Satoh A, Hamada S. Nationwide epidemiological survey of acute pancreatitis in Japan. Pancreas 2011;40:503–7.
5. Shen HN, Lu CL, Li CY. Epidemiology of first-attack acute pancreatitis in Taiwan from 2000 through 2009: a nationwide population-based study. Pancreas 2012;41:696–702.
6. Whitcomb DC. Clinical practice. Acute pancreatitis. N Engl J Med 2006;354:2142–50.
7. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the Unit States: 2012 update. Gastroenterology. 2012;143:1179–87.e1–3.
8. Guda NM, Romagnuolo J, Freeman ML. Recurrent and relapsing pancreatitis. Curr Gastroenterol Rep 2011;13:140–9.
9. Wilcox CM, Kilgore M. Cost minimization analysis comparing diagnostic strategies in unexplained pancreatitis. Pancreas 2009;38:117–21.
10. Elta GH. Sphincter of Oddi dysfunction and bile duct microlithiasis in acute idiopathic pancreatitis. World J Gastroenterol 2008;14:1023–6.
11. Gullo L, Migliori M, Olah A, Farkas G, Levy P, Arvanitakis C, Lankisch P, Beger H. Acute pancreatitis in five European countries: etiology and mortality. Pancreas 2002;24:223–7.
12. Gullo L, Migliori M, Pezzilli R, Olah A, Farkas G, Levy P, Arvanitakis C, Lankisch P, Beger H. An update on recurrent acute pancreatitis: data from five European countries. Am J Gastroenterol 2002;97:1959–62.
13. Saraswat VA, Sharma BC, Agarwal DK, Kumar R, Negi TS, Tandon RK. Biliary microlithiasis in patients with idiopathic acute pancreatitis and unexplained biliary pain: response to therapy. J Gastroenterol Hepatol 2004;19:1206–11.
14. Levy MJ, Geenen JE. Idiopathic acute recurrent pancreatitis. Am J Gastroenterol 2001;96:2540–55.
15. Garg PK, Tandon RK, Madan K. Is biliary microlithiasis a significant cause of idiopathic recurrent acute pancreatitis? A long-term follow-up study. Clin Gastroenterol Hepatol 2007;5:75–9.

16. Takuma K, Kamisawa T, Hara S, Tabata T, Kuruma S, Chiba K, Kuwata G, Fujiwara T, Egashira H, Koizumi K, Fujiwara J, Arakawa T, Momma K, Igarashi Y. Etiology of recurrent acute pancreatitis, with special emphasis on pancreaticobiliary malformation. Adv Med Sci 2012;57:244–50.
17. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med 1994;330:1198–210.
18. Wehrmann T. Long-term results (>/=10 years) of endoscopic therapy for sphincter of Oddi dysfunction in patients with acute recurrent pancreatitis. Endoscopy 2011;43:202–7.
19. Vidarsdottir H, Moller PH, Vidarsdottir H, Thorarinsdottir H, Bjornsson ES. Acute pancreatitis: a prospective study on incidence, etiology, and outcome. Eur J Gastroenterol Hepatol. 2013;25:1068–75
20. Wilcox CM, Varadarajulu S, Eloubeidi M. Role of endoscopic evaluation in idiopathic pancreatitis: a systematic review. Gastrointest Endosc 2006;63:1037–45.
21. Draganov P, Forsmark CE. "Idiopathic" pancreatitis. Gastroenterology 2005;128:756–63.
22. Lapis JL, Orlando RC, Mittelstat CA, Staab EV. Ultrasonography in the diagnosis of obstructive jaundice. Ann Intern Med 1978;89:61–3.
23. Pasanen PA, Partanen KP, Pikkarainen PH, Alhava EM, Janatuinen EK, Pirinen AE. A comparison of ultrasound, computed tomography and endoscopic retrograde cholangiopancreatography in the differential diagnosis of benign and malignant jaundice and cholestasis. Eur J Surg 1993;159:23–9.
24. Salem S, Vas W. Ultrasonography in evaluation of the jaundiced patient. J Can Assoc Radiol 1981;32:30–4.
25. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400-15; 1416.
26. Ortega AR, Gomez-Rodriguez R, Romero M, Fernandez-Zapardiel S, Cespedes Mdel M, Carrobles JM. Prospective comparison of endoscopic ultrasonography and magnetic resonance cholangiopancreatography in the etiological diagnosis of "idiopathic" acute pancreatitis. Pancreas 2011;40:289–94.
27. Trna J, Vege SS, Pribramska V, Chari ST, Kamath PS, Kendrick ML, Farnell MB. Lack of significant liver enzyme elevation and gallstones and/or sludge on ultrasound on day 1 of acute pancreatitis is associated with recurrence after cholecystectomy: a population-based study. Surgery 2012;151:199–205.
28. Okoro N, Patel A, Goldstein M, Narahari N, Cai Q. Ursodeoxycholic acid treatment for patients with postcholecystectomy pain and bile microlithiasis. Gastrointest Endosc 2008;68:69–74.
29. Sahoo SK, Tudu D. Role of duodenal bile crystal analysis in idiopathic pancreatitis. Trop Gastroenterol 2001;22:205–6.
30. Nojgaard C, Becker U, Matzen P, Andersen JR, Holst C, Bendtsen F. Progression from acute to chronic pancreatitis: prognostic factors, mortality, and natural course. Pancreas 2011;40:1195–200.
31. Takeyama Y. Long-term prognosis of acute pancreatitis in Japan. Clin Gastroenterol Hepatol 2009;7:S15–7.
32. Ballinger AB, Barnes E, Alstead EM, Fairclough PD. Is intervention necessary after a first episode of acute idiopathic pancreatitis? Gut 1996;38:293–5.
33. Roberts JR, Romagnuolo J. Endoscopic therapy for acute recurrent pancreatitis. Gastrointest Endosc Clin N Am 2013;23:803–19.
34. Kaw M, Brodmerkel GJ, Jr. ERCP, biliary crystal analysis, and sphincter of Oddi manometry in idiopathic recurrent pancreatitis. Gastrointest Endosc 2002;55:157–62.
35. Freund H, Pfeffermann R, Durst AL, Rabinovici N. Gallstone pancreatitis. Exploration of the biliary system in acute and recurrent pancreatitis. Arch Surg 1976;111:1106–7.
36. Dowsett JF, Rode J, Russell RC. Annular pancreas: a clinical, endoscopic, and immunohistochemical study. Gut 1989;30:130–5.
37. Okada A, Higaki J, Nakamura T, Fukui Y, Kamata S. Pancreatitis associated with choledochal cyst and other anomalies in childhood. Br J Surg 1995;82:829–32.
38. Misra SP, Dwivedi M. Pancreaticobiliary ductal union. Gut 1990;31:1144–9.
39. Steer ML, Waxman I, Freedman S. Chronic pancreatitis. N Engl J Med 1995;332:1482–90.
40. Perrault J. Hereditary pancreatitis. Gastroenterol Clin North Am 1994;23:743–52.
41. Bouwense SA, Besselink MG, van Brunschot S, Bakker OJ, van Santvoort HC, Schepers NJ, Boermeester MA, Bollen TL, Bosscha K, Brink MA, Bruno MJ, Consten EC, Dejong CH, van Duijvendijk P, van Eijck CH, Gerritsen JJ, van Goor H, Heisterkamp J, de Hingh IH, Kruyt PM, Molenaar IQ, Nieuwenhuijs VB, Rosman C, Schaapherder AF, Scheepers JJ, Spanier MB, Timmer R, Weusten BL, Witteman BJ, van Ramshorst B, Gooszen HG, Boerma D, Dutch Pancreatitis Study G. Pancreatitis of biliary origin, optimal timing of cholecystectomy (PONCHO trial): study protocol for a randomized controlled trial. Trials 2012;13:225.
42. Cote GA, Imperiale TF, Schmidt SE, Fogel E, Lehman G, McHenry L, Watkins J, Sherman S. Similar efficacies of biliary, with or without pancreatic, sphincterotomy in treatment of idiopathic recurrent acute pancreatitis. Gastroenterology. 2012;143:1502–9 e1.
43. Romagnuolo J, Bardou M, Rahme E, Joseph L, Reinhold C, Barkun AN. Magnetic resonance cholangiopancreatography: a meta-analysis of test performance in suspected biliary disease. Ann Intern Med 2003;139:547–57.
44. Nguyen GC, Rosenberg M, Chong RY, Chong CA. Early cholecystectomy and ERCP are associated with reduced readmissions for acute biliary pancreatitis: a nationwide, population-based study. Gastrointest Endosc 2012;75:47–55.
45. Testoni PA, Mariani A, Curioni S, Zanello A, Masci E. MRCP-secretin test-guided management of idiopathic recurrent pancreatitis: long-term outcomes. Gastrointest Endosc 2008;67:1028–34.
46. Sherman S, Freeman ML, Tarnasky PR, Wilcox CM, Kulkarni A, Aisen AM, Jacoby D, Kozarek RA. Administration of secretin (RG1068) increases

the sensitivity of detection of duct abnormalities by magnetic resonance cholangiopancreatography in patients with pancreatitis. Gastroenterology. 2014;147:646–54
47. Jacob L, Geenen JE, Catalano MF, Geenen DJ. Prevention of pancreatitis in patients with idiopathic recurrent pancreatitis: a prospective nonblinded randomized study using endoscopic stents. Endoscopy 2001;33:559–62.
48. Ballard D, Flueckiger, J.F., Fogel, E.L., McHenry, L., Lehman, G.A., Watkins, J.L., Sherman, S., Cote, G.A. Testing adults with pancreatic disease for genetic abnormalities: factors associated with having a positive genetic test. Abstract. Gastroenterology 2013;144:S460.
49. Bertin C, Pelletier AL, Vullierme MP, Bienvenu T, Rebours V, Hentic O, Maire F, Hammel P, Vilgrain V, Ruszniewski P, Levy P. Pancreas divisum is not a cause of pancreatitis by itself but acts as a partner of genetic mutations. Am J Gastroenterol 2012;107:311–7.
50. Chen Y, Zak Y, Hernandez-Boussard T, Park W, Visser BC. The epidemiology of idiopathic acute pancreatitis, analysis of the nationwide inpatient sample from 1998 to 2007. Pancreas 2013;42:1–5.
51. van Baal MC Besselink MG Bakker OJ van Santvoort HC Schaapherder AF Nieuwenhuijs VB Gooszen HG van Ramshorst B Boerma D Dutch Pancreatitis Study G. Timing of cholecystectomy after mild biliary pancreatitis: a systematic review. Ann Surg 2012;255:860–6.
52. Frossard JL, Sosa-Valencia L, Amouyal G, Marty O, Hadengue A, Amouyal P. Usefulness of endoscopic ultrasonography in patients with "idiopathic" acute pancreatitis. Am J Med 2000;109:196–200.
53. Liu CL, Lo CM, Chan JK, Poon RT, Fan ST. EUS for detection of occult cholelithiasis in patients with idiopathic pancreatitis. Gastrointest Endosc 2000;51:28–32.
54. Norton SA, Alderson D. Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis. Br J Surg 2000;87:1650–5.
55. Tandon M, Topazian M. Endoscopic ultrasound in idiopathic acute pancreatitis. Am J Gastroenterol 2001;96:705–9.
56. Yusoff IF, Raymond G, Sahai AV. A prospective comparison of the yield of EUS in primary vs. recurrent idiopathic acute pancreatitis. Gastrointest Endosc 2004;60:673–8.
57. Sherman S, Troiano FP, Hawes RH, Lehman GA. Sphincter of Oddi manometry: decreased risk of clinical pancreatitis with use of a modified aspirating catheter. Gastrointest Endosc 1990;36:462–6.
58. Whitcomb DC. Value of genetic testing in the management of pancreatitis. Gut 2004;53:1710–7.
59. Whitcomb DC, LaRusch J, Krasinskas AM, Klei L, Smith JP, Brand RE, Neoptolemos JP, Lerch MM, Tector M, Sandhu BS, Guda NM, Orlichenko L, Alkaade S, Amann ST, Anderson MA, Baillie J, Banks PA, Conwell D, Cote GA, Cotton PB, DiSario J, Farrer LA, Forsmark CE, Johnstone M, Gardner TB, Gelrud A, Greenhalf W, Haines JL, Hartman DJ, Hawes RA, Lawrence C, Lewis M, Mayerle J, Mayeux R, Melhem NM, Money ME, Muniraj T, Papachristou GI, Pericak-Vance MA, Romagnuolo J, Schellenberg GD, Sherman S, Simon P, Singh VP, Slivka A, Stolz D, Sutton R, Weiss FU, Wilcox CM, Zarnescu NO, Wisniewski SR, O'Connell MR, Kienholz ML, Roeder K, Barmada MM, Yadav D, Devlin B. Common genetic variants in the CLDN2 and PRSS1-PRSS2 loci alter risk for alcohol-related and sporadic pancreatitis. Nat Genet 2012;44:1349–54.
60. Coyle WJ, Pineau BC, Tarnasky PR, Knapple WL, Aabakken L, Hoffman BJ, Cunningham JT, Hawes RH, Cotton PB. Evaluation of unexplained acute and acute recurrent pancreatitis using endoscopic retrograde cholangiopancreatography, sphincter of Oddi manometry and endoscopic ultrasound. Endoscopy 2002;34:617–23.
61. Hamilton I, Bradley P, Lintott DJ, McMahon MJ, Axon AT. Endoscopic retrograde cholangiopancreatography in the investigation and management of patients after acute pancreatitis. Br J Surg 1982;69:504–6.
62. Feller ER. Endoscopic retrograde cholangiopancreatography in the diagnosis of unexplained pancreatitis. Arch Intern Med 1984;144:1797–9.
63. Lee MJ, Choi TK, Lai EC, Wong KP, Ngan H, Wong J. Endoscopic retrograde cholangiopancreatography after acute pancreatitis. Surg Gynecol Obstet 1986;163:354–8.
64. Venu RP, Geenen JE, Hogan W, Stone J, Johnson GK, Soergel K. Idiopathic recurrent pancreatitis. An approach to diagnosis and treatment. Dig Dis Sci 1989;34:56–60.
65. Mariani A, Arcidiacono PG, Curioni S, Giussani A, Testoni PA. Diagnostic yield of ERCP and secretin-enhanced MRCP and EUS in patients with acute recurrent pancreatitis of unknown aetiology. Dig Liver Dis 2009;41:753–8.
66. Freeman ML. Adverse outcomes of ERCP. Gastrointest Endosc 2002;56:S273–82.
67. Ong TZ, Khor JL, Selamat DS, Yeoh KG, Ho KY. Complications of endoscopic retrograde cholangiography in the post-MRCP era: a tertiary center experience. World J Gastroenterol 2005;11:5209–12.
68. Eversman D, Fogel EL, Rusche M, Sherman S, Lehman GA. Frequency of abnormal pancreatic and biliary sphincter manometry compared with clinical suspicion of sphincter of Oddi dysfunction. Gastrointest Endosc 1999;50:637–41.
69. Leung WD, Sherman S. Endoscopic approach to the patient with motility disorders of the bile duct and sphincter of Oddi. Gastrointest Endosc Clin N Am 2013;23:405–34.
70. Baillie J. Sphincter of Oddi dysfunction. Curr Gastroenterol Rep 2010;12:130–4.
71. Cotton PB, Durkalski V, Romagnuolo J, Pauls Q, Fogel E, Tarnasky P, Aliperti G, Freeman M, Kozarek R, Jamidar P, Wilcox M, Serrano J, Brawman-Mintzer O, Elta G, Mauldin P, Thornhill A, Hawes

R, Wood-Williams A, Orrell K, Drossman D, Robuck P. Effect of endoscopic sphincterotomy for suspected sphincter of Oddi dysfunction on pain-related disability following cholecystectomy: the EPISOD randomized clinical trial. JAMA 2014;311:2101–9.
72. Khuroo MS, Zargar SA, Yattoo GN. Efficacy of nifedipine therapy in patients with sphincter of Oddi dysfunction: a prospective, double-blind, randomized, placebo-controlled, cross over trial. Br J Clin Pharmacol 1992;33:477–85.
73. Sand J, Nordback I, Koskinen M, Matikainen M, Lindholm TS. Nifedipine for suspected type II sphincter of Oddi dyskinesia. Am J Gastroenterol 1993;88:530–5.
74. Vitton V, Delpy R, Gasmi M, Lesavre N, Abou-Berdugo E, Desjeux A, Grimaud JC, Barthet M. Is endoscopic sphincterotomy avoidable in patients with sphincter of Oddi dysfunction? Eur J Gastroenterol Hepatol 2008;20:15–21.
75. Jathal A, Sherman S, Fogel EL, Phillips SD, Kochell AE, Shelly LA, Bucksot L, Lehman G. Long-term clinical outcome of endoscopic pancreatobiliary sphincterotomy (PBES) versus biliary sphincterotomy (BES) alone in sphincter of Oddi dysfunction associated with idiopathic recurrent pancreatitis. Gastrointest Endosc 2001;53:AB93.
76. Samavedy R, Schmidt S, Fogel EL, McHenry L, Watkins JL, Sherman S, Lehman GA, Howard TJ. Long term outcomes of endoscopic therapy for idiopathic acute recurrent pancreatitis (IARP). Abstract. Gastrointest Endosc 2007;65:AB248.
77. Guelrud M, Plaz J, Mendoza S, Beker B, Rojas O, Rossiter G. Endoscopic treatment in type-II pancreatic sphincter dysfunction. Abstract. Gastrointest Endosc 1995;41:398.
78. Catalano MF, Sivak MV, Falk GW, Howerton HD, Achkar E. Idiopathic pancreatitis (IP)—Diagnostic role of sphincter of Oddi manometry (SOM) and response to endoscopic sphincterotomy (ES). Abstract. Gastrointest Endosc 1993;39:310.
79. Draganov PV, Kowalczyk L, Forsmark CE. Prospective trial comparing solid-state catheter and water-perfusion triple-lumen catheter for sphincter of Oddi manometry done at the time of ERCP. Gastrointest Endosc 2009;70:92–5.
80. Mosler P, Akisik F, Sandrasegaran K, Fogel E, Watkins J, Alazmi W, Sherman S, Lehman G, Imperiale T, McHenry L. Accuracy of magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum. Dig Dis Sci 2012;57:170–4.

ERCP in Other Pancreatic Disorders

15

Surinder Singh Rana and Robert H. Hawes

Pancreas Divisum

Case

A 28-year-old male presented with acute abdominal pain and investigations revealed an elevated serum amylase and lipase. During the last 2 years, he had been hospitalized three times for similar complaints and carried the diagnosis of idiopathic acute recurrent pancreatitis (ARP). He denied excessive alcohol consumption, and there was no family history of pancreatitis. Liver tests, calcium, and fasting lipid profile were all normal. The gallbladder was free of stones/sludge on ultrasound. He was managed conservatively and discharged from hospital 2 weeks later. What further diagnostic tests can evaluate for an etiology of his ARP attacks?

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Introduction

Pancreas divisum (PD) is the most common congenital variant of the pancreas and occurs when the ventral and dorsal anlage fail to fuse during embryonic development [1]. This results in the (larger) dorsal gland draining via the minor papilla and the smaller, ventral pancreas draining via the major papilla. The frequency of PD has been reported to vary between 4.4 and 12% in autopsy studies and 0.3–8% in endoscopic retrograde cholangiopancreatography (ERCP) studies [1–3]. A recent systematic review described the endoscopic detection rate for PD as 2.9% with the rate being significantly higher in the USA and Europe compared to Asia [4].

PD has generated a considerable debate with some experts suggesting that this anatomical variant has little or no clinical significance because the majority of patients have no pancreatic symptoms throughout their life [5, 6]. On the other hand, the increased frequency of PD in patients with idiopathic pancreatitis lends support to the possible pathogenic role of this congenital ductal variant [1, 4–7]. It is postulated that in patients with clinical symptoms, the minor papilla orifice is critically narrowed resulting in impaired outflow of pancreatic juice. This causes increased intraductal pressure resulting in abdominal pain and pancreatitis [7]. Moreover, relief of symptoms and improvement in the clinical course of pancreatitis, which occurs in the majority of patients after minor papilla sphincterotomy, support the hypothesis of an obstructive pancreatopathy

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in divisum patients [8]. A recent community population-based study also found that the frequency of PD is higher in chronic and recurrent pancreatitis, and the authors concluded that PD should be considered a predisposing factor for chronic and recurrent pancreatitis [9].

Nonetheless, the pathophysiology and cause–effect relationship between PD and pancreatitis is not so simple and universally accepted. Recent genetic studies have challenged the "obstructive pancreatopathy" concept of endoscopists and instead suggest that molecular genetic factors are dominant. Two different groups have found an increased frequency of cystic fibrosis trans-membrane conductance regulator (CFTR) genetic mutations in patients with recurrent pancreatitis and PD [10, 11]. These investigators have suggested that it is the CFTR (or other unidentified genetic mutations) that predispose divisum patients to recurrent acute or chronic pancreatitis rather than impaired pancreatic drainage. The debate continues but many answers could be obtained from a large, multicenter trial randomizing patients to minor papilla sphincterotomy versus sham with a careful, long-term follow-up.

Symptoms and Presentation of Patients with Pancreas Divisum

The majority of patients with PD remain asymptomatic throughout life. However, a subset will present with one of the three clinical conditions: (i) ARP, (ii) chronic pancreatitis (CP) and (iii) pancreatic-type abdominal pain without evidence of pancreatitis [1–4]. The majority of patients who develop symptoms will do so as an adult. The mean age at presentation for ARP patients is 53 years, whereas those with pain only present on average a decade earlier [1, 12]. It is important to categorize patients with PD because their response to endoscopic therapy depends significantly upon the clinical presentation.

What Diagnostic Studies Can Identify Pancreas Divisum?

Radiology

ERCP is the gold standard for the diagnosis of PD but the procedure is invasive and can be challenging (Fig. 15.1). Opacification of the ventral pancreas can be difficult because of its small size. Minor papilla injection is also challenging because the orifice can be tiny and difficult to find. Successful cannulation requires excellent sedation and failure to cannulate carries a high risk of post-ERCP pancreatitis. As a result, there is a great interest in developing noninvasive tests to accurately diagnose PD. The three most useful imaging tests are abdominal contrast-enhanced multidetector row computed tomography (MDCT), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS). MDCT has been shown to have good sensitivity and specificity for the diagnosis of PD

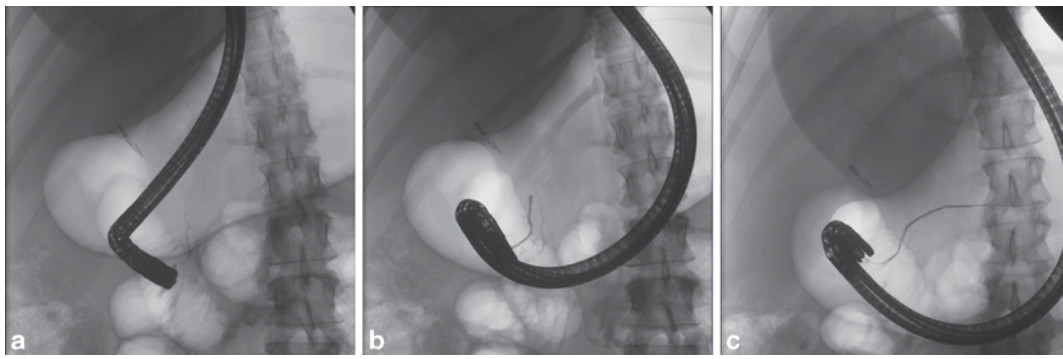

Fig. 15.1 Pancreatography obtained by ERCP showing a small ventral pancreas (**a**) and two images showing increasing filling of the dorsal duct via the minor papilla (**b, c**)

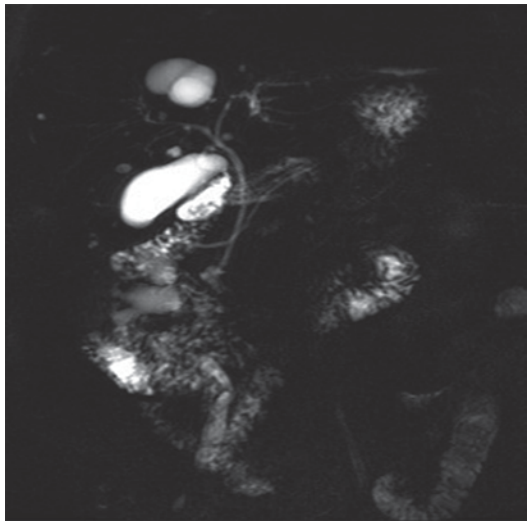

Fig. 15.2 MRCP demonstrating pancreas divisum with dorsal pancreatic duct emptying into duodenum proximal to the major papilla where the common bile duct exits. (Courtesy: Dr. Nisha Sainani Brigham and Women's Hospital, Boston, MA)

when the pancreatic ducts are prominent and can be visualized by CT scan [13, 14]. MRCP evaluates the pancreaticobiliary ductal system and has good sensitivity and specificity for the diagnosis of PD (Fig. 15.2) [15]. Secretin enhancement improves the sensitivity of MRCP in diagnosing PD from 52 to 86% with 97% specificity [16, 17]. While MRCP is better than CT, there is a considerable variation in diagnostic accuracy for PD with the typical pattern of early studies showing high sensitivity and specificity which is countered by more recent studies reporting only modest accuracy [18, 19].

Endoscopic Ultrasound

EUS images the pancreaticobiliary ductal system without the need for contrast injection and has the added advantage of being able to examine the pancreatic parenchyma in detail which provides important additional information when looking for early chronic pancreatitis. Both radial and linear echoendoscopes are capable of diagnosing PD but reports vary on the diagnostic accuracy of EUS. The inconsistency in diagnosis results from the fact that while various criteria (imaging patterns) have been proposed to suggest the presence or absence of PD, any particular EUS examination may or may not detect those patterns in that specific patient. If certain patterns are seen, then PD can be definitively ruled in or out. With other criteria, increasing the number of diagnostic criteria needed to diagnose PD increases the specificity but decreases sensitivity for PD [20]. The EUS diagnostic criteria that have been evaluated include the absence of stack sign, presence of crossed duct sign, visualizing the pancreatic duct cross the dorsal-ventral anlage, and inability to follow the pancreatic duct from the major papilla to the pancreatic body [21]. The stack sign is assessed using a radial echoendoscope in the long position in the duodenal bulb with the tip at the apex of the bulb. In this position, the bile duct, pancreatic duct, and portal vein should be visualized running parallel to each other in a "stack." The crossed duct sign is present when the dorsal duct is seen crossing the common bile duct (CBD) from the bulb with a radial echoendoscope. The absence of stack sign is suggestive but not diagnostic of PD with 50% sensitivity and 97% specificity. The presence of crossed duct sign seems consistent with PD, however, has limited sensitivity. Following the pancreatic duct is very useful for ruling out PD. If the duct can be definitively traced from the major papilla to the pancreatic body or from the body dipping at the genu toward the major papilla (Video 15.1), then PD is ruled out. If it cannot be seen, is that because PD is present or the duct is just tortuous and cannot be kept in the plane of imaging? Despite these potential problems, a recent study compared the sensitivity of EUS, CT, and MRCP for the diagnosis of PD and investigators found the sensitivity for EUS to be 86.7%, which was significantly higher than that of CT and MRCP [22].

Although these investigations establish a diagnosis of PD in a large proportion of patients, PD should still remain in the differential diagnosis of patients with idiopathic recurrent acute pancreatitis despite nondiagnostic studies [19]. ERCP is the definitive test for PD, but in most cases, ERCP is reserved for those with PD in whom intervention is planned.

Case Continued

An MRCP was done and suggested the possibility of complete PD. The dorsal duct was not dilated and the biliary tract was normal. EUS using a radial echoendscope also confirmed the presence of PD as the stack sign could not be elicited and the dorsal duct could be seen crossing the CBD and entering the duodenum in the area of the minor papilla. The pancreatic parenchyma was normal revealing only echogenic strands and foci without shadowing. What should be done next?

ERCP

During ERCP, PD should be suspected if a pancreatogram cannot be obtained via the major papilla and is usually diagnostic when cannulation of the major papilla reveals a short ventral duct (Fig. 15.1). One must be careful not to misinterpret a complete duct cutoff, as seen in pancreatic cancer, with a ventral duct of PD. The ventral duct is 1–4 cm long, does not cross the spine, tapers into multiple side branches, drains promptly, and acinarization can occur quickly with contrast injection [1]. In a small group of patients with PD, the ventral duct may be absent and major papilla injection will only produce a cholangiogram [23]. These findings are suggestive but not diagnostic of PD as similar findings may be also seen in patients with benign or malignant processes that cause severe ductal obstruction. In cases where PD is suspected, minor papilla cannulation is mandatory for confirming the diagnosis.

Localization of Minor Papilla

The minor papilla is located 1–3 cm superior and anterior (cephalad and medial) to the major papilla and thus should be located in the right upper quadrant of the endoscopic field when facing the major papilla (Fig. 15.3) [1]. With the advent of newer generation video endoscopes, the minor papilla can be localized in most patients. When the minor papilla or the actual orifice cannot be identified, pancreatic juice flow can be stimulated by administering intravenous secretin. The orifice can then be identified by visualizing the resulting fountain of clear juice. In a minority of patients, even secretin stimulation is inadequate to visualize the orifice. In these cases, one can spray dilute methylene blue (1:10) in the general area of the minor papilla and then look for a clearing of the dye caused by the flow of pancreatic juice [1]. In patients where all attempts to localize the minor papilla have failed, methylene blue can be injected into the dorsal duct under EUS guidance and the flow of blue-colored pancreatic juice can help localize the minor papilla [24].

The endoscopic appearance of the minor papilla can be predictive of PD [25]. The presence of an enlarged minor papilla or an obviously patent orifice has been shown to be moderately

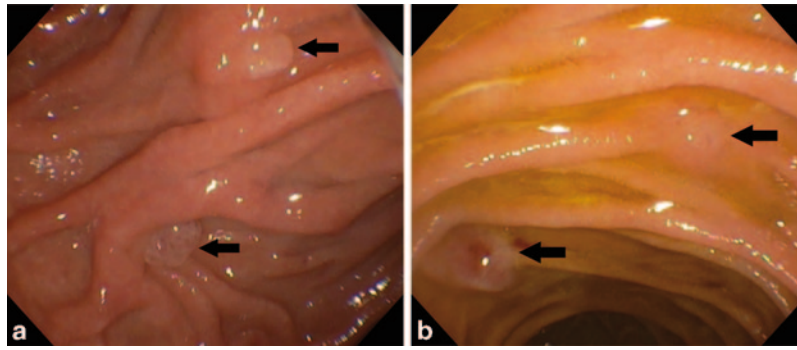

Fig. 15.3 **a, b** Endoscopic images showing the major and minor papilla (*arrows*). The minor papilla is cephalad and medial to the major papilla

predictive of the presence of PD. During intubation of the duodenum at ERCP, before the scope is advanced around the apex and shortened, one should look for the minor papilla as one gets a great view of the area cephalad and medial to the major papilla.

Cannulation of Minor Papilla

The minor papilla and orifice are quite small, and there is little if any intraduodenal segment. Cannulation requires precise technique and unique accessories. The endoscope should be in the "long" position [1]. This can be accomplished by turning left on the left-right knob, torqueing counter-clockwise and advancing the scope. Alternatively, one can begin in the stomach and advance the scope through the pylorus and begin the turn around the apex. Just past the apex, stop and look for the minor papilla rather than further advancing into the second portion and straightening the scope. The optimal accessories for cannulation are tapered cannulas or papillotomes with small caliber guidewires (0.021" or 0.018"). Place the guidewire 1–2 mm beyond the tip of the catheter and precisely insert the wire tip into the orifice. "Precision" is the operative word. One cannot "cram" the wire or catheter tip into the minor papilla. Several "abusive" attempts will cause edema and bleeding which render subsequent attempts futile. It is critical to appreciate the trajectory of the dorsal duct. Once the guidewire is insinuated, the cannula should be advanced flush to the orifice followed by contrast injection to opacify the dorsal duct. It is critical to obtain a ductogram to enable advancement of the guidewire in line with the course of the duct. The duct usually courses from right to left from the endoscope perspective. The initial guidewire trajectory will be perpendicular to the duct and the endoscopist must adjust the direction, under fluoroscopic guidance, to align with the dorsal duct to achieve deep cannulation. For therapy, the goal is always to insert the guidewire to the tail of the pancreas. The guidewire is guided under fluoroscopy with contrast in the duct to avoid advancing the guidewire into a side branch.

Types of Pancreas Divisum

Variations of the ductal anatomy in PD have been described elsewhere, and the clinical significance of these variants is the same as that of complete PD [7, 26]. Incomplete PD is characterized by the presence of a small, filamentous branch connecting the ventral with the dorsal duct. While the dorsal duct may opacify with injection into the major papilla, the connection is inadequate for drainage and most or all of the pancreatic secretions from the dorsal duct exit through the minor papilla [7, 26]. When only an isolated small segment of the dorsal pancreas drains via the minor papilla and the dorsal duct does not communicate with the ventral duct, patients have reverse PD. In this case, the majority of pancreas juice drains via the major papilla. This ductal variation has no clinical significance but an unaware endoscopist may repeatedly try to obtain a complete pancreatogram through the minor papilla suspecting PD [7]. A functional variant of PD has also been described where the entire pancreas including the uncinate process drains via the minor papilla and no pancreatic duct connects to the major papilla [26].

Identification of Patients with Minor Papilla Stenosis

A majority of patients with PD remain asymptomatic throughout their life. A subset will have pancreatic type pain or recurrent pancreatitis. The current understanding of the pathophysiology of PD and pancreatitis/pain hypothesizes the presence of ductal hypertension because of minor papilla stenosis as the main cause of symptoms. Conversely, relief of the obstruction by endoscopic or surgical therapy has been shown to relieve pain in the majority of patients with minor papilla stenosis. A number of imaging criteria have been suggested to identify patients with PD and minor papilla stenosis:

1. An abnormal dorsal pancreatic duct with a normal ventral duct suggests minor papilla stenosis. Similarly, cystic dilatation of the

terminal portion of the dorsal duct (Santorinicele) is also thought to suggest dorsal duct outflow obstruction [1, 7]. Although these findings on ERCP/MRCP are highly suggestive of minor papilla stenosis, they are infrequently observed.

2. Dorsal duct dilatation on ultrasonography persisting for more than 15 min after intravenous secretin injection [27]. However, the precise positive criteria remain unclear [1, 7].
3. Pain provocation during the injection of contrast into the dorsal duct. However, this does not occur universally in all patients and is of uncertain significance [1, 7].
4. Collection of pure pancreatic juice from the dorsal duct after secretin stimulation and analyzing bicarbonate concentration as well as the volume of pancreatic juice secreted. This will help in diagnosing early CP localized to the draining area of dorsal duct [7].
5. Manometry of minor papilla: There are only a handful of studies that have evaluated the minor papilla pressures as this is technically difficult and the normal pressures have not been established [1]. One study found that patients with PD had higher dorsal duct pressures compared to pressures at the major papilla of patients with normal pancreatic duct anatomy [28]. However, Satterfield et al found the basal and phasic pressures to be similar at both the major and minor papilla in 4 patients with PD and ARP [29].
6. Once deep cannulation of the dorsal duct has been achieved, minor papilla stenosis can be subjectively gauged by observing resistance to sequential passage of 3, 4, and 5 Fr catheters [7].
7. Trial of opening the minor papilla: The minor papilla orifice can be temporarily enlarged by placing a transpapillary stent. Such a strategy might be helpful in patients with daily or weekly symptoms but is problematic if the patient has infrequent episodes of pancreatitis because of the potential for ductal damage induced by the stent [1, 7]. Most pathology studies suggest that there is no sphincter associated with the minor papilla so injection of Botulinum Toxin is not helpful.

As evident above, there are a number of tests and imaging findings that may suggest minor papilla stenosis but their sensitivity and specificity have not been evaluated by prospective studies. Additionally, a high suspicion of a tight minor papilla does not always guarantee the success of endoscopic or surgical therapy [1, 7]. With current evidence, the presence of recurrent pancreatitis without a defined cause is the best indicator of minor papilla stenosis [30]. Some patients with typical pancreatic pain without pancreatitis will respond to minor papilla sphincterotomy, but this is in highly selected patients, and there is much less evidence to support this approach.

Endoscopic Therapy for Pancreas Divisum: Dilate, Stent, or Cut?

Endoscopic techniques for opening the minor papilla consist of dilatation by sequentially larger tapered catheters, balloons, or by stenting and sphincterotomy [1, 7]. However, balloon dilatation of a naïve papilla has been associated with a significant risk of pancreatitis as well as duct disruption and therefore should not be employed in the presence of a relatively normal or moderately dilated dorsal duct [7]. A recent small retrospective study from Asia does, however, suggest the safety and efficacy of balloon dilation in PD [31]. In their study of 16 patients with symptomatic PD from ARP or CP, balloon dilation of the minor papilla to 4 or 6 mm was successful with 85% clinical improvement. Mean main pancreatic duct (MPD) diameter was 4.3 mm and no complications were observed from balloon dilation.

Dorsal duct stenting has been used as a therapeutic trial on both a short- and a long-term basis for relief of pain (Fig. 15.4). A prospective randomized study comparing long-term dorsal duct stenting (1 year with stent exchanged every 4 months) with conservative medical therapy in patients with PD and idiopathic recurrent pancreatitis reported significantly greater number of hospitalizations, emergency department visits, and pancreatitis episodes in patients treated conservatively [32]. Another study on the efficacy of long-term dorsal duct stenting reported the best

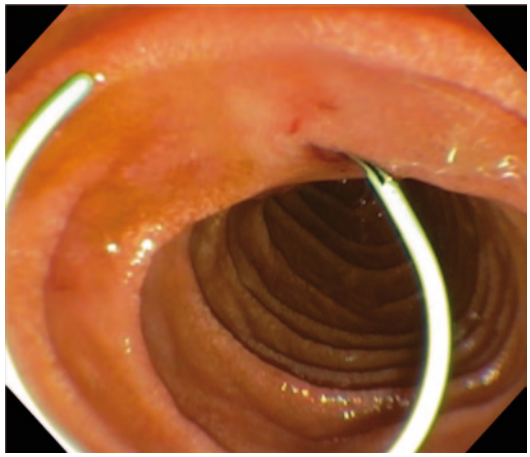

Fig. 15.4 Endoscopic image showing a pancreatic stent inserted across the minor papilla

results in patients presenting with ARP while only 13 % of patients presenting with pain alone had complete pain relief [33]. In a study of 48 patients with PD and CP, successful outcome was achieved in 96 % of patients [34]. In this study, the majority of the patients underwent a long-term ductal stenting and over a median follow-up of 67 months, 39 % required re-stenting for recurrence of symptoms. While the long-term pancreatic duct stenting may improve symptoms in PD, leaving pancreatic stents in place for weeks to months is associated with potentially serious complications including stent occlusion, migration, pancreatitis, duct perforation, and duct disruption [7]. The major concern however is stricturing of the main duct. Both ductal and parenchymal changes are seen relatively quickly after pancreatic stent placement. While these are of little significance in patients with advanced chronic pancreatitis, they can be disastrous in patients with normal pancreatic ducts [35]. Therefore, the long-term dorsal duct stenting is not advocated for patients with normal appearing ducts.

Endoscopic sphincterotomy or papillotomy of the minor papilla is considered the first-line endoscopic therapy for patients with symptomatic PD (Fig. 15.5) [1, 7]. There are two main techniques: needle-knife papillotomy (NKP) and standard pull-type papillotomy (PTP) [1, 7]. The needle-knife technique is performed at the 10- to 12-o'clock position over a pancreatic stent. The stent provides a platform to avoid cutting too deeply and provides direction. It is also a safety valve by ensuring adequate drainage in case bleeding, or patient instability causes the procedure to be prematurely halted. The standard PTP is done using a minipapillotome or a standard pull-type sphincterotome using a free-hand technique over a guidewire (Video 15.2). The landmarks for determining an adequate sphincterotomy are not standardized but the cut should be made to end flush with the duodenal wall. Sometimes, a minor papilla bulge is present, which makes it easier to determine where the minor papilla ends and the duodenal wall begins [36].

The choice of the type of papillotomy is usually based upon personal preference of the endoscopist. Lehman et al. advocate the NKP because of its directional and depth control and safety, but recent studies have shown that both techniques are equally safe and effective [36–38]. Current evidence suggests that the two sphincterotomy techniques are comparable with respect to re-stenosis and re-intervention rates. The technique applied for sphincterotomy may depend on the ductal anatomy. For example, if a patient has a very tortuous duct requiring a short stent, it may be advantageous to perform sphincterotomy first with a papillotome followed by placement of a short stent. If the ductal anatomy can accommodate a longer, more stable stent, then stent placement followed by a NKP may be optimal.

Minor papilla sphincterotomy has a higher reported complication rate when compared with the major papilla including pancreatitis, bleeding, sepsis, and perforation [26, 37–39]. The fact that interventions on the minor papilla are much less common than those on the major papilla undoubtedly contributes to the higher complication rate. As expected in PD, cannulation of only the major papilla has a very low rate of pancreatitis (1.2 %) while dorsal duct cannulation confers higher risk of pancreatitis, and patients undergoing minor papilla sphincterotomy are at the highest risk for post-ERCP pancreatitis with rates reported between 8 and 11 % [38, 39].

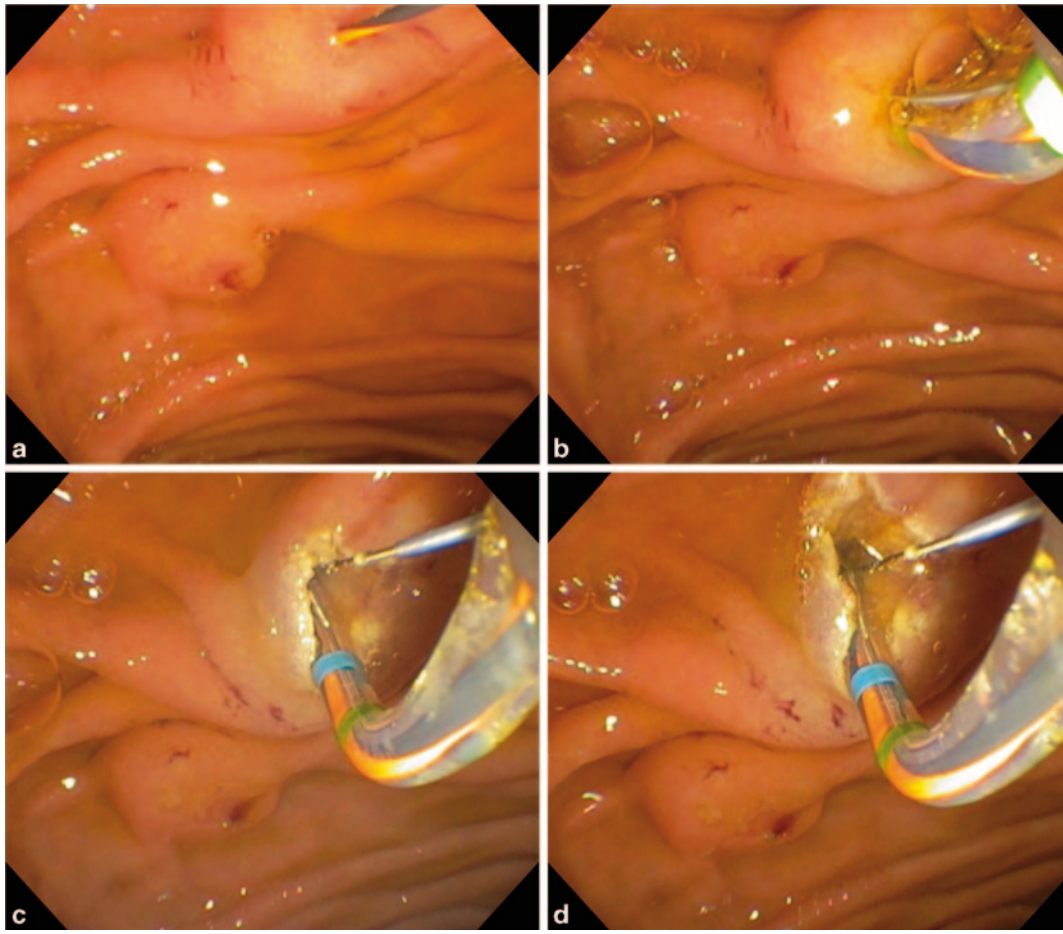

Fig. 15.5 **a–d** A series of images demonstrating minor papilla sphincterotomy using a tapered tip papillotome

Results of Endoscopic Therapy: Who Should Be Treated?

The studies evaluating the role of endoscopic therapy for PD are plagued with the limitations that are common to many studies on endotherapy and include small sample size, referral bias, patient heterogeneity, lack of control arm, short duration of follow-up, and the absence of blinding as well as randomization [7]. The majority of studies assessing the efficacy of endoscopic therapy have been retrospective case series with a small sample size and no control arm. There are no studies that prospectively compare endoscopic with surgical therapy. A recent pooled systematic analysis published in 2009 looked at the results of endoscopic therapy and reported that response rates were insignificantly lower than that of surgical therapy (69.4% vs. 74.9%, respectively; $p=0.106$) [4]. The pooled analysis reconfirmed the findings of earlier studies that had shown the best results for endoscopic and surgical therapy in patients with PD and ARP. The following response rates were noted for endoscopic and surgical therapy respectively: 79.2% and 83.2% in patients presenting with ARP, 69.0% and 66.7% in patients with CP, and the lowest response rates of 54.4% and 51.6% in patients presenting with abdominal pain only. Thus, all these studies suggest that patients with PD and ARP are the best candidates for endoscopic or surgical therapy. Patients with CP and pancreatic-type pain have lower response rates, and therefore, careful case

selection is critical to optimizing outcomes. One recent study has shown excellent response rates with aggressive endoscopic therapy even in patients with chronic pancreatitis although very few of these patients had pancreatic duct stones or strictures, supporting the importance of case selection [34]. While there is no consensus on the method of detecting restenosis after minor papillotomy, studies report restenosis rates of 10–20% leading to reintervention in these patients. The restenosis rates are comparable between the two minor papillotomy techniques [38].

In the absence of a randomized study comparing endoscopic and surgical treatment for PD and the current evidence suggesting equal efficacy, endoscopic therapy being less invasive is currently considered the first-line treatment option for symptomatic patients with PD.

Case Continued

As the patient had PD diagnosed on both MRCP and EUS with multiple attacks of documented acute pancreatitis, ERCP with minor papillotomy was planned. Our policy is to offer pancreatic endotherapy to all patients with PD who have had a single attack of severe acute idiopathic pancreatitis or >2 attacks of mild acute pancreatitis. The pancreatogram obtained through the major papilla revealed a short ventral duct, and thereafter, the minor papilla was identified and cannulated with a metal tip catheter. The pancreatogram revealed a nondilated dorsal duct, and a NKP was performed over a 3 Fr pancreatic stent without inner flanges. Plain abdominal X-ray 3 weeks later documented stent dislodgement. The patient has been asymptomatic over 2 years of follow-up.

ERCP in Autoimmune Pancreatitis: Is There a Role?

Autoimmune pancreatitis (AIP) is an uncommon form of chronic pancreatitis that in some cases can be difficult to differentiate from pancreatic cancer [40]. There was initial enthusiasm that elevated serum IgG4 levels would be diagnostic for AIP, but this enthusiasm has tempered with the realization that it has poor diagnostic performance in certain populations such as Caucasian patients [40]. It is now known that there are two types of AIP (type 1 and type 2), and serum IgG4 levels are usually normal in type 2. Type 1 AIP, also known as lymphoplasmacytic sclerosing pancreatitis, is most common in Asian countries, has an older age of onset, and usually presents with painless obstructive jaundice. It is a multisystem disease and can affect the biliary tree, salivary glands, kidneys, and retroperitoneum [41]. Serum IgG4 levels are elevated, and many IgG4+cells can be seen on immunohistochemistry in pathology specimens. Patients with type 1 AIP respond very well to steroids but recurrences are common. Type 2 AIP or idiopathic duct-centric chronic pancreatitis is more common in Europe and USA and occurs at an earlier age. Patients present either with obstructive jaundice or with acute pancreatitis, serum IgG4 levels are usually normal, and the disease is limited to the pancreas. Like type 1 AIP, these patients also respond well to steroids but recurrences are rare [41].

There is no single clinical, laboratory or imaging feature that is characteristic of AIP, and histology is the reference standard for the diagnosis. It is very difficult in routine clinical practice to obtain pancreatic tissue for histopathological analysis. Therefore, a number of groups have proposed criteria to establish the diagnosis [Japanese Pancreas Society (JPS), Korean criteria, Mayo Clinic HISORt criteria, and International Consensus Diagnostic Criteria and Algorithm (ICDC)] [40, 41]. These diagnostic criteria use a combination of imaging features, serology, evidence of other organ involvement, histology of the pancreas with immunohistochemistry, and dramatic response to steroids (Tables 15.1, 15.2, and 15.3).

In the era of advanced imaging techniques such as MRCP, MDCT, and EUS+/-FNA/core biopsy, does ERCP have a role in diagnosing AIP? This issue is controversial as evidenced by the fact that the JPS criteria mandate the use of ERCP, whereas the HISORt criteria do not re-

Table 15.1 Japan Pancreas Society Diagnostic Criteria for AIP (Proposed in 2002 and revised in 2006)

Criteria	Diagnostic criteria
Imaging	Diffuse narrowing of MPD with irregular wall (> 1/3 the length of entire pancreas) and diffuse enlargement of the pancreas
	In revised criteria, minimum extent (> 1/3 the length of the entire pancreas) of MPD removed
	Diffuse narrowing of MPD and diffuse enlargement of pancreas changed to diffuse or segmental narrowing and diffuse or localized enlargement
Laboratory finding	Abnormally elevated levels of serum gamma globulin and/or IgG, or the presence of auto antibodies
	In the revised criteria, elevated serum IgG4 included
Histology	Marked lymphoplasmacytic infiltration and dense fibrosis
	In the revised criteria, changed to marked interlobular fibrosis with prominent infiltration of lymphocytes and plasma cells

For diagnosis, imaging criterion must be present together with laboratory and/or histological criterion
MPD main pancreatic duct

Table 15.2 Korean Diagnostic Criteria for AIP (Kim Criteria at Asan Medical Centre)

Criteria	Diagnostic criteria
Imaging	(1) Diffuse enlargement (swelling) of pancreas
	(2) Diffuse or segmental irregular narrowing of the main pancreatic duct
Laboratory finding	(1) Elevated levels of IgG or IgG4 or
	(2) Detected autoantibodies
Histology	Fibrosis and lymphoplasmacytic infiltration
Response to steroids	Present

For diagnosis, imaging criterion must be present together with any of the other three criteria

Table 15.3 HISORt Diagnostic Criteria for AIP (Mayo Clinic)

Criteria	Diagnostic criteria
Histology	*1. Diagnostic (any one)*
	a. Pancreatic histology showing lymphoplasmacytic sclerosing pancreatitis
	b. Lymphoplasmacytic infiltrate with abundant (> 10 cells/HPF) IgG4-positive cells in pancreas
	2. Supportive (any one)
	a. Lymphoplasmacytic infiltrate with abundant (> 10 cells/HPF) IgG4-positive cells in extrapancreatic organ
	b. Lymphoplasmacytic infiltrate with fibrosis in pancreas
Imaging	*Typical imaging features*
	1. CT/MRI: diffusely enlarged gland with delayed (rim) enhancement
	2. ERCP: diffusely irregular and attenuated main pancreatic duct, atypical imaging features, pancreatitis, focal pancreatic mass, focal pancreatic duct stricture, pancreatic atrophy, pancreatic calcification
Serology	Elevated serum IgG4 level
Other organ involvement	Hilar/intrahepatic biliary strictures, persistent distal biliary stricture, parotid/lacrimal gland involvement, mediastinal lymphadenopathy, retroperitoneal fibrosis
Response to steroid therapy	Resolution/marked improvement of pancreatic/extrapancreatic manifestation with steroid therapy

Diagnosis: Group A, diagnostic histology alone; Group B, typical imaging features and elevated serum IgG4; Group C, unexplained pancreatic disease with serology or other organ involvement and response to steroids

quire ERCP to establish the diagnosis. The Korean criteria suggest that MRCP can be used for ductal imaging. These differences may be rooted in the prevalence of type 1 and 2 AIP and also may reflect the bias of collecting pancreatic juice versus tissue biopsy. Despite these differences, most experts suggest that the best diagnostic strategy for AIP should use a combination of all the available investigations which may include ERCP depending on serological and cross-sectional imaging results [42, 43]. In patients with typical findings of AIP on contrast-enhanced CT (CECT) (diffuse pancreatic enlargement with homogeneous enhancement with or without a "rim"), diagnostic ERCP gives limited additional information. However, when imaging findings are indeterminate (segmental or focal enlargement, dilatation or cutoff of the pancreatic duct, or a pancreatic mass), serology is nondiagnostic, there is no evidence of other organ involvement, and retrograde pancreatography can help support or refute the diagnosis (Fig. 15.6) [41, 43].

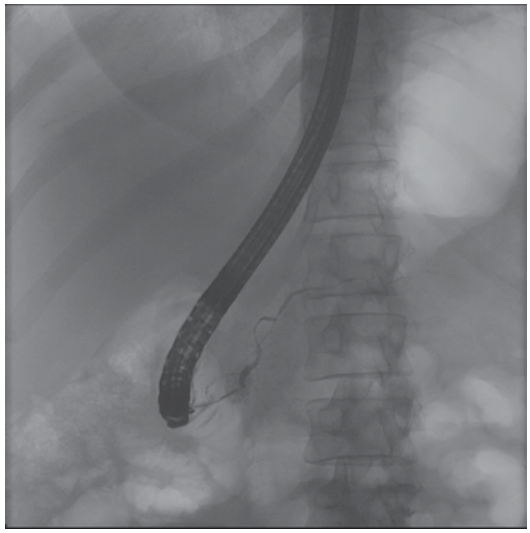

Fig. 15.6 ERP demonstrating the characteristic features of autoimmune pancreatitis with diffusely irregular and attenuated main pancreatic duct without dilation

ERCP Findings in AIP

An international multicenter study found the following features on ERCP useful in differentiating AIP from pancreatic cancer: [42].

1. Long stricture (> 1/3 the length of the MPD).
2. Lack of upstream dilatation from a stricture (< 5 mm).
3. Presence of multiple strictures.
4. Side branches arising from the strictured segment of the pancreatic duct.

None of these ERP features by themselves are diagnostic for AIP. The multicenter study found that the presence of all four features had high specificity (91%) but lower sensitivity (52%) [42]. The same study also showed that the presence of single or multiple strictures without upstream dilatation had the highest specificity for diagnosing AIP [42]. Moreover, a recent study reported that these ERP findings occur with equal frequency in both type 1 and 2 AIP. Therefore, ERCP is likely most helpful in patients suspected of type 2 AIP as they tend to be negative for IgG4 in both serum and tissue samples. While brushing or biopsy of pancreatic duct strictures can be performed to rule out malignancy, there are no data to suggest its utility in diagnosing AIP.

Because AIP is a diffuse inflammatory disease of the pancreas, the bile duct can be involved, and therefore, the cholangiographic features can be helpful in diagnosing AIP [44]. The presence of a smooth stricture of the distal bile duct as well as stenosis of the hilum or intrahepatic ducts has been reported more frequently in patients with AIP than patients with pancreatic cancer [44]. Primary sclerosing cholangitis (PSC) and cholangiocarcinoma are also included in the differential diagnosis in patients with these types of biliary strictures. Short annular or band-like strictures, diverticulum-like out pouchings, and a beaded appearance are seen more commonly in patients with PSC, whereas long strictures with more pre-stenotic dilatation is seen more commonly in IgG4-related disease [41]. When compared to patients with cholangiocarcinoma, patients with AIP have multifocal strictures and mild proximal dilatation despite a long stricture [41]. IgG4 staining of biopsies from the biliary stricture may infrequently help differentiate AIP from malignancy, and this tissue IgG4 positivity is independent of elevated serum IgG4 levels [45, 46]. The sensitivity and specificity of IgG4 staining of biliary biopsy specimens ranges from 18 to 88% and 9–100%, respectively [41]. The ampulla can also be involved in AIP, and IgG4 staining of ampullary biopsies may aid in diagnosing AIP with reported sensitivity and specificity of 60 and 97%, especially in situations when pancreatic tissue cannot be obtained [41]. Transpapillary intraductal ultrasound (IDUS) can help differentiate IgG4-related bile duct strictures from malignant strictures. The most specific IDUS finding for IgG4-related disease is bile duct wall thickening (> 1 mm) in the nonstrictured region with a reported specificity of 100% and sensitivity of 85% [41, 46]. The thickened bile duct wall is typically symmetric, homogeneous with smooth inner and outer wall layers.

Can MRCP Replace Diagnostic ERCP in Patients Suspected of AIP?

ERCP is an invasive investigation with the potential for post-ERCP pancreatitis (PEP). Despite this

potential, there are no published reports of PEP in patients with AIP. This may be due to the underlying fibrosis and decreased enzymatic activity, the same factors used to explain the decreased PEP rates in patients with established chronic pancreatitis. It also may result from under reporting since mild PEP could be masked by the patient's ongoing smoldering pancreatitis due to AIP. Because of the potential risk of ERCP, MRCP has been studied to determine whether this less invasive method of obtaining cholangiopancreatography can substitute for ERCP in the investigation of patients with suspected AIP. [41]. The new Korean criteria for the diagnosis of AIP have suggested that MRCP can replace ERCP. However, a few studies have shown that MRCP does not have equivalent diagnostic accuracy as ERCP for AIP although these studies are limited by the use of mainly older MRI scanners with few patients undergoing three-dimensional MRCP [46–48]. One study showed MRCP had modest accuracy of 65% compared to the gold standard ERCP for detecting each pancreatic duct abnormality in AIP with most of the disagreement resulting from MRCP overestimating ductal narrowing [48]. Another study found that in diffuse-type AIP, the diffuse narrowing of the pancreatic duct documented on ERCP was seen as skipped nonvisualized lesions in 50%, faint visualization in 19%, and nonvisualization in 31% on MRCP [45]. Side branches arising from the narrowed portion of pancreatic duct were visualized well on ERCP, but faintly in only 21% of patients on MRCP [45]. Also, in the segmental type of AIP, the pancreatic duct narrowing appreciated on ERCP was seen as faint visualization in 14% and nonvisualization in 86% patients on MRCP [45]. Thus, pancreatic duct narrowing and side branches arising from within a narrowed segment are rarely seen on MRCP.

Although currently MRCP cannot completely replace ERCP for diagnosis of AIP, because it is noninvasive and provides both ductal and parenchymal information, it should be used as an initial diagnostic modality in patients with suspected AIP. ERCP should be reserved for patients with indeterminate cross-sectional imaging and serology, and those who require intraductal biopsies and/or biliary decompression.

ERCP in Intraductal Papillary Mucinous Neoplasms (IPMN)

IPMNs are unique cystic tumors of the pancreas that are being increasingly diagnosed because of greater utilization and availability of high-quality cross-sectional imaging, primarily MDCT scanners. They are mucin-secreting neoplasms that arise from the epithelial lining of the MPD and/or one or more of the side branches to correspond with the main duct and branch duct forms of IPMN. The biologic behavior of IPMN can range from innocuous benign lesions to frank invasive malignancy [49]. IPMN poses two difficult yet important challenges to the treating physician: firstly, differentiating IPMN from other cystic lesions of the pancreas and secondly, distinguishing a benign from a malignant cyst. Traditionally, the diagnosis of main duct IPMN was based upon the triad of ERCP findings described by Ohashi et al. (1) patulous bulging "fish eye" papilla, (2) mucin secretion, and (3) a dilated MPD [50]. Fish mouth papilla occurs in up to 40% of patients with main duct IPMN. However, with the increased prevalence of branch duct IPMN and the availability of high-resolution imaging such as MRCP, MDCT, and EUS along with EUS-guided cyst aspiration, the role of ERCP in the diagnosis of IPMN has diminished significantly [51]. In fact, ERCP is considered contraindicated in branch duct IPMN because if the duct is injected sufficiently to visualize the dilated side branch filled with mucin, the risk of pancreatitis is very high. With the advent of pancreatoscopy and IDUS, however, ERCP can play a role in locating the lesion in main duct IPMN which can aid surgical planning. The combination of pancreatoscopy and IDUS for lesion localization along with pancreatic duct aspirate for cytology and tumor marker analysis can all be helpful in treatment planning for patients with main duct IPMN.

Pancreatoscopy

The ability to directly visualize ductal abnormalities and sample them under direct vision can help in the evaluation of patients with suspected main

duct IPMN. Despite the availability of a mother–baby cholangioscopy system for a long time, its routine clinical application has been limited due to instrument fragility, cost, the requirement of 2 experienced endoscopists, long procedure time, and modest image quality [52]. The development of a single-operator system that provides four-way tip deflection, tissue acquisition, and endotherapy has rekindled interest in pancreatoscopy to investigate main duct IPMN [52].

Scopes for Ductoscopy

The endoscopes available for pancreatoscopy can be broadly classified into single-operator or two-operator systems. The details of the various endoscopes will not be discussed in detail here and are reviewed elsewhere [53]. The two-operator system or "mother–baby" system involves a smaller diameter (baby) cholangiopancreatoscope that is inserted into the pancreatic duct through the working channel of a mother duodenoscope. Most of the available baby endoscopes have fiberoptic technology, external diameter ranging between 2.8 and 3.1 mm, and single-plane (up down) deflection only. Because of restraints on overall instrument diameter, fiberoptic technology will have only modest image resolution. Newer video baby endoscopes using charged coupled device (CCD) video chip technology have led to a significant improvement in image quality [53]. Current generation video baby scopes have a 1.2-mm operating channel with an outer diameter of 3.3 mm. The development of an ultra-miniature CCD propelled the development of a prototype electronic pancreatoscope with an external diameter of 2.1 mm and no accessory channel.

Two different endoscopy systems can be used to perform single-operator cholangiopancreatoscopy: an ultraslim gastroscope or the SpyGlass^{R} direct visualization system (Boston Scientific, Marlborough, MA). The ultraslim gastroscopes have a diameter ranging from 5 to 6 mm making insertion difficult. To date, direct pancreatoscopy using an ultraslim gastroscope has rarely been reported [54, 55]. The SpyGlass^{R} system consists of a 3.3-mm-diameter, disposable catheter with a four-way tip deflection and three channels (one for the optical probe, one for accessories including special biopsy forceps or laser or electrohydraulic lithotripsy probe, and one for water infusion). Visualization and light are delivered by an optical fiber probe passed down 1 of the channels [53]. The diameter of this instrument requires a dilated pancreatic duct for insertion and can require a generous pancreatic sphincterotomy if the pancreatic orifice is not patulous. To allow deeper and easier visualization of the pancreatic duct, a modified technique of pancreatoscopy has been proposed where the 0.8-mm fiber optic probe from the SpyGlass^{R} system is inserted into the pancreatic duct through the already-deeply inserted ERCP cannula [56]. The advantage of this method is the ability to visualize nondilated ducts without requiring sphincterotomy. Inability to sample lesions is the major limitation with this approach. Although these two systems have not been directly compared, the image quality of the SpyGlass^{R} system appears inferior to the video pancreatoscopes [53].

The technique of pancreatoscopy depends upon the degree of dilation of the MPD, the presence or absence of strictures or masses, the tortuosity of the MPD, and the degree of "patulousnes" of the pancreatic orifice. [54]. The pancreatoscope can be directly inserted into the pancreatic duct only in the presence of a patulous papilla; otherwise, pancreatic sphincterotomy is required. The depth of insertion may be limited by the presence of tortuous segments of the pancreatic duct or narrow diameter of the duct. Stiffer guidewires may help maneuver the pancreatoscope around tortuous turns through the application of tension on the wire in the opposite direction. Mucin may impair visualization. Techniques to remove the mucin include saline infusion and aspiration, balloon extraction before pancreatoscopy, or irrigation with 1% N-acetylcysteine [54].

Ductoscopy for Diagnosis and Management of IPMN

As with all other neoplasms, accurately differentiating benign from malignant lesions and delineating the exact extent of disease are critically important in determining the best treatment

strategy for patients with IPMN. Unfortunately, the currently available imaging modalities have limited accuracy for answering these questions, and therefore, pancreatoscopy, with its ability to directly visualize ductal lesions, has immense potential in guiding the management of main duct IPMN. Direct pancreatoscopy can detect unsuspected high-risk features of malignancy, such as mass lesions and tumor vessels, but most importantly, can determine the extent of disease in the main duct. IPMN can be multifocal, and pancreatoscopy can aid in determining whether a distal pancreatectomy, Whipple resection, or total pancreatectomy is indicated. Pancreatoscopy can also play a role in detecting the presence of main duct disease in suspected mixed IPMN (combination of main duct and branch duct IPMN) [54].

The various ductal findings described on pancreatoscopy in patients with IPMN include the presence of mucin, papillary projections in the main duct or from a side branch, and subtle mucosal nodular changes (Fig. 15.7) [54]. These ductal lesions on pancreatoscopy have been identified in 67–83 % of patients with IPMN [53]. Difficulty or inability to perform biopsy from these lesions is the most significant limitation of the current generation slimmer pancreatoscopes as the diameter of accessory channel is very small. Pancreatic fluid can be easily aspirated for cytology. The diagnostic yield of cytology for detecting IPMN from pancreatic juice sampled through the suction channel of a baby endoscope after saline lavage was higher compared to the fluid collected through an ERCP cannula. Cytology of the pancreatic juice collected during pancreatoscopy diagnosed malignant IPMN correctly in 50 % of patients [53, 57]. This higher yield is hypothesized to result from the ability to collect pancreatic juice immediately adjacent to the culprit lesion under direct vision. Recent studies of detecting newer markers, such as pancreatic secretory trypsin inhibitor (PSTI) or staining the pancreatic juice with mucin stain, have shown increased accuracy for diagnosing as well as differentiating benign from malignant IPMN [58, 59]. The addition of IDUS and NBI imaging to pancreatoscopy may improve our diagnostic ability to differentiate benign from malignant IPMN [53, 60, 61].

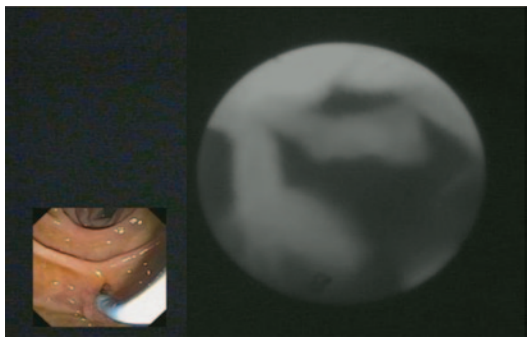

Fig. 15.7 Pancreatoscopy image using SpyGlass scope (Boston Scientific) on the *right* demonstrating typical papillary projections seen in main duct IPMN. Endoscopic view on the *left* showing Spyscope inserted into the pancreatic duct. (Courtesy: Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

Pancreatoscopy is generally a safe procedure, and post-procedure pancreatitis is rare. This probably reflects the fact that only experienced endoscopists undertake this challenging procedure. When pancreatitis occurs, it is usually because the MPD is insufficiently dilated to accommodate the diameter of the baby endoscope or the pancreatic orifice is not adequately patent [53]. The primary issue in pancreatoscopy is maintaining adequate visualization. Mucin easily obscures the optic and light fibers; clearing mucin requires saline or water infusion. During pancreatoscopy, the pancreatic duct can behave like a closed space, especially in a narrow duct, upstream from a stricture with a nonpatulous pancreatic orifice. Infusion of water within a closed space will lead to pancreatitis. Balancing adequate visualization while not overfilling the pancreatic duct is the major technical challenge of pancreatoscopy.

ERCP in Malignant Pancreatic Duct Strictures

Pancreatic cancer has dismal prognosis as most are unresectable at diagnosis. The key to good prognosis is early diagnosis, and EUS has considerably improved our ability to visualize as well as sample small pancreatic lesions. However, the

diagnostic yield of EUS-fine needle aspiration in chronic pancreatitis and isolated ductal strictures is low [62]. Although the majority of ductal strictures in chronic pancreatitis are benign, early pancreatic cancers or pancreatic intraepithelial neoplasia can present as isolated ductal strictures in up to 12% of patients [63]. In these clinical situations ERCP may help differentiate benign from malignant strictures. Various pancreatographic findings of the main duct, branch ducts or the acinar field of the pancreas have been described in the literature [64]. However, these findings have poor discriminating efficacy, and even the addition of conventional brush cytology has limited diagnostic accuracy [65]. Direct ductal inspection and image-guided tissue acquisition by pancreatoscopy may improve diagnostic yield in indeterminate pancreatic duct strictures. However, clinical experience with pancreatoscopy is limited to small case series only, which have described various pancreatoscopic findings in ductal adenocarcinoma including coarse mucosa, friability, erythema, protrusion, tumor vessels, and papillary projections [54, 66]. Similar to IPMN, increased diagnostic yield from cytology of pancreatic juice aspirated during pancreatoscopy has been reported for pancreatic adenocarcinoma [67]. A major limitation of pancreatoscopy in a substantial number of patients is the inability to reach the stricture because of a mismatch between the size of the duct and the baby endoscope.

Malignant pancreatic strictures may occasionally lead to obstructive pain, which is defined as postprandial pain in the epigastric or left upper quadrant region lasting 1–2 h [68]. Stenting may help relieve obstructive pain although gaining wire access through the stricture may be difficult. Smaller caliber (0.018 in.), hydrophilic, or angled guidewires may help. Tight strictures may require balloon or bougie dilation prior to inserting a plastic stent. There are case reports of successful metal stent placement as well [69]. Small case series suggest 66–81% technical success rate for inserting a stent with accompanying partial or complete pain relief in 62–100% of patients and no reported complications [70].

Key Points

- PD is the most common congenital variant of the pancreas and its increased frequency in patients with idiopathic pancreatitis lends support to its possible pathogenic role.
- A minority of patients with PD present with one of three clinical conditions: ARP, chronic pancreatitis, or pancreatic type abdominal pain without evidence of pancreatitis.
- ERCP is the gold standard for diagnosing PD, but CT, MRCP, s-MRCP, and EUS have fairly good accuracy as well. Therefore, ERCP should be reserved for therapeutic management.
- Recurrent pancreatitis without a defined cause is the best indicator of minor papilla stenosis, and these patients respond best to endoscopic therapy.
- The preferred endoscopic approach for opening the minor papilla is papillotomy, which can be performed via needle-knife papillotomy or standard pull-type papillotomy.
- No single clinical, laboratory, or imaging feature is diagnostic of AIP, and histology is the reference standard for the diagnosis.
- ERCP can help in diagnosing difficult cases of AIP, especially if the imaging findings are indeterminate, serology is nondiagnostic, and there is no evidence of other organ involvement.
- The main role of ERCP in intraductal papillary mucinous neoplasm (IPMN) is in localizing the lesion in main duct IPMN using pancreatoscopy and intraductal ultrasound, which can aid surgical planning.
- Stenting malignant pancreatic strictures can help patients with obstructive pancreatic pain.

Conflict of Interest The authors declare no conflict of interest.

Video Captions

Video 15.1 EUS for diagnosing pancreas divisum. This video shows the body, genu, and head of the pancreas using a radial echoendoscope.

The normal nondilated MPD can be seen to the left of the screen diving downward toward the ventral pancreas and major papilla from the body and genu. This excludes PD

Video 15.2 Minor sphincterotomy

References

1. Klein SD, Affronti JP. Pancreas divisum, an evidence-based review: part I, pathophysiology. Gastrointest Endosc. 2004;60:419–25.
2. Bernard JP, Sahel J, Giovannini M, Sarles H. Pancreas divisum is a probable cause of acute pancreatitis: a report of 137 cases. Pancreas.1990;5:248–54.
3. Cotton PB. Pancreas divisum—curiosity or culprit? Gastroenterology. 1985;89:1431–5.
4. Liao Z, Gao R, Wang W, Ye Z, Lai XW, Wang XT, Hu LH, Li ZS. A systematic review on endoscopic detection rate, endotherapy, and surgery for pancreas divisum. Endoscopy. 2009;41:439–44.
5. Spicak J, Poulova P, Plucnarova J, Rehor M, Filipova H, Hucl T. Pancreas divisum does not modify the natural course of chronic pancreatitis. J Gastroenterol. 2007;42:135–9.
6. Hayakawa T, Kondo T, Shibata T, Sugimoto Y, Kitagawa M, Suzuki T, Ogawa Y, Kato K, Katada N, Sano H. Pancreas divisum. A predisposing factor to pancreatitis? Int J Pancreatol. 1989;5:317–26.
7. Fogel EL, Toth TG, Lehman GA, DiMagno MJ, DiMagno EP. Does endoscopic therapy favorably affect the outcome of patients who have recurrent acute pancreatitis and pancreas divisum? Pancreas. 2007;34:21–45.
8. Klein SD, Affronti JP. Pancreas divisum, an evidence-based review: part II, patient selection and treatment. Gastrointest Endosc. 2004;60:585–9.
9. Gonoi W, Akai H, Hagiwara K, Akahane M, Hayashi N, Maeda E, Yoshikawa T, Tada M, Uno K, Ohtsu H, Koike K, Ohtomo K. Pancreas divisum as a predisposing factor for chronic and recurrent idiopathic pancreatitis: initial in vivo survey. Gut. 2011;60:1103–8.
10. Choudari CP, Imperiale TF, Sherman S, Fogel E, Lehman GA. Risk of pancreatitis with mutation of the cystic fibrosis gene. Am J Gastroenterol. 2004;99:1358–63.
11. Gelrud A, Sheth S, Banerjee S, Weed D, Shea J, Chuttani R, Howell DA, Telford JJ, Carr-Locke DL, Regan MM, Ellis L, Durie PR, Freedman SD. Analysis of cystic fibrosis gene product (CFTR) function in patients with pancreas divisum and recurrent acute pancreatitis. Am J Gastroenterol. 2004;99:1557–62.
12. Cotton PB. Congenital anomaly of pancreas divisum as cause of obstructive pain and pancreatitis. Gut. 1980;21:105–14.
13. Soto JA, Lucey BC, Stuhlfaut JW. Pancreas divisum: depiction with multi-detector row CT. Radiology. 2005;235:503–8.
14. Asayama Y, Fang W, Stolpen A, Kuehn D. Detectability of pancreas divisum in patients with acute pancreatitis on multi-detector row computed tomography. Emerg Radiol. 2012;19:121–5.
15. Bret PM, Reinhold C, Taourel P, et al. Pancreas divisum: evaluation with MR cholangiopancreatography. Radiology. 1996;199:99–103.
16. Matos C, Metens T, Deviere J, Delhaye M, Le Moine O, Cremer M. Pancreas divisum: evaluation with secretin enhanced magnetic resonance cholangiopancreatography. Gastrointest Endosc. 2001;53:728–33.
17. Rustagi T, Njei B. Magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum: a systematic review and meta-analysis. Pancreas. 2014;43(6):823–8.
18. Mosler P, Akisik F, Sandrasegaran K, et al. Accuracy of magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum. Dig Dis Sci. 2012;57:170–4.
19. Carnes ML, Romagnuolo J, Cotton PB. Miss rate of pancreas divisum by magnetic resonance cholangiopancreatography in clinical practice. Pancreas. 2008;37:151–3.
20. Rana SS, Gonen C, Vilmann P. Endoscopic ultrasound and pancreas divisum. J Pancreas. 2012;10:252–7.
21. Rana SS, Bhasin DK, Sharma V, Rao C, Singh K. Role of endoscopic ultrasound in the diagnosis of pancreas divisum. Endosc Ultrasound. 2013;2:7–10
22. Kushnir VM, Wani SB, Fowler K, et al. Sensitivity of endoscopic ultrasound, multidetector computed tomography, and magnetic resonance cholangiopancreatography in the diagnosis of pancreas divisum: a tertiary center experience. Pancreas. 2013;42:436–41.
23. Benage D, McHenry R, Hawes RH, O'Connor KW, Lehman GA. Minor papilla cannulation and dorsal ductography in pancreas divisum. Gastrointest Endosc. 1990;36:553–7.
24. DeWitt J, McHenry L, Fogel E, LeBlanc J, McGreevy K, Sherman S. EUS-guided methylene blue pancreatography for minor papilla localization after unsuccessful ERCP. Gastrointest Endosc. 2004;59:133–6.
25. Alazmi WM, Mosler P, Watkins JL, McHenry L, Fogel EL, Sherman S, Lehman GA. Predicting pancreas divisum by inspection of the minor papilla: a prospective study. J Clin Gastroenterol. 2007;41:422–6.
26. Lehman GA, Sherman S. Diagnosis and therapy of pancreas divisum. Gastrointest Endosc Clin N Am. 1998;8:55–77.
27. Tulassay Z, Jakab Z, Vadàsz A, Kelemen E, Gupta R. Secretin provocation ultrasonography in the diagnosis of papillary obstruction in pancreas divisum. Gastroenterol J. 1991;51:47–50.
28. Staritz M, Meyer zum Büschenfelde KH. Elevated pressure in the dorsal part of pancreas divisum: the cause of chronic pancreatitis? Pancreas. 1988;3:108–10.
29. Satterfield ST, McCarthy JH, Geenen JE, Hogan WJ, Venu RP, Dodds WJ, Johnson GK. Clinical experience in 82 patients with pancreas divisum:

preliminary results of manometry and endoscopic therapy. Pancreas. 1988;3:248–53.
30. Gerke H, Byrne MF, Stiffler HL, Obando JV, Mitchell RM, Jowell PS, Branch MS, Baillie J. Outcome of endoscopic minor papillotomy in patients with symptomatic pancreas divisum. JOP. 2004;5:122–31.
31. 31. Yamamoto N, Isayama H, Sasahira N, Tsujino T, Nakai Y, Miyabayashi K, Mizuno S, Kogure H, Sasaki T, Hirano K, Tada M, Koike K. Endoscopic minor papilla balloon dilation for the treatment of symptomatic pancreas divisum. Pancreas. 2014;43(6):927–30.
32. Lans JI, Geenen JE, Johanson JF, Hogan WJ. Endoscopic therapy in patients with pancreas divisum and acute pancreatitis: a prospective, randomized, controlled clinical trial. Gastrointest Endosc. 1992;38:430–4.
33. Linder JD, Bukeirat FA, Geenen JE, et al. Long term response to pancreatic duct stent placement in symptomatic patients with pancreas divisum. Gastrointest Endosc. 2003;57:208A
34. Bhasin DK, Rana SS, Sidhu RS, Nagi B, Thapa BR, Poddar U, Gupta R, Sinha SK, Singh K. Clinical presentation and outcome of endoscopic therapy in patients with symptomatic chronic pancreatitis associated with pancreas divisum. JOP. 2013;14:50–6.
35. Sherman S, Hawes RH, Savides TJ, Gress FG, Ikenberry SO, Smith MT, Zaidi S, Lehman GA. Stent-induced pancreatic ductal and parenchymal changes: correlation of endoscopic ultrasound with ERCP. Gastrointest Endosc. 1996;44:276–82.
36. Saltzman JR. Endoscopic treatment of pancreas divisum: why, when, and how? Gastrointest Endosc. 2006;64:712–5.
37. Lehman GA, Sherman S, Nisi R, Hawes RH. Pancreas divisum: results of minor papilla sphincterotomy. Gastrointest Endosc. 1993;39:1–8.
38. Attwell A, Borak G, Hawes R, Cotton P, Romagnuolo J. Endoscopic pancreatic sphincterotomy for pancreas divisum by using a needle-knife or standard pull-type technique: safety and reintervention rates. Gastrointest Endosc. 2006;64:705–11.
39. Moffatt DC, Coté GA, Avula H, Watkins JL, McHenry L, Sherman S, Lehman GA, Fogel EL. Risk factors for ERCP-related complications in patients with pancreas divisum: a retrospective study. Gastrointest Endosc. 2011;73:963–70.
40. Kamisawa T, Chari ST, Lerch MM, Kim MH, Gress TM, Shimosegawa T. Recent advances in autoimmune pancreatitis: type 1 and type 2. Gut. 2013;62:1373–80.
41. Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. Gastrointest Endosc. 2012;76:645–56.
42. Sugumar A, Levy MJ, Kamisawa T, Webster GJ, Kim MH, Enders F, Amin Z, Baron TH, Chapman MH, Church NI, Clain JE, Egawa N, Johnson GJ, Okazaki K, Pearson RK, Pereira SP, Petersen BT, Read S, Sah RP, Sandanayake NS, Takahashi N, Topazian MD, Uchida K, Vege SS, Chari ST. Endoscopic retrograde pancreatography criteria to diagnose autoimmune pancreatitis: an international multicentre study. Gut. 2011;60:666–70.
43. Kim JH, Kim MH, Byun JH, Lee SS, Lee SJ, Park SH, Lee SK, Park DH, Lee MG, Moon SH. Diagnostic strategy for differentiating autoimmune pancreatitis from pancreatic cancer: is an endoscopic retrograde pancreatography essential? Pancreas. 2012 Jan 5.
44. Song TJ, Kim JH, Kim MH, Jang JW, Park do H, Lee SS, Seo DW, Lee SK, Yu E. Comparison of clinical findings between histologically confirmed type 1 and type 2 autoimmune pancreatitis. J Gastroenterol Hepatol. 2012;27:700–8.
45. Takuma K, Kamisawa T, Tabata T, Inaba Y, Egawa N, Igarashi Y. Utility of pancreatography for diagnosing autoimmune pancreatitis. World J Gastroenterol. 2011;17:2332–7.
46. Naitoh I, Nakazawa T, Ohara H, Ando T, Hayashi K, Tanaka H, Okumura F, Takahashi S, Joh T. Endoscopic transpapillary intraductal ultrasonography and biopsy in the diagnosis of IgG4-related sclerosing cholangitis. J Gastroenterol. 2009;44:1147–55.
47. Otsuki M, Chung JB, Okazaki K, Kim MH, Kamisawa T, Kawa S, Park SW, Shimosegawa T, Lee K, Ito T, Nishimori I, Notohara K, Naruse S, Ko SB, Kihara Y, Research Committee of Intractable Pancreatic Diseases provided by the Ministry of Health, Labour and Welfare of Japan and the Korean Society of Pancreatobiliary Diseases. Asian diagnostic criteria for autoimmune pancreatitis: consensus of the Japan-Korea Symposium on Autoimmune Pancreatitis. J Gastroenterol. 2008;43:403–8.
48. Park SH, Kim MH, Kim SY, Kim HJ, Moon SH, Lee SS, Byun JH, Lee SK, Seo DW, Lee MG. Magnetic resonance cholangiopancreatography for the diagnostic evaluation of autoimmune pancreatitis. Pancreas. 2010;39:1191–8.
49. Conlon KC. Intraductal papillary mucinous tumors of the pancreas. J Clin Oncol. 2005;23:4518–23.
50. Ohashi K, Murakami Y, Maruyama M. Four cases of mucin producing cancer of the pancreas on specific findings of the papilla of Vater [in Japanese]. Prog Dig Endosc. 1982;20:348–51.
51. Belyaev O, Seelig MH, Muller CA, Tannapfel A, Schmidt WE, Uhl W. Intraductal papillary mucinous neoplasms of the pancreas. J Clin Gastroenterol. 2008;42:284–94.
52. Nguyen NQ. Getting most out of SpyGlass cholangio-pancreatoscopy: how and when? J Gastroenterol Hepatol. 2012;27:1263–5.
53. Nguyen NQ, Binmoeller KF, Shah JN. Cholangioscopy and pancreatoscopy (with videos). Gastrointest Endosc. 2009;70:1200–10.
54. 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;19:601–13.
55. Cheon YK, Moon JH, Choi HJ, Lee JE, Lee YN, Cho YD, Lee TH, Park SH, Kim SJ. Direct peroral pancreatoscopy with an ultraslim endoscope

for the evaluation of intraductal papillary mucinous neoplasms. Endoscopy. 2011;43(Suppl 2 UCTN):E390–1.
56. Kawakubo K, Isayama H, Sasahira N, Kogure H, Takahara N, Miyabayashi K, Mizuno S, Yamamoto K, Mohri D, Sasaki T, Yamamoto N, Nakai Y, Hirano K, Tada M, Koike K. Clinical utility of single-operator cholangiopancreatoscopy using a SpyGlass probe through an endoscopic retrograde cholangiopancreatography catheter. J Gastroenterol Hepatol. 2012;27:1371–6.
57. Yamaguchi T, Shirai Y, Ishihara T, Sudo K, Nakagawa A, Ito H, Miyazaki M, Nomura F, Saisho H. 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.
58. Shirai Y, Sogawa K, Yamaguchi T, Sudo K, Nakagawa A, Sakai Y, Ishihara T, Sunaga M, Nezu M, Tomonaga T, Miyazaki M, Saisho H, Nomura F. Protein profiling in pancreatic juice for detection of intraductal papillary mucinous neoplasm of the pancreas. Hepatogastroenterology. 2008;55:1824–9.
59. Hara T, Ikebe D, Odaka A, Sudo K, Nakamura K, Yamamoto H, Itami M, Hirata T, Kashimura J, Yamaguchi T. Preoperative histological subtype classification of intraductal papillary mucinous neoplasms (IPMN) by pancreatic juice cytology with MUC Stain. Ann Surg. 2013;257:1103–11.
60. 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;122:34–43.
61. Itoi T, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Arisaka Y, Moriyasu F. 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;66:793–7.
62. Krishna NB, Mehra M, Reddy AV, et al. EUS/EUS-FNA for suspected pancreatic cancer: influence of chronic pancreatitis and clinical presentation with or without obstructive jaundice on performance characteristics. Gastrointest Endosc. 2009;70:70–9.
63. Kalady MF, Peterson B, Baillie J, et al. Pancreatic duct strictures: identifying risk of malignancy. Ann Surg Oncol. 2004;11:581–8.
64. Fukumoto K, Nakajima M, Murakami K, Kawai K. Diagnosis of pancreatic cancer by endoscopic pancreatocholangiography. Am J Gastroenterol. 1974;62:210–3.
65. Athanassiadou P, Grapsa D. Value of endoscopic retrograde cholangiopancreatography-guided brushings in preoperative assessment of pancreaticobiliary strictures: what's new? Acta Cytol. 2008;52:24–34.
66. Yamao K, Ohashi K, Nakamura T, et al. Efficacy of peroral pancreatoscopy in the diagnosis of pancreatic diseases. Gastrointest Endosc. 2003;57:205–9.
67. Uehara H, Nakaizumi A, Tatsuta M, Iishi H, Kitamura T, Ohigashi H, Ishikawa O, Takenaka A. Diagnosis of carcinoma in situ of the pancreas by peroral pancreatoscopy and pancreatoscopic cytology. Cancer. 1997;79:454–61.
68. Gouma DJ, Busch OR, Van Gulik TM. Pancreatic carcinoma: palliative surgical and endoscopic treatment. HPB (Oxford). 2006;8:369–76.
69. Keeley SP, Freeman ML. Placement of self-expanding metallic stents in the pancreatic duct for treatment of obstructive complications of pancreatic cancer. Gastrointest Endosc. 2003;57:756–9.
70. Sharaiha RZ, Widmer J, Kahaleh M. Palliation of pancreatic ductal obstruction in pancreatic cancer. Gastrointest Endosc Clin N Am. 2013;23:917–23.

Part IV
Special Considerations

Bleeding from the Papilla

16

Simon K. Lo

Introduction

Bleeding from the papilla is often referred to as hemobilia, implying a bile duct source of hemorrhage. In reality, blood can also come down from the pancreatic duct, and this is known as hemoductal or hemosuccus pancreaticus. Iatrogenic injury of the bile duct caused by percutaneous cholangiography, tissue ablation, or liver biopsy is the leading source of hemobilia [1, 2] (Table 16.1). On the other hand, the most common cause of hemosuccus pancreaticus is rupture of an arterial pseudoaneuysm within the pancreas, caused by acute or chronic pancreatitis (Table 16.2). There is no accurate account of how common hemobilia and hemosuccus are, as they are both unusual pancreaticobiliary conditions. The clinician should have a strong index of suspicion of these problems in order to anticipate their occurrences. Whenever a pancreatic or biliary complaint accompanies overt gastrointestinal (GI) bleeding, hemosuccus, or hemobilia must be listed high on the differential diagnosis.

Hemobilia and hemosuccus pancreaticus are rarely encountered in daily practice. Given their variable presentations, we have selected a few of our own cases to highlight the key features and clinical scenarios in which bleeding from the papilla may occur.

Case 1

A 33-year-old man presented with right upper quadrant pain and jaundice. He underwent a cholecystectomy, common duct exploration and T-tube placement for acute cholecystitis and a large common bile duct stone. He remained deeply jaundice after surgery and had required six units of packed red blood cell transfusion over the next week. He then developed intermittent low grade fever. During this time, both the T-tube and percutaneous subhepatic drain had low outputs of blood tinged fluid.

What is the Differential Diagnosis?

An extensive biliary and gallbladder surgery, followed by cholangitis and persistent jaundice, is worrisome for a bile duct injury such as extrahepatic bile duct transection, retained stone or diffuse liver injury. The low T-tube output suggested a patent bile duct or T-tube malfunction. The latter possibility was supported by difficult bedside irrigation through this small-caliber tube. The blood tinged fluid via the percutaneous drain and T-tube pointed to bleeding within and outside of the biliary tract, raising suspicion for both bleeding and communication between these two drains. On the other hand, having

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Table 16.1 Causes of hemobilia

Iatrogenic	Liver biopsy
	Transhepatic cholangiography
	Transhepatic ablative therapy
	Transhepatic biliary drainage
	Cholecystectomy
	Bile duct surgery
	Endoscopic retrograde cholangiopancreatography (ERCP) manipulation (stenting, sphincterotomy, biopsy, lithotripsy, stricture dilation, etc.)
Trauma	Penetrating injury to liver or bile duct
	Blunt liver trauma
Neoplastic	Primary liver cancer
	Gallbladder cancer
	Bile duct cancer
	Benign liver tumor
	Metastatic cancer to liver/bile duct
Gallstones	Gallstone irritation
Gallbladder/bile duct	Inflammation
Vascular	Pseudoaneurysm from inflammatory condition
	Arteritis
	Arteriovenous malformation
	Arterial aneurysm
Pancreatic	Pseudocyst
	Cancer invasion
Infection	Parasite
	Liver abscess

Table 16.2 Causes of hemosuccus pancreaticus

Pancreatitis	Pancreatic necrosis
	Pseudocyst
	Splenic artery pseudoaneurysm
Pancreatic tumor	Pancreatic cancer
	Neuroendocrine tumor
	Metastatic cancer to the pancreas
	Serous cystadenoma
Vascular disease	Aneurysm of the celiac or splenic artery
	Segmental arterial mediolysis
	Pancreatic arteriovenous malformation
Pancreatic trauma	Penetrating injury
	Blunt trauma
Iatrogenic pancreatic injury	Needle aspiration of pancreatic cyst
	Endoscopic necrosectomy
	Pancreatic stenting
	Ductal dilation
	Pancreatic stone lithotripsy
Pancreatic infection	Brucellosis
	Tuberculosis

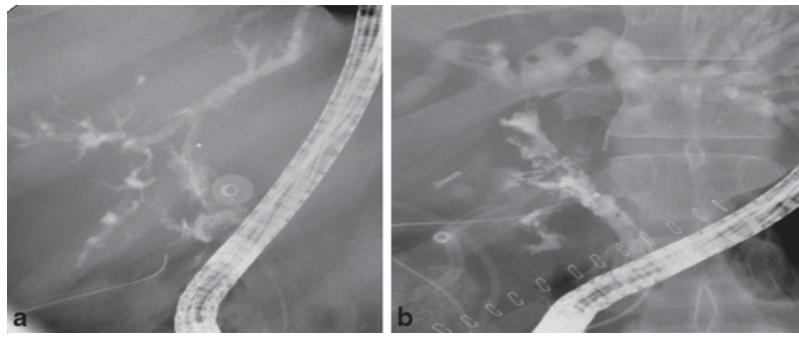

Fig. 16.1 Hemobilia occurring after cholecystectomy. **a** Initial contrast injection was difficult, and cholangiogram showed extensive filling defects in the common and right hepatic ducts. **b** After sweeping clear some blood clots from the extrahepatic bile duct, contrast was noted leaking out of the cystic duct stump and the T-tube insertion site of the bile duct

some minor oozing after extensive manipulations of the bile duct was not definitive evidence of a bleeding complication. Of the four possible ways to investigate the integrity of the biliary tract, including radionuclide biliary scan, T-tube cholangiograms, magnetic resonance cholangiopancreatography (MRCP), and endoscopic retrograde cholangiopancreatography (ERCP). ERCP is perhaps most accurate and potentially therapeutic. Before doing so, an abdominal computed tomography (CT) should be done to exclude an abscess, hematoma, or biloma.

Case Continued

An abdominal CT showed no significant fluid collection or abscess cavity. On post-operation day number 12, an ERCP was performed. At the procedure, the papilla appeared normal. Initial contrast injection was difficult, as the entire bile duct was packed with some ill-defined filling defects. After a sphincterotomy, balloon sweeps retrieved a large amount of fresh blood and clots. Bile leak was discovered at the cystic duct stump and at the T-tube site (Fig. 16.1). After evacuating blood and debris from the bile duct, two 10 French plastic stent biliary stents were placed. This patient recovered uneventfully after the ERCP, without further jaundice, fever, or bleeding. The stents were removed 2 months later.

Hemobilia

Iatrogenic injury of the bile duct or liver tissue is the most common cause of hemobilia, accounting for roughly two thirds of all such cases [2]. Transient bleeding via the papilla is often noted after a percutaneous liver biopsy and is thought to be due to the close proximity between the intrahepatic bile duct, hepatic artery, and portal vein [3]. Needle puncture can easily penetrate these structures to form arteriovenous fistula, arterial bile duct fistula, or venous bile duct fistula. Venous bile duct fistula bleeding is typically mild and self-limited, rarely requiring any therapeutic intervention. Transhepatic cholangiography and percutaneous biliary drainage, which causes hemorrhage in 2−2.5% of the procedures [4], may result in life-threatening hemobilia through injury to the hepatic artery or portal vein [5]. Even internal biliary stents, particularly metallic prosthesis, may result in direct vascular puncture or formation of pseudoaneurysm of the hepatic artery [6].

A strong clue to hemobilia is the presence of the triad of overt GI bleeding, jaundice, and right upper quadrant pain [7]. However, this is often the exception rather than the rule, as all three signs exist only in 22% of all hemobilia cases [2]. More commonly, the endoscopist discovers blood either within the bile duct or oozing from the major papilla during an ERCP. Rarely, hemobilia is the cause of unexplained obscure GI

bleeding. Depending on the location of bleeding, cholangitis, cholecystitis, pancreatitis have all been reported. Massive hemorrhage can mimic lower GI bleeding.

Evaluation for hemobilia depends on the clinical presentation and suspicion for hemobilia [1]. In patients with high suspicion for hemobilia, CT angiography is the test of choice not only to identify presence of bleeding, but also to identify the source and plan for potential therapeutic angiography. Otherwise, patients displaying signs and symptoms of GI bleeding should be evaluated with upper endoscopy. A side-viewing duodenoscope is necessary to visualize the papilla adequately. In patients presenting with cholangitis or biliary obstruction, ERCP is a reasonable initial diagnostic procedure with or without antecedent radiology imaging such as transabdominal ultrasound, CT or MRCP. On cholangiography, blood clots are poorly outlined and they do not retain a constant shape like gallstones do. These ghost-like filling defects may mimic those from neoplastic tissues. Interestingly, fresh blood and blood clots are best seen during the initial contrast filling of the bile duct. When the bile duct is more saturated with contrast, the filling defects may disappear. Therefore, it is always a good practice to observe the fluoroscopy or obtain radiographs at the beginning of contrast injection. The ultimate proof of hemobilia is visualization of blood coming out of the bile duct, usually occurring at the time of a balloon sweep. Depending on the duration of clot formation, some of this material may appear as soft hemorrhagic tumors. Indeed, blood in the bile duct often contains tumor cells and should be suctioned into a container for cytology evaluation.

A trivial amount of bleeding may be seen during ERCP following balloon stricture dilation, forceps biopsy, or stone extraction and is not out of the ordinary or a major issue. However, when encountering spontaneous and large quantity bleeding, it is important to think about the probable cause, extent of disease and back-up plan before embarking on a more thorough investigation or manipulation of the bile duct. In particular, biliary bleeding in advanced portal hypertension [8], pseudoaneurysm, indwelling stent erosion into the periductal vasculature, and sphincterotomy bleeding related blood reflux into the bile duct should all be taken seriously. Fatal hemobilia has been reported in the literature [9]. Sudden exsanguination may occur in these settings, and a good anticipatory plan should be in place before proceeding further. In massive bleeding that does not stop spontaneously, one possible way to temporize the situation is to occlude the bile duct with a retrieval balloon. Among the ultimate treatment options are emergency angiographic embolization [10], balloon tamponade, fully-covered metal stenting, and a full range of endoscopic bleeding treatment modalities.

Not all patients with hemobilia require treatment as most iatrogenic bleeding after percutaneous liver biopsy or percutaneous biliary drainage stop spontaneously. For ongoing or recurrent bleeding, angiography with embolization is the treatment of choice with reports of 75–100% success [1]. ERCP does not have a role in treating bleeding and is only indicated for establishing biliary drainage.

This case illustrates that multiple biliary complications, including bile leak, hemorrhage, biliary obstruction, and cholangitis, can take place simultaneously when an adverse event has occurred during gallbladder surgery. In spite of the potential devastation, these problems can be successfully treated with simple biliary stenting. While fully covered metal stents have been reported as effective [8, 11, 12], even plastic stents as were used here may be just as useful.

Case 2

A 46-year-old female presented with jaundice and a suspected hilar mass. A transhepatic study failed to pass through her biliary stricture. ERCP showed a high grade obstruction of the proximal common hepatic duct, with dilated right and left hepatic ducts (Fig. 16.2). Catheter aspiration of the intrahepatic fluid showed bloody

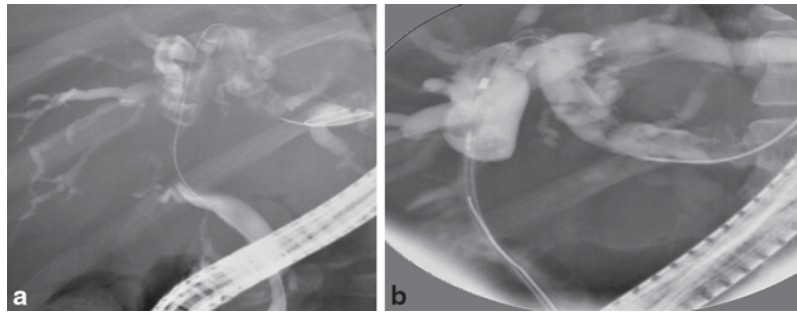

Fig. 16.2 Cholangiograms after a failed transhepatic drainage of common hepatic duct stricture. **a** High grade obstruction of the common hepatic duct. Note: Blood appears as linear serpiginous filling defects. **b** Further contrast injection shows different appearance of the intrahepatic duct filling defects, characteristic of blood clots in the bile duct

material with some pus. Further injection of contrast demonstrated ill-defined filling defects throughout the obstructed ducts, consistent with hemobilia or tumor infiltration. After stricture brushing and dilation, a 10 French plastic stent was placed, draining a large amount of bloody fluid. The brush cytology was positive for adenocarcinoma.

Another Iatrogenic Cause of Hemobilia

This case demonstrates that transhepatic needle punctures may lead to hemobilia, especially after an extended effort made to access the bile duct for drainage. The initial cholangiograms show linear, serpiginous, filling defects that might represent biliary ascaris or tumor infiltration and not hemobilia. Of course, the only way to confirm biliary hemorrhage is to visualize blood through a patent biliary stent or balloon sweeps. While bleeding from a failed puncture attempt is usually self-limited, hemorrhage from an indwelling transhepatic catheter may present recurrently from a pseudoaneurysm [13]. It has previously been reported that 50% of biliary source of bleeding takes place in the intrahepatic bile ducts and the other half is from the extrahepatic system and the gallbladder [14]. With increasing transhepatic therapies, there are probably more intrahepatic bleeding cases in these days.

Case 3

A 44-year-old male presented to an outside facility with jaundice and right upper quadrant pain. ERCP showed a liver hilum mass and blood clots in the extrahepatic bile duct, with bile duct biopsy showing hepatocellular carcinoma. Multiple subsequent ERCPs and stenting failed to improve his liver function and he was referred to our institution for further evaluation. Upon removal of his internal stents, a large amount of blood passed through the papilla. Some materials that were swept out appeared to be soft tumor tissue or well-formed clots (Fig. 16.3). Cholangiograms showed extensive, irregularly shaped, filling defects. Despite multiple plastic stents, metal stent, and even a nasobiliary drain placement over the next few weeks, the patient remained jaundice with on-going blood transfusion requirements. He ultimately underwent a very difficult biliary surgical resection and lived for another 2 years.

A Non-iatrogenic Cause of Hemobilia

Hemobilia is a common presentation of hepatocellular carcinomas that locate centrally and have invaded the bile duct. These tumors are highly vascular and bleeding can be massive or continuous as in this case. The diagnosis should be suspected in spontaneous intraductal bleeding in the proximal common hepatic duct or intrahepatic ducts. However, we have observed some

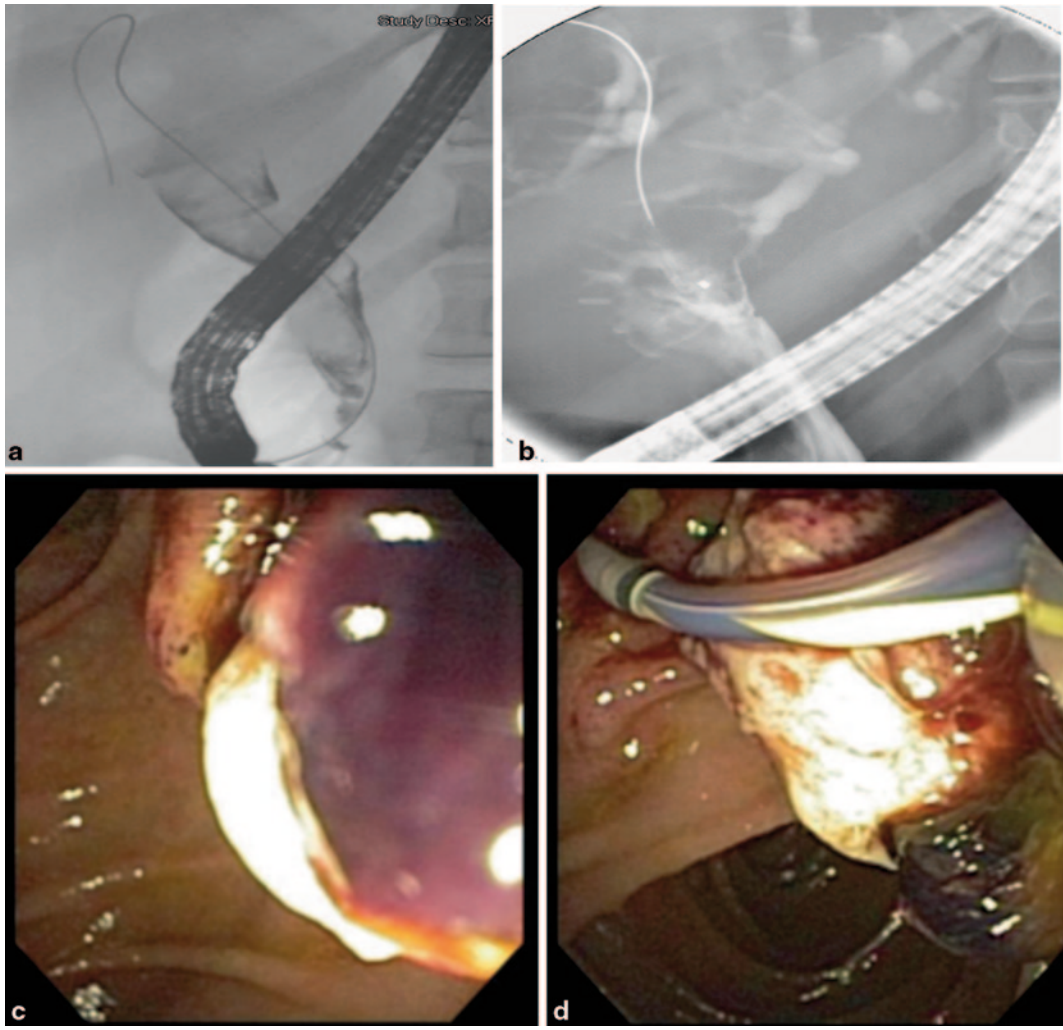

Fig. 16.3 Hepatocellular carcinoma presenting with hemobilia. **a** Initial cholangiogram shows blood filling the entire bile duct, leaving narrow spaces around the bile duct to be filled with contrast, giving the appearance of double contrast outlining of the extrahepatic bile duct. **b** Blood clots mixed with hilar liver cancer, presenting as a large mass occupying the bile duct bifurcation. **c** A large blood clot being extracted from the bile duct. **d** This large soft mass appears to be a cross between a clot and a tumor, containing tissue positive for hepatocellular carcinoma

hepatocellular carcinomas that extended down the entire bile duct and even infiltrated the papilla. Tissue acquisition for diagnosis is readily achieved in these cases, as either the blood clots or exophytic tissues are easily obtained to determine the nature of the cancer. Most of these lesions are unresectable and are difficult to manage. As opposed to stenting a tumor with minimal bleeding tendency, palliative stenting of a hepatoma that causes hemobilia is frequently ineffective, as continuous hemorrhage may lead to early stent failure and clogging. Even large caliber metallic biliary stents do not ensure adequate patency because of the large blood clots. Likewise, transhepatic or vascular interventions may be ineffective in stopping bleeding of these highly vascular lesions. Chemotherapy treatment of advanced hepatocellular carcinoma had been linked to fatal hemobilia and should be used with caution in patients with a prior history of hemo-

bilia [15]. This case is a perfect example of such a problematic situation. Despite the risk and technical difficulty, surgical resection may be the only viable option in some cases. Rarely, blood clots and even sloughed tumors may act like gallstones and induce acute pancreatitis [16, 17], requiring sphincterotomy for relief. The finding of pancreatitis in these cases may mislead us to consider hemosuccus pancreaticus instead of hemobilia.

Case 4

A 91-year-old female was referred from an outside facility for severe choledocholithiasis. Before coming to our center, she had undergone two ERCPs and had sphincterotomy and biliary stenting done. In spite of the procedures, her liver tests continued to be elevated and her white blood cell count was further elevated. Endoscopic examination at our unit showed a small amount of blood oozing out of the papilla. However, there was no definite evidence of bleeding from the old sphincterotomy. Injection of contrast was difficult, as if the bile duct was very small or congested with stones. Indeed, there were extensive filling defects in the bile duct, which all turned out to be fresh blood and clots (Fig. 16.4). No stone was seen during balloon extraction. After biliary stenting, three endoscopic clips were placed over the sphincterotomy cut edge. No further bleeding or cholangitis was encountered.

Bleeding Mimicking Choledocholithiasis

Biliary tract obstruction following ERCP and stone extraction should automatically raise the suspicion that there are more biliary stones left behind or new stones have come down from an in-situ gallbladder. Additional explanations would include sphincter edema due to recent manipulations or sphincter occlusion from a missed ampullary infiltrating lesion. One rarely considered entity is post-sphincterotomy bleeding [18], with blood accumulating inside the bile duct, mimicking residual stones. Interestingly, the sphincterotomy site may appear dry, like this case, without the obvious signs of bleeding. Sphincterotomy bleeding should always be considered as the source of hemobilia whenever an ERCP has been performed within the previous few days. The approach to persistent jaundice in this situation is to first investigate for the cause by repeating an ERCP. While it is easy to find blood inside the bile duct, it may be difficult to determine where it is coming from. Sweep clearance and careful inspection of the bile duct should be done to ex-

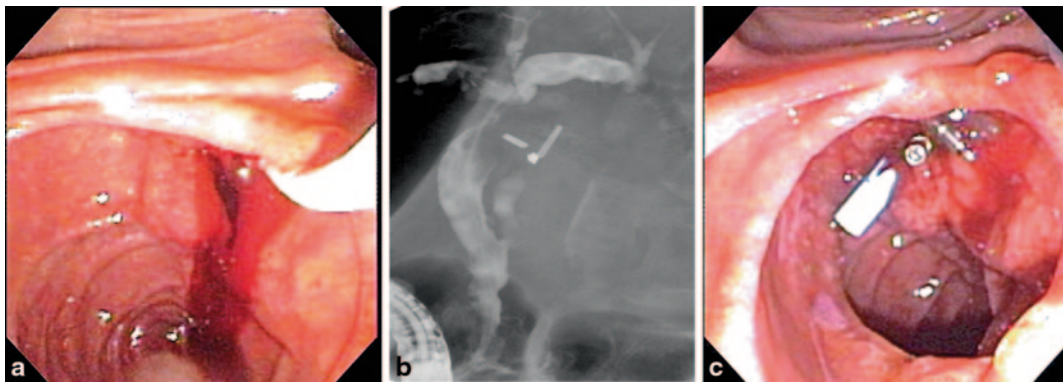

Fig. 16.4 Sphincterotomy bleeding presenting as hemobilia. **a** The papilla initially appeared clear of any bleeding. Balloon sweep shows blood coming out of the papilla. **b** Bile duct contrast showed extensive filling defects made of blood clots. **c**: Bleeding stopped after biliary stenting and clip placement on the upper edge of the sphincterotomy

clude missed lesions and bile duct injury from the recent procedure. After eliminating a ductal cause of bleeding, sphincterotomy hemorrhage should be seriously considered as the etiology. Whenever a clear cut diagnosis cannot be established, a biliary stent should be placed to maintain biliary patency. A fully covered stent may be considered to additionally address potential recurrent bleeding by providing tamponade against the papilla. Alternatively, the cut edges of the papilla can be treated with clipping, cautery, or submucosal injection, depending on the skill and personal preference of the endoscopist.

Case 5

A 78-year-old male had a cholecystectomy done for acute cholecystitis. Due to technical difficulty, the laparoscopic procedure was converted to an open surgery with drain placement. A large amount of bile was noted in the drainage device and the diagnosis of bile leak was made. The patient then underwent an ERCP, which showed extensive ductal extravasation at the mid common hepatic bile duct, and right and left intrahepatic systems. After clearing out bile and blood clots from the ducts, multiple leaks and probable necrosis of the right lobe of the liver were noted (Fig. 16.5). The operative report of hepatic artery injury requiring repair provided probable cause for the extensive bile leak and liver injury. Multiple plastic stents were placed and exchanged bimonthly over the next 24 months. The bile leak eventually resolved and the abdominal drain was removed. However, he went on to develop numerous right and left intrahepatic ischemic biliary strictures, advanced cirrhosis, and recurrent cholangitis, leading to his demise.

Severe Iatrogenesis

Severe vascular injuries during cholecystectomy, leading to acute liver necrosis, have been reported [19]. Hemobilia in this patient was most likely induced by tissue necrosis and bleeding from direct ductal trauma. Alternatively, blood within the surgical dissection field might have entered through the large defects of the extrahepatic bile duct, leading to hemobilia. Bleeding from liver injury is usually self-limited, as in this case. On the other hand, cavity formation, abscess development, recurrent cholangitis, ischemic biliary strictures, and ultimately secondary biliary cirrhosis may become bigger issues. Patients with both bile duct and vascular injury develop liver necrosis with or without abscess in up to 75% [19]. Vascular studies and a surgical consultation are necessary to consider arterial reconstruction and liver resection, even though bile leakage can be readily handled with internal biliary stenting. Unfortunately, the patient's liver and bile duct injuries were felt by our liver surgeons to

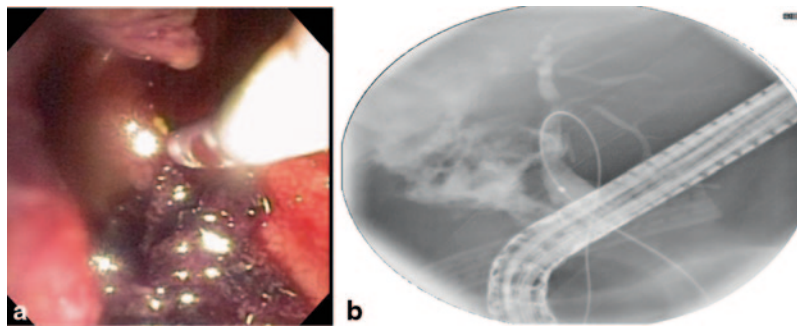

Fig. 16.5 Post-cholecystectomy bleeding. **a** Blood clots readily removed from the bile duct. **b** The normal right hepatic system was replaced by contrast extravasating into the liver parenchyma, representing loss of ductal integrity and likely liver necrosis

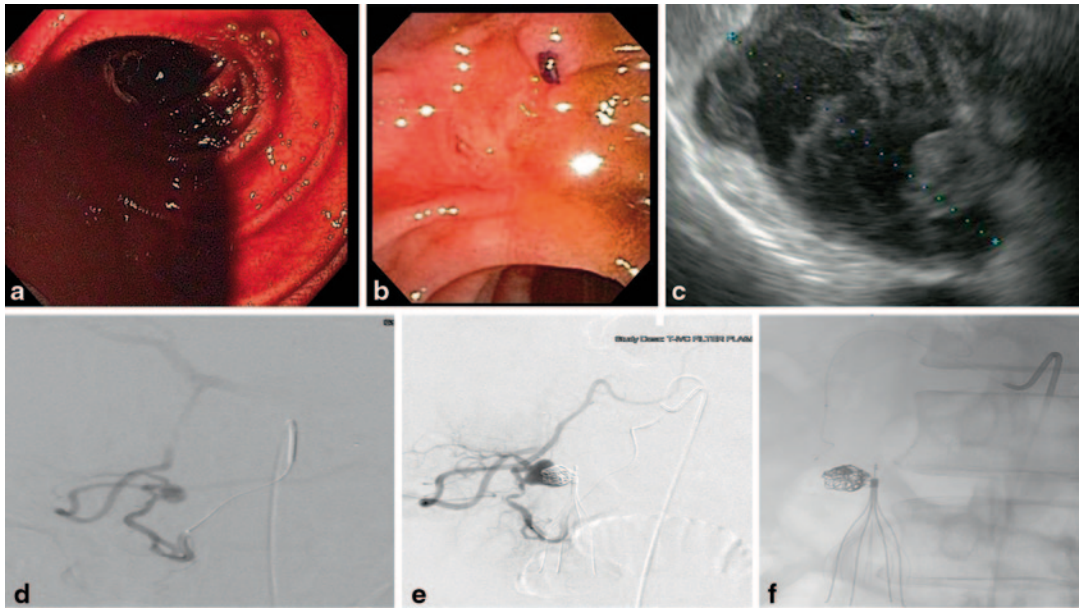

Fig. 16.6 Hemosuccus pancreaticus with severe bleeding. **a** Initial examination of the duodenum for gastrointestinal bleeding showed a large amount of fresh blood. **b** After cleaning up the duodenum, a blood clot was noted to be protruding from the papilla. **c** Endosonography (EUS) discovered a large, heterogeneous filling defect within a cyst of the pancreas. **d** Angiogram showed a pseudoaneurym of the splenic artery. **e** Coils were placed inside the pseudoaneurys. **f** Radiograph of the abdomen after the coil embolization was complete

be too extensive to benefit from biliary bypass or segmental liver resection. The only treatment option was liver transplantation, which was not possible due to his age and poor health.

Case 6

A 53-year-old male was transferred from an outside hospital for management of upper GI bleeding and pancreatitis. He had a history of chronic pancreatitis secondary to alcohol use and had been admitted to the hospital 2 weeks earlier with hematemesis. During that hospitalization, upper endoscopy and colonoscopy investigations were unremarkable. A CT scan demonstrated a peripancreatic fluid collection anterior to the stomach. On this admission, he initially presented with an acute flare of pancreatitis. He then developed two episodes of hematemesis, with hemoglobin dropping to 5 g. He received nine units of packed blood transfusion during this hospitalization. On upper endoscopy, fresh blood and clots were noted in the duodenum (Fig. 16.6). A side viewing scope identified a clot protruding from the ampulla. Endosonography (EUS) was performed to investigate for possible gastric varices or bleeding within the pseudocyst, and it revealed a 9 cm, well circumscribed but heterogeneous, cystic structure in the region of the body and tail of the pancreas without definite Doppler flow. Needle aspiration revealed grossly bloody fluid. Interestingly, his serum liver and pancreatic enzymes remained normal throughout the hospital stay. An angiographic study showed a splenic artery pseudoaneurysm and coil embolization was done to occlude two feeding vessels. No further bleeding was encountered during the next 8 months of follow up.

Hemosuccus Pancreaticus

Hemosuccus pancreaticus, also referred to as hemoductal pancreaticus, Wirsungorrhaghia and pseudohemobilia, occurs less often than

hemobilia and is potentially life threatening. It is most commonly seen in the setting of acute or chronic pancreatitis when the splenic artery is directly involved in the inflammatory process, giving rise to a pseudoaneurysm. While the splenic artery is the predominant vessel (60–65 %) involved in this condition, hepatic, gastroduodenal, and pancreaticoduodenal arteries have all been linked to hemosuccus [20, 21]. When the pseudoaneurysm ruptures and blood escapes through a short fistula into the pancreatic duct, bleeding occurs via the major or minor papilla [22, 23]. Contrary to hemobilia, hemosuccus is more difficult to diagnose. Analogous to the triad for hemobilia, hemosuccus may present with intermittent and recurrent epigastric pain, GI bleeding, and elevated amylase. The lack of obvious clinical signs, such as jaundice and abnormal liver enzymes, and intermittent nature of bleeding may lead to a delay in investigation and therefore missing the critical moment of witnessing blood coming out of the papilla. Endoscopic visualization of bleeding from the papilla, such as in this case, is uncommon although blood may be present in the duodenum in about half these cases [24, 25]. Intermittent epigastric pain followed by an overt episode of GI bleeding typically melena and less commonly hematemesis within 30–40 min is an important clue to hemosuccus [26]. Bleeding is usually intermittent and recurrent often leading to anemia and does not typically cause hemodynamic instability although massive hemorrhage has been reported. Elevation of the pancreatic enzyme may also be helpful in raising the suspicion [25], although it may be caused by hemobilia rather than hemosuccus. In the present case, the relapsing epigastric pain from chronic pancreatitis might have masked the episodic occurrence of pain related to hemosuccus. Despite endoscopic confirmation, this patient did not have any elevation of liver or pancreatic enzymes, indicating that they are not essential evidences for this condition. Even when blood is definitively confirmed as coming from the pancreatic duct, localization of the point of bleeding may still be difficult unless an aneurysm is documented on imaging studies [27]. Radiologic investigation can include transabdominal ultrasound with Doppler, contrast enhanced CT scan, which may suggest the diagnosis especially if a sentinel clot is visualized in the pancreatic duct on CT, and magnetic resonance imaging (MRI). Angiography is the ultimate gold standard for definitive diagnosis and also offers potential therapy with success reported in 60–100 % of cases although mortality rates have been reported ranging from 8 to 14 % either from failed embolization or complications. [26] This patient has splenic arterial pseudoaneurysm as the definitive proof, which responded to angiographic coil embolization. It should be emphasized that the rich collateral blood supplies of the pancreas may require embolization of more than one feeding vessel in order to stop the bleeding, as was the case in this patient. Surgery typically involving partial pancreatectomy is indicated for failed angiography with ongoing or recurrent bleeding, which occurs in about 30 % of cases, or severe uncontrollable bleeding.

Case 7

A 79-year-old female presented with mild abdominal pain, passage of melena and severe anemia. Over the course of the next few days, she required 20 units of packed cells blood transfusion. On upper endoscopy, she was found to have blood coming out of her major papilla (Fig. 16.7). Cross-sectional imaging identified probable pancreatic carcinoma and liver metastasis. Angiography could not identify the bleeding vessel. At ERCP, catheter insertion into the pancreatic duct reviewed blood in the lumen. Blood clots came through the pancreatic orifice after the performance of a sphincterotomy. A short pancreatic duct stricture was noted at the head of the pancreas, with contrast filling up an ill-defined cystic structure, thought to be caused by tumor necrosis. The pancreatic duct upstream was dilated and filled with defects, likely representing blood elements. Tamponade using a dilating balloon did not stop the bleeding. A pancreatic stent was placed, but it did not result in

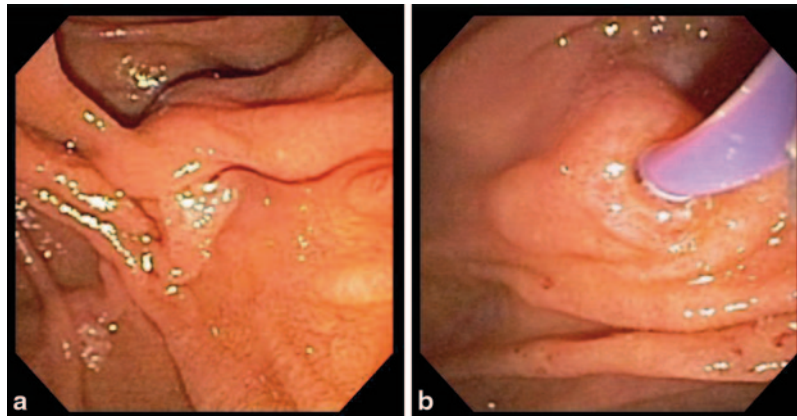

Fig. 16.7 Hemosuccus pancreaticus caused by a pancreatic head cancer. **a** Inspection of the papilla showed a small streak of blood coming out of the major papilla. **b** Catheter aspiration, placed inside the pancreatic duct, retrieved fluid that was obviously bloody

slowing of bleeding either. The patient declined further intervention and was transferred back to her originating hospital for comfort care.

Hemosuccus Pancreaticus in Pancreatic Cancer

Pancreatic cancer is a well-known cause of hemosuccus pancreaticus, as are metastatic tumors to the pancreas [28]. Even benign tumors of the pancreas, such as serous cystadenomas and mucinous cystic neoplasms, have been reported to cause spontaneous bleeding through the pancreatic orifice [29, 30]. Since many patients with known pancreatic or metastatic cancer have chronic anemia, hemosuccus may not be readily suspected unless they present with melena, hematemesis, or hematochezia. Aside from witnessing blood coming out of the papilla and pancreatograhic evidence of poorly outlined filling defects, ERCP may identify changes characteristic of the tumor. In this case, the ductal stricture typical of pancreatic cancer was found. Furthermore, a cavity caused by tumor necrosis was also visualized. However, normal pancreatic duct, nonspecific ductal irregularity, or changes of chronic pancreatitis may be observed as well. ERCP therapies, such as stenting and balloon tamponade, do not have a role in the treatment of spontaneous tumor related bleeding except perhaps for relief of pain caused by the buildup of blood clots. Angiographic embolization and surgery are usually the only treatment options [31].

Case 8

A 47-year-old male presented with intermittent episodes of melena, usually associated with short durations of intense abdominal pain. He had a remote history of alcohol abuse and pancreatitis but without any clinical or radiographic evidence of pancreatitis at the time of this presentation. As a result of his bleeding, he had been hospitalized continuously for 4 weeks and had required over 60 units of packed cells blood transfusion. His work up included upper and lower endoscopies, serum liver and pancreatic enzyme tests, two abdominal CT studies with intravenous contrast, two mesenteric angiograms, two capsule endoscopies, two push enteroscopies (deep balloon enteroscopy was not available at the time), and an intraoperative total enteroscopy. All these studies yielded negative results. Because of the epigastric pain related bleeding, an ERCP was performed and the pancreatic ductogram showed a mid-body smooth polypoid nodule and mild post-obstructive ductal dilation (Fig. 16.8). Even with the catheter probing the nodule, bleeding could not be induced. A linear array EUS showed that the nodular lesion had an anechoic,

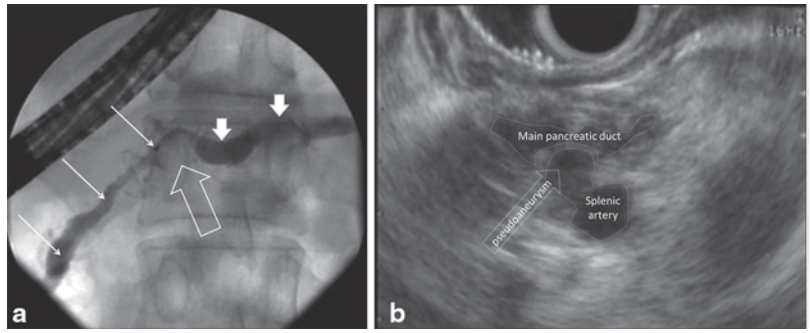

Fig. 16.8 Hemosuccus pancreaticus presenting as severe obscure overt gastrointestinal bleeding. **a** ERCP showed a normal caliber pancreatic duct up to the neck of the pancreas. An ERCP catheter with a black dot at its tip (*long thin arrows*) was inserted to probe the polypoid structure at the neck of the pancreas (*large arrow*). The pancreatic duct upstream was mildly dilated (*small solid arrows*). **b** Endosonography (EUS) demonstrated that the main pancreatic duct nodule (*large arrow*) was actually a pseudoaneurysm of the splenic artery

Doppler positive component to it and that it was contiguous with the splenic artery. This finding was highly suggestive of a pseudoaneurysm of the splenic artery, resulting in a mid-pancreatic resection with tissue confirmation of the vascular abnormality. These bleeding episodes stopped immediately after the surgical resection.

Role of EUS in Hemosuccus Pancreaticus

This was an amazing case of challenging obscure GI bleeding caused by pseudoaneurysm of the splenic artery, almost certainly due to past episodes of acute pancreatitis. Despite many imaging studies focusing on the pancreas, there was no confirmative finding pointing to hemosuccus pancreaticus. A very high index of suspicion, combined with some degree of desperation, led to the performance of ERCP and ultimately discovery of the ductal aneurysmal lesion. In hind sight, EUS would have identified the vascular lesion and the potentially higher risk ERCP might have been avoided. Regardless of whether ERCP should have been done, this case illustrates how difficult it can be to confirm hemosuccus as the cause of obscure GI bleeding and the value of EUS in identifying vascular lesions [32]. Case reports have noted the utility of EUS in diagnosing pseudoaneurysms even following failed detection by abdominal CT, and that 1 % of EUSs performed for what appeared to be pancreatic cysts ultimately were diagnosed as aneurysms by CT [33, 34]. This report of four cases noted a typical “donut” appearance of the aneurysms with a thick wall and anechoic center on EUS. One of these aneurysms did not demonstrate flow with Doppler leading to fine-needle aspiration (FNA) returning blood, which could occur in aneurysms with sluggish flow, calcified wall, or thrombus, or if the Doppler is oriented perpendicular to the direction of vascular flow. When aspirates show blood, FNA must be stopped and the lesion observed for any hyperechoic changes suggestive ongoing bleeding in addition to administering prophylactic antibiotics. Follow-up imaging should be performed to evaluate for aneurysms. Similar to tumor induced bleeding, endoscopy has very little role in treating aneurysmal bleeding. Perhaps the only time that hemosuccus can be effectively treated endoscopically is when dealing with bleeding and fistula formation in an acute injury or post-pancreatic resection.

Conclusion

In conclusion, bleeding from the papilla is rarely suspected before ERCP. It must be considered whenever there are pancreatic or biliary

signs and symptoms, along with evidence of active GI bleeding. Concurrent pancreatic tumor, pancreatitis, bile duct condition, and recent surgery and liver instrumentation are common conditions in which hemobilia or hemosuccus pancreaticus arises. Traumatic or iatrogenic cause of hemobilia may resolve spontaneously, and initial management is usually focused on keeping the biliary tract patent with ERCP. A variety of endoscopic, radiologic, and surgical modalities are available to treat hemobilia. By contrast, endoscopy has a very small role in the management of clinically significant hemosuccus pancreatitis. Angiographic interventions are typically the first line therapy, with surgery reserved for treatment failures. High clinical suspicion must be maintained based on the patient's history in order to diagnose these conditions.

Key Points

- Always consider and maintain a high suspicion for hemobilia and hemosuccus pancreaticus as potential sources of obscure GI bleeding based on the patient's clinical history.
- When hemorrhage from the papilla is noted, determine if the origin is in the bile duct, pancreatic duct, or the major papilla.
- Recent biliary, pancreatic, papillary, or liver instrumentation provides a strong clue to the origin of the bleeding.
- In significant hemobilia, consider empiric placement of a fully covered biliary metal stent to maintain biliary patency and possibly deliver tamponade-induced hemostasis depending on the bleeding site.
- Selective angiographic embolization is the therapy of choice in many cases of hemosuccus pancreaticus and hemobilia.

Video Caption

Video 16.1 Hemobilia during stent removal

References

1. Chin MW, Enns R. Hemobilia. Curr Gastroenterol Rep. 2010;12:121–9
2. Green MH, Duell RM, Johnson CD, Jamieson NV. Haemobilia. Br J Surg. 2001;88:773–86
3. Zhou HB. Hemobilia and other complications caused by percutaneous ultrasound-guided liver biopsy. World J Gastroenterol. 2014;20:3712–5
4. Burke DR, Lewis CA, Cardella JF, et al., Society of Interventional Radiology Standards of Practice Committee. Quality improvement guidelines for percutaneous transhepatic cholangiography and biliary drainage. J Vasc Interv Radiol. 2003;14:S243-6.
5. Saad WEA, Davies MG, Darcy MD. Management of bleeding after percutaneous transhepatic cholangiography or transhepatic biliary drain placement. Tech Vasc Interv Radiol. 2008;11:60–71
6. Rai R, Rose J, Manas D. Potentially fatal haemobilia due to inappropriate use of an expanding biliary stent. World J Gastroenterol. 2003;10:2377–8
7. Quinke H. Ein fall von aneurysma der leberarterie. Klin Wochenschr. 1871;8:349–51
8. Goenka MK, Harwani Y, Rai V, Goenka U. Fully covered self-expandable metal biliary stent for hemobilia caused by portal biliopathy. Gastrointest Endosc. 2014;80:1175. (pii: S0016-5107(14)01298–X). doi:10.1016/j.gie.2014.03.029. [Epub ahead of print]
9. Rhim H, Lim HK, Kim YS, Choi D, Lee KT. Hemobilia after radiofrequency ablation of hepatocellular carcinoma. Abdom Imaging. 2007;32:719–24
10. Nicholson T, Travis S, Ettles D, Dyet J, Sedman P, Wedgewood K, et al. Hepatic artery angiography and embolization for hemobilia following laparoscopic cholecystectomy. Cardiovasc Intervent Radiol. 1999;22:20–4
11. Aslinia F, Hawkins L, Darwin P, Goldberg E. Temporary placement of a fully covered metal stent to tamponade bleeding from endoscopic papillary balloon dilation. Gastrointest Endosc. 2012;76:911–3
12. Song JY, Moon JH, Choi HJ, Kim DC, Choi MH, Lee TH, Cha SW, Cho YD, Park SH. Massive hemobilia following transpapillary bile duct biopsy treated by using a covered self-expandable metal stent. Endoscopy. 2014;46(Suppl 1):E161–2
13. Siablis D, Papathanassiou ZG, Karnabatidis D, Christeas N, Vagianos C. Hemobilia secondary to hepatic artery pseudoaneurysm: an unusual complication of bile leakage in a patient with a history of a resected IIIb Klatskin tumor. World J Gastroenterol. 2005;11:5229–31
14. Yoshida J, Donahue PE, Nyhus LM. Hemobilia: review of recent experience with a worldwide problem. Am J Gastroenterol. 1987;82:448–53
15. Verset G, Maréchal R, Bali MA, Devière J, Van Laethem JL. Fatal hemobilia in advanced hepatocellular carcinoma invading biliary tract after treatment with sorafenib and biliary stenting. Ann

Oncol. 2010;21(6):1381–2. doi:10.1093/annonc/mdq071. Epub 2010 Mar 23
16. Tseng LJ, Jao YT, Mo LR. Acute pancreatitis caused by hemobilia secondary to hepatoma with bile duct invasion. Gastrointest Endosc. 2002;55:240–1
17. Hsieh YY, Sung KF, Liu NJ. Combined endoscopic sphincterotomy and trans-catheter arterial embolization for the treatment and prevention of acute pancreatitis induced by hemobilia from hepatocellular carcinoma. Acta Gastroenterol Belg. 2012;75:283–4
18. Tseng CW, Chou YC, Hsieh YH. An unusual cause of biliary obstruction after endoscopic sphincterotomy. Gastroenterology. 2012;142:e1–2
19. Felekouras E, Megas T, Michail OP, Papaconstantinou I, Nikiteas N, Dimitroulis D, Griniatsos J, Tsechpenakis A, Kouraklis G. Emergency liver resection for combined biliary and vascular injury following laparoscopic cholecystectomy: case report and review of the literature. South Med J. 2007;100:317–20
20. Stanley JC, Frey CF, Miller TA, Lindenauer SM, Child CG 3rd. Major arterial hemorrhage: a complication of pancreatic pseudocysts and chronic pancreatitis. Arch Surg. 1976;111:435–40
21. Fernandez-Cruz L, Pera M, Vilella A, Llovera JM, Navasa M, Teres J. Hemosuccus pancreaticus from a pseudoaneurysm of the hepatic artery proper in a patient with a pancreatic pseudocyst. Hepatogastroenterology. 1992;39:149–51
22. Camishon RC, Pello MJ, Spence RK, et al. Hemoductal pancreatitis. Surgery. 1992;111:86–9
23. Vázquez-Iglesias JL, Durana JA, Yañez J, Rodriguez H, Garcia-Vallejo L, Arnal F. Santorinirrhage: hemosuccus pancreaticus in pancreas divisum. Am J Gastroenterol. 1988;83:876–8
24. Naitoh I, Ando T, Shimohira M, Nakazawa T, Hayashi K, Okumura F, Miyabe K, Yoshida M, Togawa H, Sasaki S, Shibamoto Y, Joh T. Hemosuccus pancreaticus associated with segmental arterial mediolysis successfully treated by transarterial embolization. JOP. 2010;11:625–9
25. Rammohan A, Palaniappan R Ramaswami S, Perumal SK, Lakshmanan A, Srinivasan UP, Ramasamy R Sathyanesan J. Hemosuccus pancreaticus: 15-year experience from a tertiary care GI bleed centre. ISRN Radiol. 2013;191794:1–6.
26. Peroux JL, Arput JP, Saint-Paul MC, Dumas R, Hastier P, Caroli FX, et al. Wirsungorrhagia complicating chronic pancreatitis associated with a neuroendocrine tumor of the pancreas. Gastroenterol Clin Biol. 1994;18:1142–5
27. Setoyama T, Miyamoto S, Fukuda K. Hemosuccus pancreaticus diagnosed with concurrent endoscopic retrograde pancreatography and selective angiography. Clin Gastroenterol Hepatol. 2012;10:A28
28. Kassabian A, Stein J, Jabbour N, Parsa K, Skinner D, Parekh D, Cosenza C, Selby R. Renal cell carcinoma metastatic to the pancreas: a single-institution series and review of the literature. Urology. 2000;56:211–5
29. Kanno A, Satoh K, Hamada S, Hirota M, Masamune A, Motoi F, Egawa S, Unno M, Ishida K, Kimura K, Shuin T, Shimosegawa T. Serous cystic neoplasms of the whole pancreas in a patient with von Hippel–Lindau disease. Intern Med. 2011;50:1293–8
30. Shinzeki M, Hori Y, Fujino Y, Matsumoto I, Toyama H, Tsujimura T, Sakai T, Ajiki T, Kuroda Y, Ku Y. Mucinous cystic neoplasm of the pancreas presenting with hemosuccus pancreaticus: report of a case. Surg Today. 2010;40:470–3
31. Han B, Song ZF, Sun B. Hemosuccus pancreaticus: a rare cause of gastrointestinal bleeding. Hepatobiliary Pancreat Dis Int. 2012;11:479–88
32. Risti B, Marincek B, Jost R, Decurtins M, Ammann R. Hemosuccus pancreaticus as a source of obscure upper gastrointestinal bleeding: three cases and literature review. Am J Gastroenterol. 1995;90:1878–80
33. Seicean A, Badea R, Stan-Iuga R, Iancu C, Seicean R. Double splenic artery pseudoaneurysm associating splenic infarction in chronic pancreatitis. J Gastrointest Liver Dis. 2012;21:313–5.
34. Varadarajulu S, Eloubeidi MA. Diagnosis of an aneurysm masquerading as a pancreatic-cyst lesion on EUS. Gastrointest Endosc. 2007;65:721–5.

ERCP in Post-Surgical Patients

17

Jemilat O. Badamas and Patrick I. Okolo

Introduction

Pancreatobiliary problems in patients with altered gastrointestinal anatomy present a special challenge. The difficulties are distributed across all the relevant clinical domains including diagnosis, endoluminal access (as a result of the altered length), technical modifications of the procedure and aftercare. Indications for endoscopic retrograde cholangiopancreatography (ERCP) in patients who are post-surgical encompass all the indications for the procedure in patients with native gastrointestinal anatomy. Some conditions are more common in patients who have undergone weight loss surgery. Rapid weight loss increases bile lithogenicity and thus the likelihood of gallstone formation in those patients with intact gallbladders.

Making a prompt diagnosis of pancreatobiliary conditions in patients with altered anatomy may require a heightened index of suspicion and a nuanced approach to the interpretation of axial imaging. Biliary sepsis in patients with altered anatomy, for example, may not always present with all the elements of fever, jaundice and biochemical dysfunction. Appreciation of this possibility enables a clinician to make a prompt diagnosis when the clinical picture is subtle.

Technically, endoluminal access and the approach to the pancreatic and bile ducts depend on two major considerations:

a. The presence of an intact ampulla versus a surgical anastomosis
b. The distance of the pancreatobiliary limb from the portal of entry (usually the mouth)

These considerations are summarized in Table 17.1. Generally speaking, deep enteroscopy or trans-abdominal access is necessary if the ampulla or surgical pancreatobiliary anastomoses cannot be reached within 180 cm from the point of insertion (Fig. 17.1). In these cases, ERCP can be performed using device-assisted enteroscopy with single- or double-balloon enteroscopy, short double-balloon enteroscopy, spiral overtube enteroscopy or through-the-scope balloon enteroscopy. When these techniques are technically overly onerous, unavailable or unsuccessful, the bile and pancreatic ducts can be accessed via percutaneous gastrostomy/jejunostomy or during laparoscopy via a port. There are ever-increasing reports in the literature of successful ERCP in patients with altered surgical anatomy using a variety of endoscopes across the spectrum of altered anatomy. The success rates are variable with very high rates reported for Billroth II and the most difficult being accessing an intact ampulla in a patient with long-limb Roux-en-Y gastric bypass (RYGB). It is against this backdrop that it is imperative to consider risk–benefit ratio, details of the actual surgical operation, availability of appropriate endoscope and/or assistive

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Table 17.1 Surgical alteration relevant to altered anatomy ERCP

Type of procedure	Common indication	Approximate afferent (biliopancreatic) limb length[a]	Biliary drainage
Roux-en-Y gastric bypass	Weight management	Long limb > 100 cm	Intact papilla
Billroth II gastrojejunostomy	Complications of peptic ulcer disease	Short limb < 50 cm	Intact papilla
Total gastrectomy with esophagojejunostomy	Gastric cancer	Short limb < 50 cm	Intact papilla
Pancreaticoduodenectomy (Whipple) resection	Pancreatic head cancer	Short limb < 50 cm	Bilioenteric anastomosis
Roux-en-Y hepatico- or choledochojejunostomy	Bile duct injury, cholangiocarcinoma, liver transplant	Variable	Bilioenteric anastomosis

[a] Please note that the lengths do not include the distance to the entero-enteric anastomosis

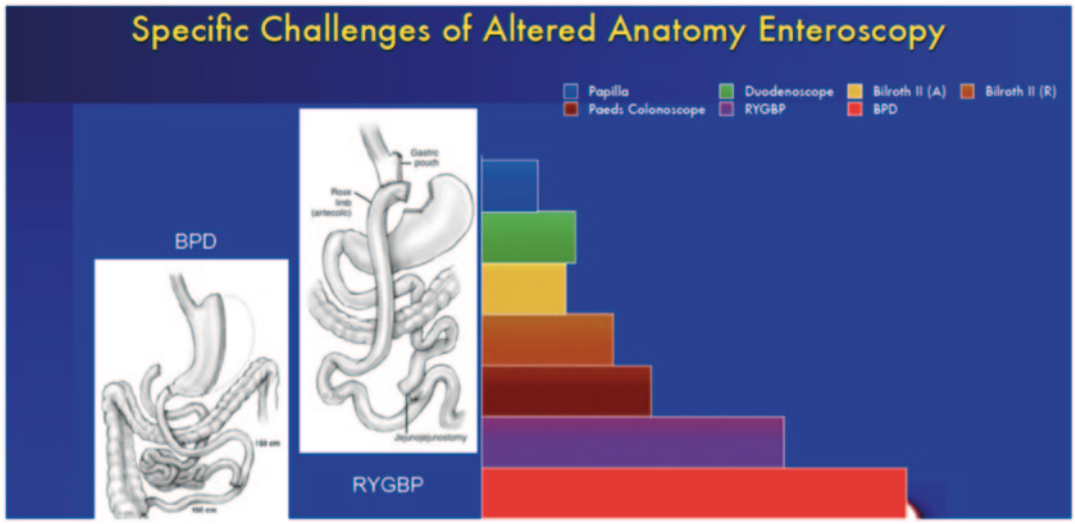

Fig. 17.1 Standard scope length and distance from the mouth to the biliary orifice following surgical alteration of the gastrointestinal tract. *BPD* biliopancreatic diversion, *RYGBP* Roux-en-Y gastric bypass procedure

technologies, and availability of necessary endoscopic expertise prior to contemplating ERCP in these patients.

Case Study

Initial Presentation

A 62-year-old gentleman who works as a chiropractor presented with 1 day of fevers, chills and right upper quadrant pain. He had experienced similar symptoms in the past; however, these were always transient. Persistence and profound worsening of his symptoms prompted entry to the emergency room. His physical exam was notable for a fever of 102 °F, scleral icterus, well-healed laparoscopy port entry scars and RUQ abdominal tenderness. He was found to have total bilirubin 3.8, alkaline phosphatase 641, ALT 440 and AST 152. His white blood cell count was elevated at 16,600 with neutrophil predominance. His past medical history was significant for sleep apnea and type II diabetes, both of which had improved to the point of resolution following weight loss from RYGB. After RYGB 2 years prior, he

had lost a total of 76 kg (167.2 lbs). In the ER, a diagnosis of acute cholangitis was made. A right upper quadrant ultrasound demonstrated a 14-mm dilated common bile duct without accompanying filling defect. A CT scan of the abdomen demonstrated the aforementioned biliary dilatation and post-surgical changes. He was not enthusiastic about a percutaneous biliary procedure and was referred for consideration of ERCP. His surgical records were reviewed, revealing a standard laparoscopic gastric bypass. Following administration of intravenous fluids and antibiotics, deep enteroscopy with ERCP was planned. He was orotracheally intubated and placed in supine position for ERCP examination.

What Techniques Enable Reaching the Ampulla or Pancreatobiliary-Enteric Anastomosis?

The initial choice of scope to try to reach the ampulla or pancreatobiliary-enteric anastomosis depends on the surgical anatomy.

Billroth II Surgery

In contrast to RYGB, a standard duodenoscope or forward-viewing pediatric colonoscope readily accesses the afferent limb in most patients with Billroth II anatomy depending on the available expertise. In a single-center study of 855 ERCPs in 537 patients with Billroth II, all procedures began with a standard duodenoscope, and the duodenal stump and papilla were identified 89% (477/537) of the time. There was a 2% (11/537) jejunum perforation rate [1]. Therefore, most patients with Billroth II anatomy can be approached using a standard duodenoscope or, as an alternative, a pediatric colonoscope. Standard colonoscope insertion techniques including loop reduction, abdominal pressure and turning the patient may aid in Billroth II and other surgical anatomies.

Whipple Surgery

Similarly, in Whipple patients, the area of the pancreatobiliary-enteric anastomoses in the afferent limb is successfully reached in 86–93% by using the duodenoscope in 76% of cases and the rest accessed with a gastroscope and adult or pediatric colonoscope [2–4]. Complications occurred in 1% consisting of conservatively managed retroperitoneal perforation. The challenges the endoscopist face in reaching the anastomoses in Whipple patients include entering the afferent limb and advancing to the anastomoses. Tips to aid in entering and reaching the anastomoses include changing to a forward-viewing endoscope, application of abdominal pressure to prevent endoscope looping, changing the patient's position, inserting a stiffening wire (Enteroscope stiffening device, Zutron Medical, Lenexa, KS) into the accessory channel to stiffen the scope and tattooing the entrance to the afferent limb.

Roux-en-Y Anatomy

Patients with a RYGB will require an alternative method to reach the afferent limb due to its long length. Device-assisted enteroscopy (DAE) with double balloon (DBE), short double balloon, single balloon (SBE) and spiral enteroscopy (SE) is one such method. It has improved our ability to reach the ampulla or bilioenteric anastomosis to perform therapy in RYGB patients, although it has limitations. Several reports of DAE-ERCP using DBE, short double balloon and SBE in patients with altered anatomy have been published in the literature with success rates ranging from 60 to 95%. A multicenter study of 129 patients with post-surgical anatomy (63 RYGB, 30 with other Roux-en-Y anatomy) who had DAE-ERCP reported that enteroscopy success (visualizing papilla or pancreatobiliary-enteric anastomosis) was achieved in 92 of 129 (71%). The most common reason for ERCP failure was inability to reach the papilla or pancreatobiliary anastomosis [5]. Despite the possible increased success of reaching the ampulla or pancreatobiliary-enteric anastomosis with DAE-ERCP, this technique is

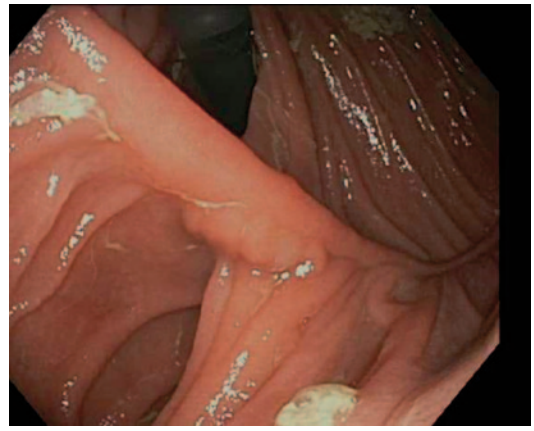

Fig. 17.2 Endoscopic view of jejuno-jejunal anastomosis in RYGB with enteroscope seen emerging from the Roux limb in the *upper left*. The entrance to the afferent/pancreaticobiliary limb is seen *below* to the *left*. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

limited due to the absence of an elevator on the enteroscopes and the limited number of enteroscope-compatible ERCP accessories.

In DAE, the use of a balloon or rotating overtube to sequentially reduce and pleat the small bowel over a standard enteroscope allows for deep intubation into the small bowel. During DAE-ERCP, the enteroscope and overtube are advanced through the mouth, across the end-to-side gastrojejunostomy and down the jejunal Roux limb to the jejuno-jejunostomy (Fig. 17.2). To facilitate insertion, low insufflation and sequential inflation/deflation of the overtube balloon accompanied by aggressive pleating of the small bowel should be performed. One challenge at the jejuno-jejunal anastomosis is to identify the biliopancreatic limb. At the anastomosis, the endoscopist may visualize 2 lumens. An additional blind-end lumen may be present if the anastomoses have been created in an end-to-side fashion. Though not infallible, the direction of the *valvulae conniventes* provides a more reliable guide than the presence of bile, which is frequently found in both limbs. The use of fluoroscopy may help identify the biliopancreatic limb. Inadvertent entry into the common channel/efferent limb is often followed by the appearance of multiple intestinal loops in the pelvis on fluoroscopy. An enterogram obtained by injecting contrast via the accessory scope channel can often delineate the likely positions of the biliopancreatic and the common limb. When the common limb is unintentionally intubated, the enteroscope should be withdrawn slowly to the level of the jejuno-jejunostomy. A submucosal tattoo placed at the entrance to the common limb is very helpful to minimize repeated inadvertent entry to that limb.

Often, the biliopancreatic limb is situated at an obtuse angle and requires abdominal counter pressure and good endoscopic technique to enter this limb. A change in the patient's position may facilitate this process. Passage of a colon length dilator or special length stone extraction balloon into the biliopancreatic limb and inflating the balloon can sometimes simplify entry into this limb by stiffening the enteroscope and providing counter traction. A stiffening wire advanced into the accessory channel of the enteroscope can also aid when looping. The overtube or balloon also acts as a splint which allows negotiation of these acute angulations often found at the gastrojejunal or jejuno-jejunal anastomoses.

Regardless of the approach, it is optimal for the bare enteroscope to enter the limb followed by the overtube. Following an established position in the biliopancreatic limb, pleating of the small bowel assists navigation to the ampulla or bilioenteric anastomosis. In RYGB patients, the

pylorus and excluded stomach denote the end of the navigation portion of the procedure as does the blind end of the loop in patients with a Roux-en-Y loop.

Attempts to traverse the afferent limb endoscopically have been made with varying success using the side-viewing duodenoscope, pediatric colonoscope and push-enteroscope. The side-viewing duodenoscope is the preferred endoscope to perform ERCP and duct cannulation. The side view of the papilla is optimal, and the presence of the elevator makes selective duct cannulation easier. However, reaching the ampulla with a duodenoscope is usually unsuccessful in Roux-en-Y anatomy with its long afferent limbs. One study reported the papilla could be reached in only 33 % of patients with Roux-en-Y anatomy using a duodenoscope [6].

The pediatric colonoscope offers the advantage of a longer working length (164 cm) but the forward-view approach and lack of elevator make cannulation of the bile duct challenging. One way to overcome these challenges is to use the pediatric colonoscope or push-enteroscope to reach the papilla, place a long stiff guidewire over which the colonoscope or enteroscope is removed under fluoroscopy and the duodenoscope is subsequently advanced back to the papilla over the wire. A 15- or 18-mm stone extraction balloon can be advanced as far down the afferent limb as possible or into the excluded stomach in RYGB, inflated, and then used to pull the duodenoscope into position. Despite this, success rates remain variable. One study that looked at ERCP using adult or pediatric colonoscopes in patients who had Roux-en-Y hepaticojejunostomy for orthotopic liver transplant reported 29 % failure at reaching the papilla [7]. In another study that employed the guidewire exchange technique in 15 patients with long Roux-en-Y anatomy and a native papilla, the papilla was reached in 67 % (10/15) of patients. The main reason for failure was the inability to advance the duodenoscope to the region of the papilla. In some cases, the duodenoscope was pulled into the afferent limb with a wire-guided balloon passed retrograde into the afferent limb. Cannulation and therapy were primarily performed with a duodenoscope after exploration and placement of a guidewire in the afferent limb with a forward-viewing colonoscope. Of note, the five patients in whom ERCP was not possible all had RYGB anatomy, which highlights the need for alternative methods to perform successful ERCP in this specific patient population [8].

At the Papilla—Now What?

Identifying the Ampulla and Pancreatobiliary-Enteric Anastomoses

Native papillae are typically readily identified endoscopically. Unfortunately, pancreatobiliary-enteric anastomoses may be very difficult to identify, and simply reaching the end of the afferent limb/Roux-en-Y jejunal loop does not guarantee success. Techniques to aid in identifying the anastomoses include the following: observing for an air cholangiogram on fluoroscopy, carefully examining the antimesenteric side of the afferent limb, filling the jejunum with contrast and repositioning the patient to encourage the contrast to reflux into the ducts, spraying methylene blue in the area where the anastomoses may be located, and injecting secretin to elicit pancreatic secretions (Fig. 17.3). In Whipple patients, the choledochojejunostomy is typically located downstream from the pancreaticojejunostomy, which is found near the end of the afferent limb. The anastomoses are often variable in position and a number of findings may denote their location—the presence of surgical material such as sutures/staples and a frequently bland appearance of the mucosa surrounding the perimeter of the anastomosis (Fig. 17.4). In some instances, high-volume contrast enterography once the endoscope is situated in the periphery of the anastomoses may help identify the position of the anastomoses. The choledochojejunostomy is more readily identified in 85 % of cases and is an end-to-side anastomosis [4]. The sutured pancreaticojejunostomy may be end-to-side or end-to-end and is located in only 42–50 % of patients.

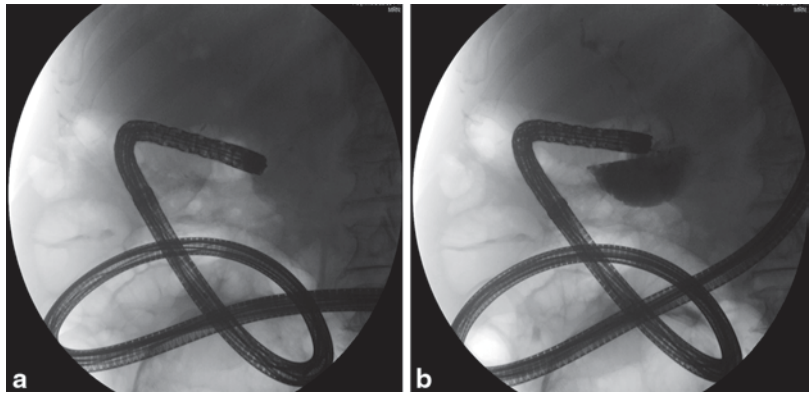

Fig. 17.3 **a**. Fluoroscopy of ERCP in patient following Whipple surgery and another Roux-en-Y reconstruction using pediatric colonoscope with partial air cholangiogram visualized superior to the end of the colonoscope **b**. Contrast filling the jejunal loop and refluxing back through the choledochojejunostomy into the CBD. These techniques allowed endoscopic identification of the choledochojejunostomy. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

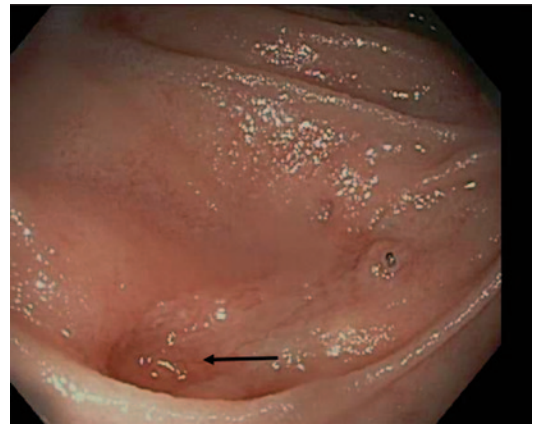

Fig. 17.4 Choledochojejunostomy (*arrow*) with nearby suture material. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

Cannulating and Performing Therapy

Once the ampulla/pancreatobiliary-enteric anastomosis has been identified, further challenges may await. The ideal situation is having reached these orifices using a duodenoscope through which all the standard ERCP accessories may be used over an elevator. The colonoscope or shorter forward-viewing scopes will allow use of most ERCP accessories, but lack the elevator which can make cannulation difficult. The diameter of the working channel of a pediatric colonoscope will not accept 10-Fr plastic stents. Finally, the 2-m-long single- and double-balloon enteroscope platforms are too long to permit use of standard length sphincterotomes and accessories. A special length stone extraction balloon (Tri-Ex extraction balloon), sphincterotome (Classic Cotton cannulatome), needle knife sphincterotome (Zimmon needle knife papillotome), dilation balloon (Quantum TTC biliary balloon dilator), dilation catheter (Soehendra biliary dilation catheter) and extra-long guidewire (Tracer metro direct guidewire 600 cm long) are all commercially available through Cook Medical (Bloomington, IN) and well suited for use via the 2.8-mm accessory channel of the enteroscope. The short double-balloon enteroscope system uses an enteroscope that is 152 cm long and allows use of standard ERCP accessories. Regardless, the 2.8-mm channel of

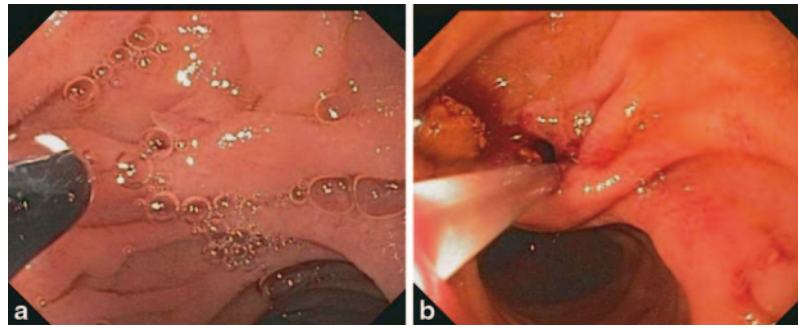

Fig. 17.5 **a**. Normal-appearing ampulla approached retrograde via SBE-ERCP in patient following RYGB **b**. Small sphincterotomy performed followed by balloon sphincteroplasty and extraction of a biliary stone seen to the *left* of the dilated sphincterotomy site. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

these enteroscopes limits the size of deployable stents to 7-Fr stents. At the author's institution, the use of a through-the-scope balloon with an adult colonoscope for these procedures is evolving and permits the placement of the entire armamentarium of stents. This is a single-use balloon catheter advanced through the accessory channel ahead of the scope and requires at least a 3.7 mm channel diameter. After inflating the balloon, the scope is advanced to the balloon while holding counter traction on the balloon catheter, the balloon is deflated and the cycle repeated [9]. Data are awaited on the use of this device in ERCP. If DAE-ERCP is planned, careful preparation must be done beforehand to ensure that the appropriate accessories are available.

Success rates of DAE-ERCP are lower in cases with an intact papilla (50–60%) versus bilioenteric anastomoses (80–90%) although a recent large retrospective series suggested comparable cannulation success rates for native papilla and anastomoses [5, 10–13]. Cannulating the ampulla or anastomosis can be technically intricate for multiple reasons including the forward-viewing approach and the absence of an elevator. From the author's personal experience, manipulating the ampulla to a near 6 o'clock position whenever possible is often helpful as well as approaching the ampulla using the closest en-face position possible. The special length sphincterotomes do not provide much of an arc, and this position enables precise sphincterotome placement using the torque of the endoscope shaft with or without abdominal counter pressure. Placement of a pancreatic duct stent prior to biliary cannulation is a very helpful consideration in patients with altered surgical anatomy as it enables true orientation with regard to the position of the bile duct. This "real-time" orientation facilitates both biliary cannulation and the orientation for sphincterotomy and is superior in most instances to an a priori "guestimate" of the position and orientation of the bile duct. The simplest and safest way to approach performing a sphincterotomy is to place a stent in the bile or pancreatic duct to act as a guide. Sphincterotomy is then performed using a needle knife over the stent. Another relatively straightforward technique which may mitigate some perforation risk is to perform a partial or "small" sphincterotomy in the cephalad direction followed by balloon sphincteroplasty (Fig. 17.5).

In Whipple patients, cannulation of the bile or pancreatic duct is successful once the anastomoses have been identified [3, 4]. Cannulation is also highly successful in Billroth II patients with success rates from 91 to 100% although it may be more challenging when using a forward-viewing scope without an elevator [14]. Additionally, in Billroth II anatomy, the ampulla is oriented upside-down or reversed from the normal anatomy with the bile duct coursing along the 5–6 o'clock rather than the 11–12 o'clock position. Wire-guided cannulation through a Billroth II papillotome with the cutting wire oriented in the inferior position (opposite the normal position on a standard sphincterotome), rotatable sphincterotomes

and sphincterotomes with an S-shaped tip aid in cannulating [15–17]. Straight-tipped catheters may also be used, and molding the tip with a downward curve may help. Sphincterotomy in the setting of a Billroth II surgery is reversed and in the caudad rather than cephalad direction; the Billroth II papillotome can be quite helpful. In the author's experience, a rotatable sphincterotome like the Autotome RX (Boston Scientific, Marlborough, MA) provides more precise orientation for performing sphincterotomy in the setting of a Billroth II ampulla. Once the sphincterotome is down the channel of the endoscope, rotating the handle may not get transmitted to the tip of the instrument in a 1:1 fashion. Tips to overcome this problem include the following: pulling and pushing the sphincterotome back and forth inside the biopsy channel, straightening the endoscope, and lubricating the channel with silicone or lubricating jelly. Because the orientation of the bile duct is reversed, placing a stent within the bile duct and performing a needle knife papillotomy over the stent is another option.

How are Accessories Exchanged During Enteroscopy-Assisted ERCP?

Exchanging accessories can be challenging whenever a 2-m enteroscope is used. The specialized ERCP accessories, such as the G22732 Cotton cannulatome and 275 cm Tri-Ex balloon (Cook Medical, Bloomington, IN), are not especially suited for wire exchange, and it is critical not to lose ductal access during a wire exchange. Whenever possible, the longest 600 cm guidewire should be used. Delivering and exchanging the guidewire through a hole created in the side of the distal portion of the sphincterotome greatly facilitate exchange. A 60-cc water-filled syringe can be attached to the sphincterotome or another accessory, and the counter pressure applied using a static column of water will often maintain ductal access during exchange.

Case Continued

The ampulla was reached, identified and subsequently cannulated using a special long-length sphincterotome and a standard 450-cm guidewire. Contrast was injected in retrograde fashion demonstrating a dilated common hepatic and intrahepatic duct with a moderate amount of amorphous sludge in the common hepatic duct. The gallbladder was surgically absent; however, there was a filling defect in a dilated cystic duct remnant and the distal common bile duct with a short 1.5-cm benign appearing biliary stricture distally. A 7-fr, 7-cm plastic Cotton-Leung stent was placed, which was the largest diameter possible through the enteroscope. Following stent placement, there was copious drainage of discolored bile and particulate material from the ducts.

How Successful is ERCP in Surgically Altered Anatomy?

Despite improved technology and techniques, the overall success of ERCP in patients with surgically altered anatomy is variable. This variability reflects the diversity of surgically altered anatomy (Figs. 17.6, 17.7, and 17.8). In one study of patients who had Roux-en-Y hepaticojejunostomy for orthotopic liver transplant using colonoscope for ERCP, overall 71% (22/31) diagnostic and therapeutic success rate was reported with median procedure time of 43 min and no complications [7]. A small study of 15 patients with long Roux-en-Y anatomy and native papilla using the guidewire technique to ultimately advance the duodenoscope noted successful biliary sphincterotomy in 100% of patients in whom the papilla was reached.[8] Mean procedure time was 137 min with no complications when the papilla was not reached. Complications occurred in 16% of patients following completed ERCP (2 mild-to-moderate pancreatitis and 1 mild bleeding).

In the large single-center study of 537 patients with Billroth II anatomy mainly using a duode-

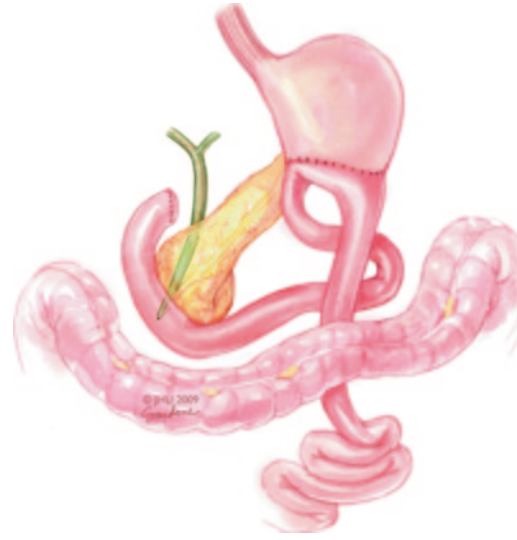

Fig. 17.6 Billroth II anatomy: Note antrectomy and end-to-side gastro-enteral anastomosis

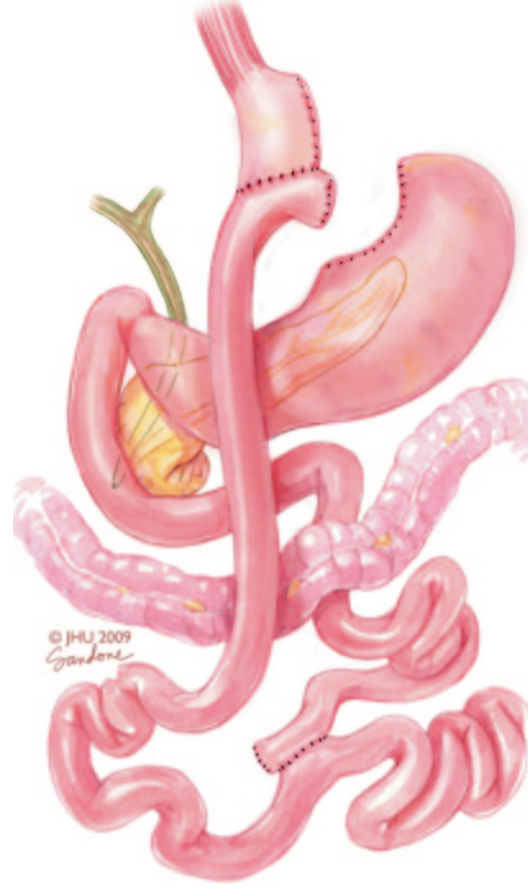

Fig. 17.7 Roux-en-Y gastric bypass (*RYGB*): Note gastric pouch, gastrojejunal anastomosis and jejuno-jejunal anastomosis

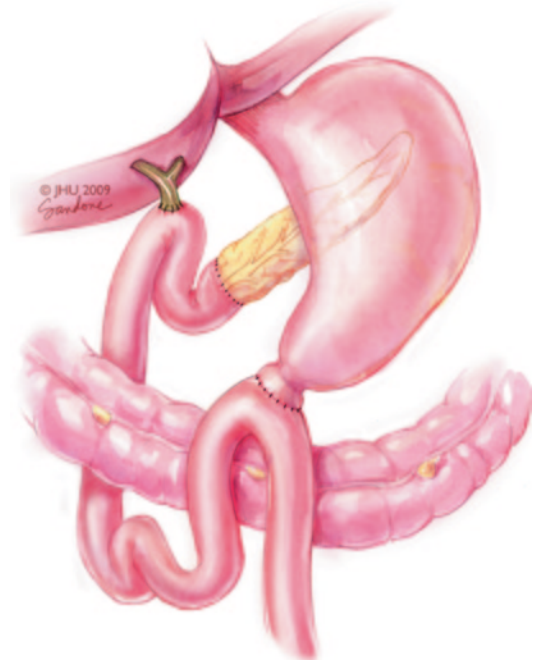

Fig. 17.8 Pyloric-sparing Whipple: Note pancreatic, biliary and duodenal resection, a short duodenojejunostomy and the afferent (*biliopancreatic*) and efferent loops

noscope, biliary or pancreatic duct cannulation was successful in 93% of these cases [1]. An older study randomly assigned 45 patients with Billroth II to ERCP using a duodenoscope or pediatric colonoscope. Cannulation of the papilla was successful in 68% (15 of 22) of the duodenoscope group, and in 87% (20 of 23) from the colonoscope group. Sphincterotomy was successfully completed in 80% (8 of 10) of the duodenoscope group, and in 83% (10 of 12) from the colonoscope group. The cannulation failures in the duodenoscope arm were mainly due to four cases of jejunal perforation while no perforation occurred in the colonoscope group [18]. Another study randomized Billroth II patients to sphincterotomy using a needle knife over a biliary stent or balloon sphincteroplasty and found no significant differences in overall success (83–88%), median procedure time (63 and 40 min, respectively) or complications (39 versus 19%, respectively) [19]. One caveat to this study is the small sample size which precluded sample size calculation.

In Whipple patients, technical success dramatically differed between those with a biliary compared to a pancreatic indication for ERCP (84 versus 8%, $p<0.001$) [2]. This mainly results from the difficulty in locating the pancreaticojejunostomy despite use of adjunctive techniques including spraying methylene blue and secretin injection.

A recent comprehensive review of DAE-ERCP (DBE, SBE, spiral enteroscopy) included 945 procedures in 679 patients with a variety of surgical anatomies and reported overall 74% success in completing the intended ERCP procedure (ERCP success) and 3.4% major complications [13]. Perforation was most common with nearly half requiring surgery followed by pancreatitis and rarely bleeding. Success rates were highest in Billroth II patients with 96% endoscopic success defined as reaching and identifying the ampulla or pancreatobiliary-enteric anastomosis and 90% ERCP success. As expected, RYGB patients had lowest success rates (80% endoscopic success, 70% ERCP success) while other Roux-en-Y anatomies (Whipple and hepaticojejunostomy) had 85% endoscopic success and 76% ERCP success. Cannulation rates of native ampulla and anastomosis were similar (90 and 92%, respectively).

The US multicenter study of 129 patients with post-surgical anatomy undergoing 945 ERCPs using DAE (SBE, DBE, spiral enteroscopy) found that ERCP success, defined as completing the intended pancreatobiliary procedure, was achieved in 81 of 129 (63%) patients. When the ampulla or pancreatobiliary-enteric anastomosis could be visualized, ERCP was accomplished successfully in 81 of 92 (88%) patients. ERCP and native papilla cannulation success were independent of the type of DAE used. Median procedure time ranged from 90 to 120 min. Complications occurred in 12% of patients and included pancreatitis, bleeding, perforation (one required surgery for afferent limb perforation in a Whipple patient) and a death from an embolic stroke [5].

Another study compared the diagnostic and therapeutic yield of SBE to spiral-assisted (SE) ERCP in 34 patients with Roux-en-Y who underwent 54 ERCP procedures. There were no significant differences between the two approaches including rates of successful cannulation (48% SBE and 40% SE) and therapy (100% SBE and 89% SE). No differences in procedure time and rates of complication were reported [10].

A recent retrospective series evaluated the utility of the short double-balloon enteroscope in post-surgical patients [20]. Overall success was 81% with nearly all cases of failure to reach the ampulla or anastomosis occurring in RYGB patients. Cannulation was achieved in 90% of patients in whom the ampulla or anastomosis was reached with most cannulation failures resulting from inability to identify the papilla or anastomosis. Therefore, the short double-balloon enteroscope may be a useful tool especially for non-RYGB patients allowing the use of standard ERCP accessories.

Transabdominal Approach to ERCP

When ERCP is not successful using one of the previously described endoscopic techniques, a transabdominal approach via a mature gastrostomy tract or 15 mm trocar at laparoscopy may be required. The advantage to using this approach for ERCP is that a duodenoscope and all other standard ERCP accessories can be used. The gastrostomy tract can be created percutaneously (by interventional radiology or gastroenterology via DAE), laparoscopically or via open surgery. ERCP through a gastrostomy in a Roux-en-Y anatomy was first reported by Baron et al in 1998 [21]. An open Stamm gastrostomy of the bypassed stomach was created with placement of a 24-F Malecot tube. The gastrostomy tract was allowed to mature for 2 weeks, then the tube was removed and wire-guided dilation of the tract was performed, permitting insertion of the duodenoscope to perform the ERCP. Since then, several versions of the same method have been reported with good success rates [22–28]. One case series included 28 patients with RYGB who underwent laparoscopic gastrostomy for pancreatobiliary access and reported 100% success rate in pancreatobiliary cannulation. One of the laparoscopies had to be converted to open access. Complications in this series included pancreatitis, superficial wound infection and gastrostomy leak [23]. A modification on the original technique allows single-session ERCP through a gastrostomy in RYGB patients. The excluded stomach is reached with DAE followed by placement of three T-tags around the intended gastrostomy site to appose the stomach and abdominal walls. Following creation of the gastrostomy, a fully covered esophageal stent is deployed, dilated and held in place while ERCP is performed through it. Finally, a 26-Fr gastrostomy tube is left in place followed by removal of the stent after it is cut longitudinally [29].

A retrospective study compared 28 DBE-ERCP with 44 ERCP through a gastrostomy in RYGB patients [30]. Indications for ERCP, procedure length, success and complications all significantly differed between the two groups. Sphincter of Oddi dysfunction was the most common reason for ERCP through a gastrostomy while choledocholithiasis and malignant strictures were the most common indications in the DBE-ERCP group. Compared with DBE-ERCP, gastrostomy-ERCP was significantly shorter (mean 46 versus 101 min) and more successful (100 versus 56%). Complications were also more common with gastrostomies than DBE (15

versus 3%); however, this was attributable to gastrostomy-related issues. While gastrostomy-ERCP appears appealing, it requires waiting nearly a month for the tract to mature. Single-session ERCP with gastrostomy creation requires further study.

Laparoscopic-assisted ERCP is another well-established method of performing ERCP in Roux-en-Y patients. This method involves close coordination between the surgeon and the endoscopist. The surgeon creates a laparoscopic access into the gastric remnant or small bowel in addition to a trochar that measures up to 15 mm for introduction of the duodenoscope. The endoscopist then advances a sterile standard duodenoscope through the trochar into the laparoscopic access point created. This method has been reported in several case series with high success rates (90–100%) and low complication rates, mostly mild pancreatitis [24, 27, 31, 32]. One study compared 24 laparoscopic-assisted ERCP to 32 DAE-ERCP. Laparoscopic-assisted ERCP was superior for papilla identification (100 versus 72%, $p=0.005$), cannulation rate (100 versus 59%, $p<0.001$) and therapeutic success (100 versus 59%, $p<0.001$). Total length of the Roux limb combined with the biliopancreatic limb being greater than 150 cm was associated with poor therapeutic success during DAE-ERCP [26]. Thus, in patients with total limb length greater than 150 cm, laparoscopic-assisted ERCP may be considered the first approach if the expertise is available.

Case Continued

Given the ERCP findings, anticipated need for multiple ERCPs in the future, and the background of a comprehensive pre-procedure discussion with the patient and his daughter, a decision was made to establish a gastrostomy to offer easy access for subsequent procedures. The excluded stomach was entered, a point of unequivocal transillumination was identified, and a standard 20-Fr PEG tube was placed. To facilitate passage via the overtube, an ERCP hybrid guidewire was used instead of the standard kit guidewire (Video 17.1).

After biliary decompression, the patient improved clinically and was discharged following resolution of pain and fevers. His biochemistries resolved over a fortnight. He returned 7 weeks later for stent revision. The gastrostomy tube was removed and a small caliber endoscope inserted via the PEG tract to the duodenojejunal angle beyond the ampulla. A guidewire was placed into the jejunum and the endoscope withdrawn. Over this wire, sequential dilatation of the gastrostomy site was performed using Savary dilators. In the author's experience, this offers the safest effective option for dilating the tract prior to transabdominal ERCP. A diagnostic duodenoscope was inserted without difficulty and the ampulla reached within 20 cm. The biliary stent was removed with a snare. A complete biliary sphincterotomy was performed without difficulty. A wire-guided lithotripter compatible basket was used to easily capture and crush the biliary stone. To treat the distal CBD stricture, a 10×60 mm fully covered self-expandable metal stent (Wallflex, Boston Scientific, Marlborough, MA) was placed. This is the largest caliber stent that can be placed using a diagnostic duodenoscope. Following placement, there was marked egress of stone debris and particulate material from the bile duct. The scope was withdrawn and a 24-Fr low-profile gastrostomy button was inserted into the gastrostomy. He returned 8 months later for another transabdominal ERCP. The stent was removed and repeat cholangiogram demonstrated complete resolution of the distal CBD stricture. The PEG tube was removed, and the gastrostomy was left to close spontaneously. The patient has remained asymptomatic, and his liver function tests are being monitored on a quarterly basis.

Key Points

- Post-surgical anatomy portends challenges for pancreatobiliary procedures due to the distance to the papilla and the approach for cannulation. The best approach must be determined for each individual case.
- Based on the type of surgery, the expected limb length and biliary orifice (native papilla

versus anastomosis) should be known. Cannulating a native papilla is more challenging via a retrograde approach.

- Standard duodenoscopes may be successful in known short Roux limbs as with Billroth II anatomy. If this approach is unsuccessful, a pediatric colonoscope or enteroscope may be used to perform the ERCP or allow the insertion of a guidewire over which a duodenoscope can be advanced.
- Device-assisted enteroscopy has increased ERCP success rates in Roux-en-Y anatomy. Though scant, present data suggest no differences in outcome with the type of device used.
- For patients with a long Roux limb and native papilla, the better option is often transabdominal ERCP through a gastrostomy or jejunostomy or a laparoscopic-assisted ERCP if the expertise is available.

Video Caption

Video 17.1 The patient in this video had undergone a laparoscopic cholecystectomy complicated by biliary injury requiring Roux-en-Y hepaticojejunostomy. Many years later, she presented with biliary colic and elevated LFTs. MRCP demonstrated biliary stones with mild narrowing of the distal bile duct and anastomosis. This video demonstrates device-assisted enteroscopy using single-balloon enteroscopy to navigate across the jejuno-jejunal anastomosis and then to the hepaticojejunostomy where migrated suture material is visible emerging from the bile duct with a bland appearance of the mucosa surrounding the anastomosis. Cholangiogram (not shown here) showed mild distal biliary/anastomotic deformity and narrowing. Balloon dilation of the distal bile duct and anastomosis was performed using a hydrostatic balloon over a long guidewire. Note subsequent direct endoscopic visualization of stones followed by balloon extraction of the stones. Subsequent to the video, the migrated suture was removed using argon plasma coagulation

References

1. Familiari P, Tringali A, Iacopini F, et al. ERCP in patients with prior Billroth II gastrectomy: report of a two decades experience. Endoscopy. 2005; 37:A280.
2. Chahal P, Baron TH, Topazian MD, Petersen BT, Levy MJ, Gostout CJ. Endoscopic retrograde cholangiopancreatography in post-Whipple patients. Endoscopy. 2006;38:1241–5.
3. Matsushita H, Takakuwa H, Uchida K, Nishio A, Okazaki K. Techniques to facilitate ERCP with a conventional endoscope in patients with previous pancreatoduodenectomy. Endoscopy. 2009;41:902–6.
4. Farrell J, Carr-Locke D, Garrido T, Ruymann F, Shields S, Saltzman J. Endoscopic retrograde cholangiopancreatography after pancreaticoduodenectomy for benign and malignant disease: indications and technical outcomes. Endoscopy. 2006;38:1246–9.
5. Shah RJ, Smolkin M, et al. A multicenter, U.S. experience of single-balloon, double-balloon, and rotational overtube-assisted enteroscopy ERCP in patients with surgically altered pancreatobiliary anatomy (with video). Gastrointest Endosc. 2013;77(4):593.
6. Hintze RE, Adler A, Veltzke W, Abou-Rebyeh H. Endoscopic access to the papilla of Vater for endoscopic retrograde cholangiopancreatography in patients with Billroth II or Roux-en-Y gastrojejunostomy. Endoscopy. 1997;29(2):69.
7. Chahal P, Baron TH, Poterucha JJ, Rosen CB. Endoscopic retrograde cholangiography in post-orthopic liver transplant population with Roux-en-Y biliary reconstruction. Liver Transpl. 2007;13:1168–73.
8. Wright BE, Cass OW, Freeman ML. ERCP in patients with long-limb Roux-en-Y gastrojejunostomy and intact papilla. Gastrointest Endosc. 2002;56:225–23.
9. Kumbhari V, Storm AC, Khashab MA, Canto MI, Saxena P, Akshintala VS, Messallam AA, Singh VK, Lennon AM, Shin EJ, Law JK, Okolo III PI. Deep enteroscopy with standard endoscopes using a novel through-the-scope balloon. Endoscopy. 2014;46:685–9.
10. Lennon AM, et al. Spiral assisted ercp is equivalent to single balloon assisted ercp in patients with roux-en-y anatomy. Dig Dis Sc. 2012;57(5):1391–8.
11. Itoi T, Ishii K, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T, Tsuji S, Ikeuchi N, Fukuzawa K, Moriyasu F, Tsuchida A. Long- and short-type double-balloon enteroscopy-assisted therapeutic ERCP for intact papilla in patients with a Roux-en-Y anastomosis. Surg Endosc. 2011;25(3):713.
12. Emmett DS, Mallat DB. Double-balloon ERCP in patients who have undergone Roux-en-Y surgery: a case series. Gastrointest Endosc. 2007;66(5):1038.
13. Skinner M, Popa D, Neumann H, Wilcox CM, Monkemuller K. ERCP with the overtube-assisted enteroscopy technique: a systematic review. Endoscopy 2014;46:560–72.

14. Cicek B, Parlak E, Disibeyaz S, Koksal AS, Sahin B. Endoscopic retrograde cholangiopancreatography in patients with Billroth II gastrectomy. J Gastroenterol Hepatol. 2007;22:1210–3.
15. Wang YG, Binmoeller KF, Seifert H, Maydeo A, Soehendra N. A new guide wire papillotome for patients with Billroth II gastrectomy. Endoscopy. 1996;28:254–5.
16. Hintze RE, Adler A, Veltzke W, Abou-Rebyeh H. 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.
17. Kim GH, Kang DH, Song GA, Heo J, Park CH, Ha TI, Kim KY, Lee HJ, Kim ID, Choi SH, Song CS. Endoscopic removal of bile-duct stones by using a rotatable papillotome and a large-balloon dilator in patients with a Billroth II gastrectomy (with video). Gastrointest Endosc. 2008;67:1134–8.
18. Kim MH, Lee SK, Lee MH, Myung SJ, Yoo BM, Seo DW, Min YI. 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(2):82.
19. Bergman JJ, van Berkel AM, Bruno MJ, Fockens P, Rauws EA, Tijssen JG, Tytgat GN, Huibregtse K. A randomized trial of endoscopic balloon dilation and endoscopic sphincterotomy for removal of bile duct stones with a prior Billroth II gastrectomy. Gastrointest Endosc. 2001;53:19–26.
20. Siddiqui AA, Chaaya A, Shelton C, Marmion J, Kowalski TE, Loren DE, Heller SJ, Haluszka O, Adler DG, Tokar JL. Utility of the short double-balloon enteroscope to perform pancreaticobiliary interventions in patients with surgically altered anatomy in a US multicenter study. Dig Dis Sci. 2013;58:858–64.
21. Baron TH, Vickers SM. Surgical gastrostomy placement as access for diagnostic and therapeutic ERCP. Gastrointest Endosc. 1998;48(6):640.
22. Baron TH, Chahal P, Ferreira LE. ERCP via mature feeding jejunostomy tube tract in a patient with Roux-en-Y anatomy (with video). Gastrointest Endosc. 2008;68(1):189.
23. Matlock J, Ikramuddin S, Lederer H, et al. Bypassing the bypass: ERCP via gastrostomy after bariatric surgery. Gastrointest Endosc. 2005;61:AB98.
24. Pimentel RR, Mehran A, Szomstein S, Rosenthal R. Laparoscopy-assisted transgastrostomy ERCP after bariatric surgery: case report of a novel approach. Gastrointest Endosc. 2004;59(2):325.
25. Gutierrez JM, Lederer H, Krook JC, Kinney TP, Freeman ML, Jensen EH. Surgical gastrostomy for pancreatobiliary and duodenal access following Roux en Y gastric bypass. J Gastrointest Surg. 2009;13(12):2170–5.
26. Schreiner MA, Chang L, Gluck M, Irani S, Gan SI, Brandabur JJ, Thirlby R, Moonka R, Kozarek RA, Ross AS. Laparoscopy-assisted versus balloon enteroscopy-assisted ERCP in bariatric post-Roux-en-Y gastric bypass patients. Gastrointest Endosc. 2012;75(4):748
27. Lopes TL, Clements RH, Wilcox CM. Laparoscopy-assisted ERCP: experience of a high-volume bariatric surgery center (with video). Gastrointest Endosc. 2009;70(6):1254.
28. Lopes TL, Clements RH, Wilcox CM. Laparoscopy-assisted transjejunal ERCP in a patient with Roux-en-Y reconstruction following partial gastrectomy. J Laparoendosc Adv Surg Tech A. 2010;20(1):55.
29. Law R, Wong Kee Song LM, Petersen BT, Baron TH. Single-session ERCP in patients with previous Roux-en-Y gastric bypass using percutaneous-assisted transprosthetic endoscopic therapy: a case series. Endoscopy 2013;45:671.
30. Choi, et al. ERCP via gastrostomy vs. double balloon enteroscopy in patients with prior bariatric Roux-en-Y gastric bypass surgery. Surg Endosc. 2013;27:2894–9.
31. Ceppa FA, GagnéDJ, Papasavas PK, Caushaj PF. Laparoscopic transgastric endoscopy after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2007;3(1):21.
32. Roberts KE, Panait L, Duffy AJ, Jamidar PA, Bell RL. Laparoscopic-assisted transgastric endoscopy: current indications and future implications. JSLS. 2008;12(1):30.

Ampullectomy

18

Andrew C. Storm and Christopher C. Thompson

Introduction

Adenomas of the ampulla of Vater are rare with prevalence of 0.04–0.12% at autopsy [1–4]. Nonetheless, these lesions are encountered not infrequently by endoscopists, likely owing to the small size at which they may result in symptoms of biliary obstruction as well as the increased use of endoscopy. The potential early onset of symptoms, in addition to increasing experience with therapeutic ERCP, likely contributes to the early detection, treatment, and excellent survival associated with these lesions.

Ampullary adenomas are most commonly small, sessile polypoid lesions. Pathologically they are generally villous and tubulovillous adenomas. They are often sporadic, though they also occur in association with genetic polyposis syndromes such as familial adenomatous polyposis (FAP), which confer a 300-fold increased risk of developing an ampullary adenoma [5, 6]. Nearly 90% of FAP patients develop ampullary adenomas in their lifetime with about 4% progressing to malignancy [7]. This contrasts with sporadic ampullary adenomas which have a reported incidence of malignant transformation ranging from 25 to 85%. Therefore, these lesions require resection or surveillance [8, 9]. Resection has historically been limited to pancreaticoduodenectomy (PD) and transduodenal excision (TDE); however, in 1993 the first report of endoscopic resection with curative intent, also known as endoscopic ampullectomy (or papillectomy), was published [10]. Since that time, with growing interest in minimally invasive techniques aimed at lowering the morbidity and mortality associated with such procedures, investigations into choosing optimal candidates for and techniques of endoscopic ampullectomy have ensued. Additionally, more optimal application of new and existing technologies, including endoscopic ultrasound (EUS), may aid in the selection of patients who will most likely benefit from therapeutic endoscopic ampullectomy.

Indications for Ampullectomy

There exist no clear and widely accepted guidelines regarding selection of patients for surveillance versus resection of ampullary adenomas [11]. There are however known differences in risk of transformation to carcinoma depending on patient characteristics, with the main differentiating factor being the presence or absence of a hereditary polyposis syndrome. Classification and plan of care differ for patients with ampullary

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adenomas in the setting of FAP compared to those with sporadic ampullary adenomas.

Case 1

A 22-year-old male with history of FAP undergoes a screening upper endoscopy during which numerous polyps are discovered throughout the stomach. At the ampulla, a smooth, 5-mm polypoid lesion is noted and biopsy results are consistent with an adenoma. What is the next step?

FAP-Associated Adenomas

Patients with FAP are often discovered to have multiple upper gastrointestinal adenomas, making resection of only an ampullary lesion unattractive if the goal of resection is total prevention of carcinoma. The risk of histologic progression of upper intestinal adenomas in FAP has been demonstrated to be low (on the order of 11% in one large study), making surveillance with biopsies of an ampullary lesion a reasonable approach in most of this patient population [7, 12]. Microscopic adenomatous changes within an endoscopically normal-appearing ampulla are common, occurring in up to 27% of patients; therefore, biopsies should be obtained of the ampulla regardless of endoscopic appearance in FAP patients [13]. The patient may be informed of the possibility of missing progression with endoscopic forceps biopsy surveillance, though studies aimed at evaluating this risk have not focused on the FAP patient population [14, 15].

After colon cancer, ampullary carcinoma is the most prevalent malignancy and leading cause of mortality in FAP patients, affecting about 5–6% of patients [16]. Spigelman et al developed a severity classification system for FAP patients with duodenal polyps, which includes ampullary lesions (Table 18.1) [17]. Using this model, points are accumulated according to number, size, pathology, and degree of dysplasia of polyps to obtain a stage classification from 0 to IV. Stage I indicates mild disease, and stages III–IV indicate severe polyposis. Most patients (80%) have stage I-III disease with 10–20% harboring stage IV disease. Over time, more patients develop advanced stage IV disease with up to 43% at age 60 and 52% by age 70 [18, 19]. Stage IV disease is also associated with higher probability (up to 36% at 10 years) of developing cancer compared to less than 1% for stages I-III; therefore, stage IV patients warrant surgical referral, as they may be candidates for pancreaticoduodenectomy [19, 20]. However, a recent study demonstrated that endoscopic management of stage IV FAP patients may be feasible. Patients with stage IV FAP underwent endoscopic treatment with removal of all duodenal polyps > 1 cm including ampullary adenomas and control of smaller polyps with intensive ongoing endoscopic surveillance. All these patients achieved Spigelman downstaging with no invasive duodenal cancer diagnosed at mean 9-year follow-up, and 8.5% required surgery for advanced neoplasia [21]. Therefore, endoscopic management of even stage IV disease by removing > 1 cm lesions with close surveillance may be successful with potentially decreased mortality from ampullary and duodenal cancers. In addition, if histologic progression is identified on biopsy surveillance, or symptoms of biliary obstruction occur with ampullary lesions, evaluation for excision of the lesion should be pursued.

Table 18.1 Spigelman classification of duodenal polyps in familial adenomatous polyposis

Score (points)	1	2	3
No. of polyps	1–4	5–20	>20
Size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage 0: 0 point, Stage I: 1–4 points, Stage II: 5–6 points, Stage III: 7–8 points, Stage IV: 9–12 points

Case 1 Continued

The patient is classified as stage II by the Spigelman classification with 5 total points. Therefore, after discussion with his gastroenterologist, he elects to continue with routine surveillance of the ampullary lesion given his relatively low risk of malignant transformation.

Sporadic Adenomas

Sporadic adenomas are most frequently discovered in patients over the age of 40, and most commonly in the seventh decade of life, during evaluation for signs or symptoms of biliary obstruction. Painless jaundice is by far the most common presenting symptom found in 50–75 % of these patients [22, 23]. Other symptoms include biliary colic, weight loss, and vague abdominal pain with reports of acute pancreatitis. In general, unlike FAP-associated adenomas, sporadic adenomas of the ampulla require resection especially when symptoms are present or histology is consistent with high-grade dysplasia.

Case 2

A 72-year-old female with severe aortic stenosis, diabetes, and prior myocardial infarction presents with new-onset painless jaundice and mild transaminitis on comprehensive metabolic profile. Right upper quadrant ultrasound reveals dilation of the common bile duct, which is confirmed on contrast-enhanced CT of the abdomen. No pancreatic mass or other signs of metastatic disease are noted on CT. What is the next step?

What Diagnostic Tools are Available?

The diagnosis and workup of an ampullary adenoma relies on endoscopic, radiographic, and histologic evaluation. Many non-adenomatous lesions including Brunner's gland tumors, inflammatory polyps, carcinoid tumors, and hamartomas may cause lesions of the ampulla (Table 18.2). The goal of this evaluation is to rule out cancer, which would require surgical intervention, and to diagnose adenomas, which may be amenable to endoscopic resection.

Table 18.2 Histopathologic lesions of the ampulla of Vater [35]

Benign	Malignant
Tubulovillous adenoma (40 %)	*Adenocarcinoma*
Villous adenoma (30 %)	*Neuroendocrine tumor*
Tubular adenoma (10 %)	*Cystadenoma*
Adenomyoma	*Signet ring cell carcinoma*
Carcinoid	*Lymphoma*
Hemangioma	
Leiomyoma	
Lipoma	
Lymphangioma	
Neurofibroma	
Hamartoma	
Fibroma	
Granular cell tumor	

Endoscopy: How Accurate is Ampullary Biopsy?

Endoscopy provides useful information from both endoscopic visualization of the ampullary lesion and histology from forceps biopsy. It is important to recognize foci of cancer may still exist within an otherwise benign-appearing adenoma, and furthermore, false-negative biopsy results may occur in 17–40 % [24–28]. Accuracy of forceps biopsy of ampullary lesions may improve by performing biopsies after sphincterotomy. An old study reported that the false-negative rate dropped to 0 % by waiting to take biopsies at least 10 days after sphincterotomy [29] while another report confirmed improved accuracy when biopsies were taken immediately after sphincterotomy [30]. However, a prospective study of ampullary biopsy before and after sphincterotomy found sensitivity of forceps biopsy for malignancy improved insignificantly

Table 18.3 TNM staging of ampullary carcinoma

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to ampulla of Vater or sphincter of Oddi
T2	Tumor invades duodenal wall
T3	Tumor invades pancreas
T4	Tumor invades peripancreatic soft tissues or other adjacent organs or structures other than pancreas
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

from 21 % to only 37 % following sphincterotomy [31]. In addition, this practice is likely not feasible unless the patient has had prior sphincterotomy or is having an ERCP for other indications necessitating a sphincterotomy at the time an ampullary lesion is discovered. Care should be taken to avoid the pancreatic orifice during biopsy as pancreatitis has been reported following ampullary biopsies [32].

Despite the problem of biopsy sampling error, recently confirmed by a large series where 53 % of invasive cancers were missed by biopsy, only 5 % of these invasive cancers were deemed endoscopically resectable. The following endoscopic findings are believed to indicate potential malignancy and therefore unsuitable for endoscopic ampullectomy: friability, ulceration, more than 50 % lateral extension, obvious duodenal infiltration with induration and firmness, and intraductal extension more than 1 cm from the papilla [10, 33]. There are growing reports of adjunctive endoscopic technologies in the evaluation of ampullary lesions including narrow band imaging and magnification endoscopy [34]. Given the inaccuracy of endoscopic biopsy for diagnosing invasive malignancy in ampullary adenomas, further evaluation may be needed. This could ultimately entail endoscopic resection of the ampulla to obtain a definitive diagnosis in addition to providing potentially curative therapy.

Radiology

Transabdominal ultrasound is commonly used as a first-line examination in patients with jaundice and may demonstrate ductal dilatation proximal to the ampullary adenoma. Pancreatic protocol multidetector row CT of the abdomen with contrast is often used to rule out a pancreatic mass and metastatic disease in patients with painless jaundice and should be performed for this indication prior to ERCP and ampullectomy. Spiral CT is likely the best modality for the evaluation of vascular invasion though its role in evaluating the presence of carcinoma in ampullary lesions is limited [35]. Magnetic resonance cholangiopancreatography (MRCP) provides non-invasive imaging of pancreatic and biliary ductal anatomy, which may not be necessary in all patients, but is useful in high-risk populations. Finally, percutaneous transhepatic cholangiography (PTC) may be used to evaluate the biliary tree in the case of a failed or difficult ERCP although this is rarely necessary.

EUS: When is EUS Indicated?

EUS offers several advantages in the workup of ampullary adenomas to evaluate for the presence of invasive cancer. Ultrasonographic architecture and three-dimensional reconstruction of the lesion may be used to detect invasive carcinoma which is not evident on forceps biopsy or other imaging techniques [36, 37]. Ampullary carcinomas are staged using the TNM staging similar to other cancers (Table 18.3). As with other cancers, M staging is best performed with radiologic imaging, typically CT or MRI. EUS and IDUS are the modalities of choice for local T staging of ampullary carcinoma (Table 18.4). Overall accuracy of EUS T staging is estimated at 78–84 % with greatest accuracy for T2 and T3 stages (T1 60 %, T2 92 %, T3 92 %, T4 50 %) [35]. Overstaging can occur from peritumoral inflammation or concomitant pancreatitis [38]. EUS accuracy for N staging ranges from 50 to 100 %. Intraductal ultrasound has the highest accuracy (70–100 %) of all modalities for T staging [39]. A recent study comparing IDUS and EUS for T staging demonstrated similar overall accuracy

Table 18.4 T and N staging accuracy of CT, MRI, EUS, and IDUS [35, 39, 75]

	CT	MRI	EUS	IDUS
T staging accuracy (%)	5–24	46	75–84	78–100
N staging accuracy (%)	33–59	77	50–100	67–93

CT computed tomography, *MRI* magnetic resonance imaging, *EUS* endoscopic ultrasound, *IDUS* intraductal ultrasound

(78 versus 63%, $p=0.1$) although there was a trend toward increased accuracy with IDUS for T1 and T2 (T1: 86 versus 62%, T2: 64 versus 45%, T3-4: 75 versus 88%) [40]. While EUS is performed before ERCP and ampullectomy, IDUS is more invasive and occurs only during ERCP after achieving bile duct cannulation by passing a 20- to 30-MHz probe over a guidewire into the bile duct and slowly withdrawing through the ampulla. A recent retrospective study reported that EUS and ERCP had comparable accuracy (91% and 84%) for determining intraductal extension of ampullary lesions. In addition, there was no difference in accuracy between radial and linear echoendoscopes [41]. Most experts agree that EUS is indicated for lesions >3 cm, displaying potentially malignant endoscopic features, or demonstrating high-grade dysplasia or carcinoma in situ on histology [42]. Others also advocate EUS for lesions >2 cm in size [35, 43]. Small benign-appearing lesions, especially those less than 1 cm, are unlikely to harbor malignancy, and EUS evaluation is generally unnecessary prior to proceeding to endoscopic snare resection [43].

The technique of EUS imaging of the ampulla uses water or saline to fill the duodenum. Once in the second portion of the duodenum, the echoendoscope is rotated counterclockwise maintaining apposition to the duodenal wall until the ampulla is visualized by EUS. Alternatively, the ampulla can be located endoscopically followed by EUS imaging of this region. It is important to assess the lesion for tissue invasion, ductal infiltration, and evidence of local lymphadenopathy. The choice of a radial or linear echoendoscope is personal preference although the ability to perform fine-needle aspiration (FNA) favors the linear scope. EUS-FNA should be performed on lymph nodes as well as ampullary masses using a 22- or 25-gauge needle as 19-gauge needles are typically difficult to use in the duodenum.

What are Indications for Endoscopic Versus Surgical Resection?

If EUS identifies invasive carcinoma, regardless of tumor staging, pancreaticoduodenectomy is the treatment of choice when the goal is curative therapy. Studies have demonstrated high recurrence rates for these lesions with transduodenal resection [14, 44]. Lesions with high-grade dysplasia, carcinoma in situ, and/or ductal invasion less than 1 cm may still be considered for endoscopic resection [39, 45, 46]. Generally endoscopic resection is reserved for ampullary masses smaller than 4–5 cm. Multivariate analysis of factors associated with malignancy identified only a negative saline lift sign as predictive of malignancy (odds ratio 28.4, $p=0.015$) while size ≥2 cm trended toward significance ($p=0.059$) [47].

Surgical excision is currently recommended for the following:

- Larger lesions (>4–5 cm)
- Lesions with carcinoma (histologic or suspicious on endoscopic evaluation)
- Lymph node involvement or significant ductal invasion (>1 cm)
- Lack of access to experienced interventional endoscopist
- Patient preference

Case 2 Continued

The patient proceeds to EUS, which reveals a 2.5-cm ampullary mass with endoscopically benign features. There is minimal ductal invasion and

no vascular invasion on EUS. Endosonographic images also reveal no submucosal invasion or signs of local metastatic disease. Biopsy results are consistent with tubular adenoma. Given her comorbid conditions and lesion characteristics, the patient elects for endoscopic ampullectomy over surgical resection.

Techniques of Ampullectomy

For benign and pre-malignant lesions, debate continues not only regarding endoscopic versus surgical resection, but also between the two most common surgical approaches to ampullectomy. Endoscopic ampullectomy for benign ampullary lesions has demonstrated equivalent efficacy and mortality with decreased morbidity compared to surgical ampullectomy [48].

Surgical Approach to Benign Adenoma

Two procedures, pancreaticoduodenectomy and transduodenal resection, may be considered. For benign adenomas, transduodenal resection is preferred given the reduced morbidity and mortality associated with the procedure although it comes with a higher recurrence rate. Using a midline or subcostal laparotomy, the mass is identified and lateral duodenectomy is performed. Circumferential ampullary resection is undertaken using needle-tip electrocautery. Morbidity and potential mortality associated with surgery may be undesirable or unacceptable for some patients with comorbid conditions.

Endoscopic Ampullectomy/ Papillectomy

Endoscopic ampullectomy (EA) may be considered in patients meeting the previously described indications for endoscopic resection and for non-surgical candidates. The technique varies greatly across centers. Regardless, the procedure requires proficiency with a side-viewing therapeutic duodenoscope, which is used to visualize the lesion and allows use of thermal ablation probes. Many institutions perform the procedure under conscious sedation, though general anesthesia may also be employed.

After inspection, a double-lumen sphincterotome and hydrophilic guidewire are used for biliary and pancreatic duct cannulation (Fig. 18.1 and Video 18.1). Contrast should be injected into both ducts to assess for intraductal extension of the ampullary adenoma. Generally, biductal sphincterotomy is performed to allow for decompression and stenting post-ampullectomy although there is a concern for potential increased risk of complications of bleeding and perforation and interference with pathologic evaluation of the resected specimen from cautery [49, 50]. Furthermore, with larger lesions it may be difficult to identify appropriate landmarks to perform sphincterotomy safely. Post-resection sphincterotomies may be done as well. Some centers place wires into the ducts and proceed with ampullectomy with wires in place. Next, submucosal injection of epinephrine diluted in saline 1:20,000 may be used to facilitate lifting the tumor from the muscularis propria. This also may provide evidence of unidentified carcinomatous invasion if lift is not accomplished (absence of the "positive lift sign") [51]. The risk of bleeding and deeper penetration of tissue burning is also mitigated by the submucosal lift technique [52]. Nevertheless, this step may make snare placement and resection more challenging and distort the ampullary anatomy, and the author usually avoids submucosal injection.

Ampullectomy is then performed, preferably en bloc, using a monopolar polypectomy snare (as in colon mucosal polypectomy) with electrocautery at 40–60 W using blended current, though currently there are neither guidelines regarding power output nor mode of current. The snare may be groomed prior to insertion to generate a slight curve at the tip of the snare to aid in en bloc resection. Typically the tip of the snare is anchored immediately above the lesion and opened to unfold around the lesion in a cephalad to caudal direction. Lesions greater than 2 cm may require piecemeal resection.

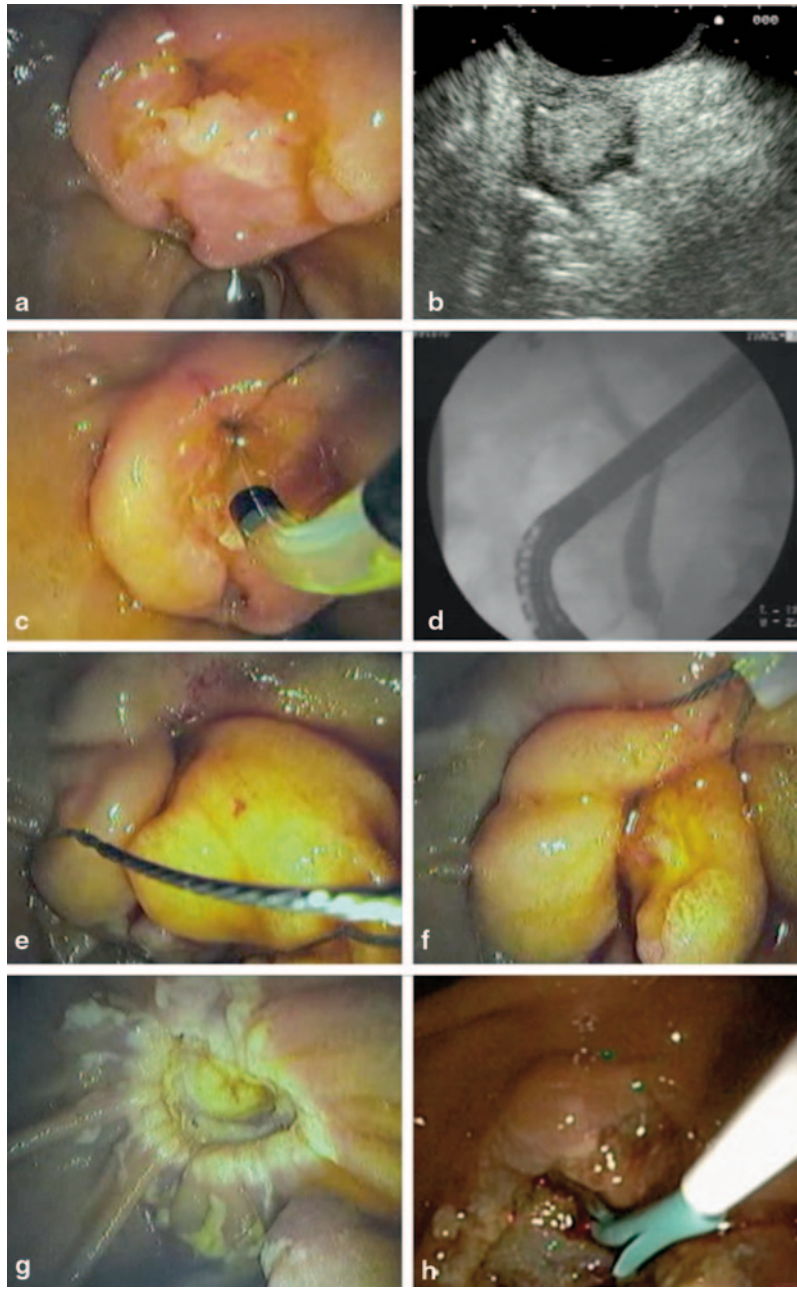

Fig. 18.1 Procedural steps of endoscopic ampullectomy. **a** Lesion is identified and margins examined. **b** EUS performed for staging prior to resection without evidence of invasion or extension into the bile duct. (**c**) Pancreatic duct sphincterotomy is performed. **d** Cholangiogram confirms no evidence of ductal invasion. **e** Snare is deployed around the ampullary lesion. **f** Snare is firmly closed around the lesion for en-bloc resection. **g** Ampullary site is examined for residual abnormal tissue. **h** Prophylactic pancreatic duct stent is placed

Immediately after resection, the specimen(s) should be retrieved to avoid loss distally, and snare or Roth net (US Endoscopy, Mentor, OH) retrieval is preferred over aspiration given the importance of maintaining specimen architecture for histologic evaluation. Administering

Table 18.5 Procedural steps of endoscopic ampullectomy. (Adapted from [35])

Inspection	Evaluate for firmness, ulceration, induration, friability, size
Cannulation	Achieve with double lumen sphincterotome and hydrophilic guidewire. Assess for intraductal invasion or stricture. Inject dilute epinephrine solution for flat lesions
Sphincterotomy	Routine pancreatic sphincterotomy recommended. Biliary sphincterotomy performed routinely or in absence of free bile flow
Resection	Polypectomy snare used to grasp adenoma at the base. Apply 45–60 W blended current to cut/cauterize
Ablation	Monotherapy for flat or small lesions. Adjunctive therapy for residual tissue post-ampullectomy
Stenting	3- or 5-Fr stent placed in PD, may be placed prior to ampullectomy for small lesions. Biliary stenting for poorly draining bile duct after sphincterotomy
Observation	Observe site for evidence of bleeding. If present, inject 1:20,000 epinephrine
Prophylaxis	Rectal indomethacin immediately post-procedure to prevent pancreatitis

intravenous glucagon is helpful to diminish peristalsis and thereby aid in tissue retrieval. Ablative therapy may be used as primary therapy for recurrent small flat lesions not amenable to snare resection, or adjuvant treatment for residual abnormal tissue in the resection bed. Various forms of ablative therapies have been suggested including monopolar or bipolar electrocautery, Nd:YAG laser photoablation, and argon plasma coagulation, with data lacking to guide the use of one approach over the other. A retrospective series of 103 patients with ampullary adenomas (both sporadic and FAP) reported that performing ablative therapy after resection did not affect long-term success of ampullectomy (81 % with ablation versus 78 % without ablation) although there was a trend toward decreased recurrence with ablation (3 versus 14 %, $p = 0.2$) [53].

After ampullectomy is performed, a short 3-Fr or 5-Fr pancreatic duct (PD) stent must be placed to reduce the risk of post-ampullectomy pancreatitis [54]. If pre-resection sphincterotomy was not performed, techniques to help identify the pancreatic orifice, in addition to careful inspection, include injecting dilute methylene blue mixed with contrast into the pancreatic duct before resection which will stain the pancreatic orifice blue and using intravenous secretin to promote flow of clear pancreatic juice. A 3-Fr pancreatic stent will typically fall out, and this should be confirmed with an abdominal X-ray. With 5-Fr stent placement, repeat duodenoscopy 2–3 weeks post-ampullectomy will allow for stent retrieval as well as excision or fulguration of any remaining abnormal tissue. Common bile duct (CBD) stenting may also be performed, though there are no data to suggest it is necessary to prevent post-ampullectomy cholangitis. In cases with smaller lesions, the PD stent may be placed prior to ampullectomy to avoid the difficulty of cannulating post-ampullectomy. This may also protect the orifice from electrocautery damage during snare resection and fulguration of any residual tissue [55]. Table 18.5 reviews the steps in performing endoscopic ampullectomy.

Complications of the procedure may occur in up to 15–28 % of cases. Post-ampullectomy pancreatitis (5–33 %) is generally mild and resolves with conservative management. Ampullectomy bleeding (2–13 %) may be controlled with conservative measures and endoscopic hemostasis. Papillary stenosis (0–8 %) may be treated with sphincterotomy, stenting and/or balloon dilation. Perforation (0–4 %) and cholangitis (0–4 %) are both infrequently encountered and mortality is exceedingly uncommon [6, 10, 29, 33, 53, 55–64].

Prophylactic Interventions

Prophylactic placement of PD and CBD stents is discussed above. Whether routine use of prophylactic antibiotics is necessary remains unanswered, but is not currently recommended [65]. There is strong evidence to support the utility of

routine prophylactic rectal indomethacin in the prevention of post-ERCP, and by corollary, post-ampullectomy pancreatitis [66].

Endoscopic Palliation

In patients who are not surgical or endoscopic ampullectomy candidates, endoscopic biliary drainage with palliative intent is very appropriate. Ampullectomy or transpapillary stent placement may be employed for decompression of the biliary or pancreatic ducts in cases of obstruction from an ampullary mass [67].

Case 2 Continued

Three months after ampullectomy, the patient returns for surveillance duodenoscopy, which reveals no residual adenoma or recurrence of her previously resected lesion. She is scheduled for another EGD in 6 months to survey for recurrence at the site of prior ampullectomy.

Surveillance

Unlike patients who undergo colectomy for colon cancer, patients do not require endoscopic surveillance following pancreaticoduodenectomy for an ampullary lesion, unless they have a polyposis syndrome. There are no guidelines on the interval and duration of endoscopic surveillance following endoscopic or transduodenal ampullectomy. An initial examination with an experienced interventional endoscopist, side-viewing duodenoscope, and biopsies at 1–6 months with repeat examination every 3–12 months for at least 2 years is recommended [11]. ERCP is not necessary in the absence of symptoms. In patients with lesions ≥ 2 cm, intraductal involvement, or high-grade dysplasia on post-resection histology, surveillance intervals should be on the more frequent end of these ranges. Technical factors with an individual case may also dictate surveillance intervals; for example, in lesions with incomplete or piecemeal resection, more frequent examinations may be required in order to prevent or detect recurrence. FAP patients should then continue with routine upper endoscopy surveillance of duodenal polyps in the upper gastrointestinal tract, which is based on the Spigelman classification (stage 0/I: every 5 years; stage II: every 3 years; stage III: every 1–2 years.) [20]. The endpoint for surveillance in patients with sporadic ampullary adenomas is unclear with experts recommending at least 2-year follow-up [68]. Very long-term follow-up studies of endoscopic ampullectomy patients are lacking, and surveillance guidelines may change when these data become available.

Recurrence

Mean endoscopic success rate with complete excision of the ampullary lesion from a review of 967 patients was 82% [64]. In patients who have undergone surgical transduodenal ampullectomy, recurrence has been reported to occur in 0–50% of patients [27, 69–73]. Reported recurrence rates following endoscopic ampullectomy for sporadic lesions are lower, ranging from 0 to 33% [33, 74]. In a recent study of FAP patients, recurrence rates after endoscopic ampullectomy are higher at 58.3% over mean 7-year follow-up [13]. The only factor predictive of recurrence was lesion size >1 cm (77 versus 36% in smaller lesions, $p=0.002$). Only 3 patients (12%) required Whipple surgery during follow-up although these were not performed due to ampullary adenoma recurrence. In a retrospective analysis of endoscopic ampullectomy, predictors of successful endoscopic ampullectomy and lower recurrence included age over 48, male sex, lesion size less than 24 mm, and absence of familial polyposis syndrome [6]. A more recent study of 182 patients following endoscopic ampullectomy noted the following factors associated with recurrence: jaundice at the time of presentation, ampullary adenocarcinoma, intraductal involvement noted on ERCP, and piecemeal resection [75, 76]. With recurrent adenomas, the treatment algorithm is the same as the initial therapeutic approach. Recurrent tumor should be removed and ablated every 2–3 months until biopsy specimens return with no residual adenoma [53].

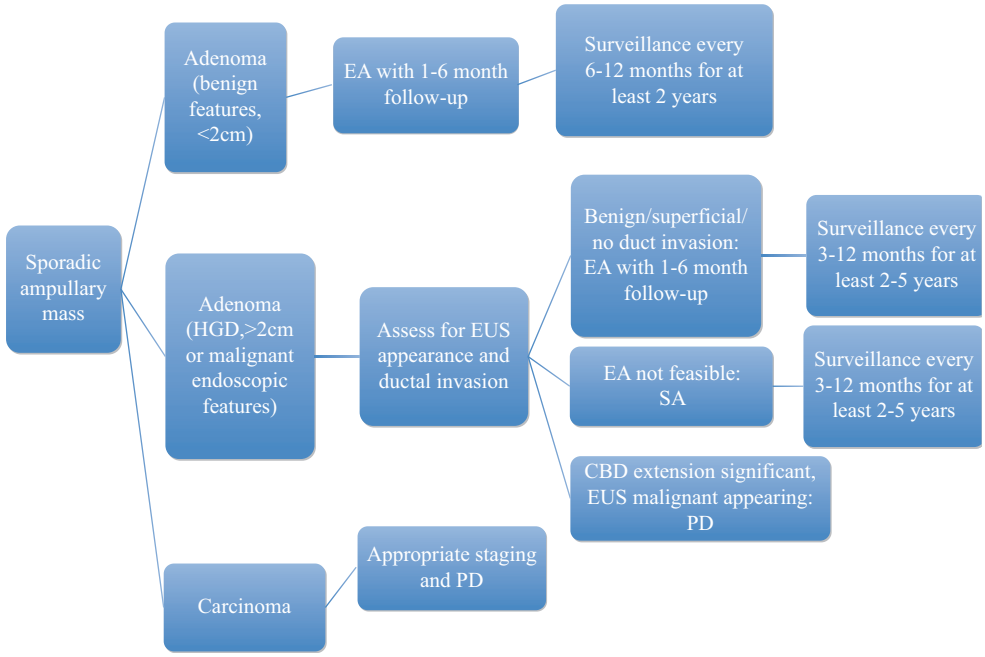

Fig. 18.2 Suggested management algorithm of a sporadic ampullary mass. *PD* pancreaticoduodenectomy, *SA* surgical ampullectomy, *EA* endoscopic ampullectomy, *HGD* high-grade dysplasia

Key Points

- Ampullary adenomas are often asymptomatic and most frequently present with painless jaundice, and 70 % are tubulovillous or villous adenomas
- Ampullary adenomas may occur sporadically or in the setting of polyposis syndromes like FAP, and the risk of progression to carcinoma is present in both, which mandates at a minimum ongoing biopsy surveillance. Sporadic adenomas should be resected (Fig. 18.2).
- EUS enables pre-therapy staging to guide the ideal choice of therapy (pancreaticoduodenectomy, transduodenal ampullectomy, or endoscopic ampullectomy) prior to resection in many patients.
- Malignant ampullary lesions should be referred for surgical resection, preferably pancreaticoduodenectomy.
- Endoscopic ampullectomy may be preferred for benign lesions less than 4–5 cm with no malignant endoscopic or EUS features given the equivalent risk of recurrence and favorable morbidity compared to surgery.
- Surveillance of all patients post-ampullectomy should continue at 3–12 month intervals for at least 2–5 years after resection.
- Recurrent adenomas should be evaluated and treated in the same way as a primary lesion.

Video Caption

Video 18.1 Endoscopic ampullectomy

References

1. Grobmyer SR, Stasik CN, Draganov P, Hemming AW, Dixon LR, Vogel SB, et al. Contemporary results with ampullectomy for 29 “benign” neoplasms of the ampulla. J Am Coll Surg. 2008;206(3):466–71.
2. Sato T, Konishi K, Kimura H, Maeda K, Yabushita K, Tsuji M, et al. Adenoma and tiny carcinoma in adenoma of the papilla of Vater-p53 and PCNA. Hepato-Gastroenterol. 1999;46(27):1959–62.

3. Shapiro PF, Lifvendahl RA. Tumors of the extrahepatic bile-ducts. Ann Surg. 1931;94(1):61–79.
4. Baker HL, Caldwell DW. Lesions of the ampulla of Vater. Surgery. 1947;21(4):523–31.
5. Jagelman DG, DeCosse JJ, Bussey HJ. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet. 1988;1(8595):1149–51.
6. Martin JA, Haber GB. Ampullary adenoma: clinical manifestations, diagnosis, and treatment. Gastrointest Endosc N Am. 2003;13(4):649–69.
7. 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(3 Pt 1):358–64.
8. Takashima M, Ueki T, Nagai E, Yao T, Yamaguchi K, Tanaka M, et al. Carcinoma of the ampulla of Vater associated with or without adenoma: a clinicopathologic analysis of 198 cases with reference to p53 and Ki-67 immunohistochemical expressions. Mod Pathol. 2000;13(12):1300–7.
9. Seifert E, Schulte F, Stolte M. Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. Am J Gastroenterol. 1992;87(1):37–42.
10. Binmoeller KF, Boaventura S, Ramsperger K, Soehendra N. Endoscopic snare excision of benign adenomas of the papilla of Vater. Gastrointest Endosc. 1993;39(2):127–31.
11. Standards of Practice C, Adler DG, Qureshi W, Davila R, Gan SI, Lichtenstein D, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc. 2006;64(6):849–54.
12. Matsumoto T, Iida M, Nakamura S, Hizawa K, Yao T, Tsuneyoshi M, et al. Natural history of ampullary adenoma in familial adenomatous polyposis: reconfirmation of benign nature during extended surveillance. Am J Gastroenterol. 2000;95(6):1557–62.
13. Ma T, Jang EJ, Zukerberg LR, Odze R, Gala MK, Kelsey PB, et al. Recurrences are common after endoscopic ampullectomy for adenoma in the familial adenomatous polyposis (FAP) syndrome. Surg Endosc. 2014;28(8):2349–56.
14. Kim JH, Kim JH, Han JH, Yoo BM, Kim MW, Kim WH. Is endoscopic papillectomy safe for ampullary adenomas with high-grade dysplasia? Ann Surg Oncol. 2009;16(9):2547–54.
15. Bellizzi AM, Kahaleh M, Stelow EB. The assessment of specimens procured by endoscopic ampullectomy. Am J Clin Pathol. 2009;132(4):506–13.
16. Iwama T, Mishima Y, Utsunomiya J. The impact of familial adenomatous polyposis on the tumorigenesis and mortality at the several organs. Its rational treatment. Ann Surg. 1993;217(2):101–8.
17. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RK. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. Lancet. 1989;2(8666):783–5.
18. Saurin JC, Gutknecht C, Napoleon B, Chavaillon A, Ecochard R, Scoazec JY, et al. Surveillance of duodenal adenomas in familial adenomatous polyposis reveals high cumulative risk of advanced disease. J Clin Oncol. 2004;22(3):493–8.
19. Bulow S, Bjork J, Christensen IJ, Fausa O, Jarvinen H, Moesgaard F, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut. 2004;53(3):381–6.
20. Vasen HF, Moslein G, Alonso A, Aretz S, Bernstein I, Bertario L, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). Gut. 2008;57(5):704–13.
21. Moussata D, Napoleon B, Lepilliez V, Klich A, Ecochard R, Lapalus MG, et al. Endoscopic treatment of severe duodenal polyposis as an alternative to surgery for patients with familial adenomatous polyposis. Gastrointest Endosc. 2014;80:817–25.
22. Taxier M, Sivak MV Jr, Cooperman A. Villous adenoma of the ampulla of Vater. Gastrointest Endosc. 1979;25(4):155–6.
23. Greco S, Cassinotti A, Massari A, Bossi I, Trabucchi E, Bianchi Porro G. Isolated ampullary adenoma causing biliary obstruction. J Gastrointest Liver Dis. 2008;17(3):329–32.
24. Yamaguchi K, Enjoji M. Carcinoma of the ampulla of vater. A clinicopathologic study and pathologic staging of 109 cases of carcinoma and 5 cases of adenoma. Cancer. 1987;59(3):506–15.
25. Yamaguchi K, Enjoji M. Adenoma of the ampulla of Vater: putative precancerous lesion. Gut. 1991;32(12):1558–61.
26. Yamaguchi K, Enjoji M, Kitamura K. Endoscopic biopsy has limited accuracy in diagnosis of ampullary tumors. Gastrointest Endosc. 1990;36(6):588–92.
27. Cahen DL, Fockens P, de Wit LT, Offerhaus GJ, Obertop H, Gouma DJ. Local resection or pancreaticoduodenectomy for villous adenoma of the ampulla of Vater diagnosed before operation. Br J Surg. 1997;84(7):948–51.
28. Sauvanet A, Chapuis O, Hammel P, Flejou JF, Ponsot P, Bernades P, et al. Are endoscopic procedures able to predict the benignity of ampullary tumors? Am J Surg. 1997;174(3):355–8.
29. Ponchon T, Berger F, Chavaillon A, Bory R, Lambert R. Contribution of endoscopy to diagnosis and treatment of tumors of the ampulla of Vater. Cancer. 1989;64(1):161–7.
30. 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(3):163–6.
31. 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(10):1227–31.
32. Ishida Y, Okabe Y, Tokuyasu H, Kaji R, Sugiyama G, Ushijima T, et al. A case of acute pancreatitis following endoscopic biopsy of the ampulla of Vater. Kurume Med J. 2013;60(2):67–70.
33. Irani S, Arai A, Ayub K, Biehl T, Brandabur JJ, Dorer R, et al. Papillectomy for ampullary neoplasm: results

of a single referral center over a 10-year period. Gastrointest Endosc. 2009;70(5):923–32.
34. Uchiyama Y, Imazu H, Kakutani H, Hino S, Sumiyama K, Kuramochi A, et al. New approach to diagnosing ampullary tumors by magnifying endoscopy combined with a narrow-band imaging system. J Gastroenterol. 2006;41(5):483–90.
35. Patel R, Varadarajulu S, Wilcox CM. Endoscopic ampullectomy: techniques and outcomes. J Clin Gastroenterol. 2012;46(1):8–15.
36. Quirk DM, Rattner DW, Fernandez-del Castillo C, Warshaw AL, Brugge WR. The use of endoscopic ultrasonography to reduce the cost of treating ampullary tumors. Gastrointest Endosc. 1997;46(4):334–7.
37. Skordilis P, Mouzas IA, Dimoulios PD, Alexandrakis G, Moschandrea J, Kouroumalis E. Is endosonography an effective method for detection and local staging of the ampullary carcinoma? A prospective study. BMC Surg. 2002;2:1.
38. Maluf-Filho F, Sakai P, Cunha JE, Garrido T, Rocha M, Machado MC, et al. Radial endoscopic ultrasound and spiral computed tomography in the diagnosis and staging of periampullary tumors. Pancreatology. 2004;4(2):122–8.
39. Menzel J, Hoepffner N, Sulkowski U, Reimer P, Heinecke A, Poremba C, et al. Polypoid tumors of the major duodenal papilla: preoperative staging with intraductal US, EUS, and CT—a prospective, histopathologically controlled study. Gastrointest Endosc. 1999; 49(3 Pt 1):349–57.
40. Ito K, Fujita N, Noda Y, Kobayashi G, Horaguchi J, Takasawa O, et al. Preoperative evaluation of ampullary neoplasm with EUS and transpapillary intraductal US: a prospective and histopathologically controlled study. Gastrointest Endosc. 2007;66(4):740–7.
41. Ridtitid W, Schmidt SE, Al-Haddad MA, LeBlanc J, DeWitt JM, McHenry L, et al. Performance characteristics of EUS for locoregional evaluation of ampullary lesions. Gastrointest Endosc. 2015;81(2):380–8.
42. Hwang JC, Kim JH, Lim SG, Yoo BM, Cho SW. Endoscopic resection of ampullary adenoma after a new insulated plastic pancreatic stent placement: a pilot study. J Gastroenterol Hepatol. 2010;25(8):1381–5.
43. Baillie J. Endoscopic ampullectomy. Am J Gastroenterol. 2005;100(11):2379–81.
44. Beger HG, Treitschke F, Gansauge F, Harada N, Hiki N, Mattfeldt T. Tumor of the ampulla of Vater: experience with local or radical resection in 171 consecutively treated patients. Archives Surg. 1999;134(5):526–32.
45. Itoh A, Goto H, Naitoh Y, Hirooka Y, Furukawa T, Hayakawa T. Intraductal ultrasonography in diagnosing tumor extension of cancer of the papilla of Vater. Gastrointest Endosc. 1997;45(3):251–60.
46. Ito K, Fujita N, Noda Y, Kobayashi G, Horaguchi J. Diagnosis of ampullary cancer. Dig Surg. 2010;27(2):115–8.
47. Kahaleh M, Shami VM, Brock A, Conaway MR, Yoshida C, Moskaluk CA, et al. Factors predictive of malignancy and endoscopic resectability in ampullary neoplasia. Am J Gastroenterol. 2004;99(12):2335–9.
48. Ceppa EP, Burbridge RA, Rialon KL, Omotosho PA, Emick D, Jowell PS, et al. Endoscopic versus surgical ampullectomy: an algorithm to treat disease of the ampulla of Vater. Ann Surg. 2013;257(2):315–22.
49. 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(2):239–43.
50. Lee SK, Kim MH, Seo DW, Lee SS, Park JS. Endoscopic sphincterotomy and pancreatic duct stent placement before endoscopic papillectomy: are they necessary and safe procedures? Gastrointest Endosc. 2002;55(2):302–4.
51. Monson JR, Donohue JH, McEntee GP, McIlrath DC, van Heerden JA, Shorter RG, et al. Radical resection for carcinoma of the ampulla of Vater. Archives Surg. 1991;126(3):353–7.
52. Yamao T, Isomoto H, Kohno S, Mizuta Y, Yamakawa M, Nakao K, et al. Endoscopic snare papillectomy with biliary and pancreatic stent placement for tumors of the major duodenal papilla. Surg Endosc. 2010;24(1):119–24.
53. Catalano MF, Linder JD, Chak A, Sivak MV J., Raijman I, Geenen JE, et al. Endoscopic management of adenoma of the major duodenal papilla. Gastrointest Endosc. 2004;59(2):225–32.
54. 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(3):367–70.
55. Desilets DJ, Dy RM, Ku PM, Hanson BL, Elton E, Mattia A, et al. Endoscopic management of tumors of the major duodenal papilla: Refined techniques to improve outcome and avoid complications. Gastrointest Endosc. 2001;54(2):202–8.
56. Park SW, Song SY, Chung JB, Lee SK, Moon YM, Kang JK, et al. Endoscopic snare resection for tumors of the ampulla of Vater. Yonsei Med J. 2000;41(2):213–8.
57. Shemesh E, Nass S, Czerniak A. Endoscopic sphincterotomy and endoscopic fulguration in the management of adenoma of the papilla of Vater. Surg Gynecol Obstetrics. 1989;169(5):445–8.
58. Cheng CL, Sherman S, Fogel EL, McHenry L, Watkins JL, Fukushima T, et al. Endoscopic snare papillectomy for tumors of the duodenal papillae. Gastrointest Endosc. 2004;60(5):757–64.
59. Norton ID, Geller A, Petersen BT, Sorbi D, Gostout CJ. Endoscopic surveillance and ablative therapy for periampullary adenomas. Am J Gastroenterol. 2001;96(1):101–6.
60. Vogt M, Jakobs R, Benz C, Arnold JC, Adamek HE, Riemann JF. Endoscopic therapy of adenomas of the papilla of Vater. A retrospective analysis with long-term follow-up. Dig Liver Dis. 2000;32(4):339–45.

61. Charton JP, Deinert K, Schumacher B, Neuhaus H. Endoscopic resection for neoplastic diseases of the papilla of Vater. J Hepato-Biliary-Pancreat Surg. 2004;11(4):245–51.
62. Patel R, Davitte J, Varadarajulu S, Wilcox CM. Endoscopic resection of ampullary adenomas: complications and outcomes. Dig Dis Sci. 2011;56(11):3235–40.
63. Nguyen N, Shah JN, Binmoeller KF. Outcomes of endoscopic papillectomy in elderly patients with ampullary adenoma or early carcinoma. Endoscopy. 2010;42(11):975–7.
64. Laleman W, Verreth A, Topal B, Aerts R, Komuta M, Roskams T, et al. Endoscopic resection of ampullary lesions: a single-center 8-year retrospective cohort study of 91 patients with long-term follow-up. Surg Endosc. 2013;27(10):3865–76.
65. Menees SB, Schoenfeld P, Kim HM, Elta GH. A survey of ampullectomy practices. World J Gastroenterol. 2009;15(28):3486–92.
66. Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. New Engl J Med. 2012;366(15):1414–22.
67. Huibregtse K, Tytgat GN. Palliative treatment of obstructive jaundice by transpapillary introduction of large bore bile duct endoprosthesis. Gut. 1982;23(5):371–5.
68. Adler DG, Qureshi W, Davila R, Gan SI, Lichtenstein D, Rajan E, et al. The role of endoscopy in ampullary and duodenal adenomas. Gastrointest Endosc. 2006;64(6):849–54.
69. Treitschke F, Beger HG. Local resection of benign periampullary tumors. Ann Oncol. 1999;10(Suppl 4):212–4.
70. Galandiuk S, Hermann RE, Jagelman DG, Fazio VW, Sivak MV. Villous tumors of the duodenum. Ann Surg. 1988;207(3):234–9.
71. Asbun HJ, Rossi RL, Munson JL. Local resection for ampullary tumors. Is there a place for it? Archives Surg. 1993;128(5):515–20.
72. Ryan DP, Schapiro RH, Warshaw AL. Villous tumors of the duodenum. Ann Surg. 1986;203(3):301–6.
73. Posner S, Colletti L, Knol J, Mulholland M, Eckhauser F. Safety and long-term efficacy of transduodenal excision for tumors of the ampulla of Vater. Surgery. 2000;128(4):694–701.
74. Han J, Kim MH. Endoscopic papillectomy for adenomas of the major duodenal papilla (with video). Gastrointest Endosc. 2006;63(2):292–301.
75. Ridtitid W, Tan D, Schmidt SE, Fogel EL, McHenry L, Watkins JL, et al. Endoscopic papillectomy: risk factors for incomplete resection and recurrence during long-term follow-up. Gastrointest Endosc. 2014;79(2):289–96.
76. Kim HK, Lo SK. Endoscopic approach to the patient with benign or malignant ampullary lesions. Gastrointest Endosc Clin N Am. 2013;23(2):347–83.

ERCP in Pregnancy

19

Bahar Madani and Paul R. Tarnasky

Introduction

Pregnancy is associated with an increased frequency of gallstones and related disease. Studies worldwide have reported the prevalence of biliary sludge as 5–31 % and cholelithiasis ranging from 2–12 % [1–4]. Physiological changes during pregnancy increase risk of cholesterol stone formation through estrogen-induced bile lithogenicity and progesterone-induced biliary stasis [5].

Most pregnant women with cholelithiasis remain asymptomatic and stones are likely to clear spontaneously during the postpartum period. However, up to one third of pregnant patients with cholelithiasis are at risk of biliary colic [1, 2]. Assuming 3 % prevalence for gallstones of which 5 % become symptomatic, even a conservative estimate is that 1/1000 pregnant women suffer from symptomatic cholelithiasis [6]. More severe complications including acute cholecystitis, cholangitis, and acute pancreatitis occur in less than 10 % of the symptomatic patients [7]. Following appendectomy, acute cholecystitis is the second most common indication for non-obstetric-related surgical intervention. The incidence of acute cholecystitis in pregnant women with gallstones is 0.05-0.08 % [8]. Generally, conservative management is provided while safely delaying any intervention until after delivery or the second trimester when surgical intervention is relatively safer.

Patients with symptomatic choledocholithiasis relapse frequently (58−72 %) and usually require repeated hospitalization [9]. Choledocholithiasis during pregnancy is uncommon and occurs in 1 out of every 1200 deliveries [10]. Choledocholithiasis and its related complications are the most common indications for ERCP during pregnancy. The rate of performing ERCP in pregnancy has been reported as 1 in 1415 births [11]. Due to the relapsing nature of biliary symptoms, performing ERCP in the setting of choledocholithiasis may be indicated to decrease the chance of recurrences and potential fetal and maternal complications.

Case Presentation

A 20-year-old Hispanic woman, gravida 1 para 0 at 35 weeks of gestation, was transferred to our institution for further evaluation and management of biliary colic.

She developed abdominal pain 5 days prior to transfer. The pain was located in the epigastric and right upper quadrant areas without radiation, and was worse with food and associated with nausea. She presented to her local emergency department with worsened pain and vomiting. She denied any fever, chills, jaundice, or diarrhea.

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Her pregnancy course had been without any complications, and she denied any prior episodes of similar symptoms. Her past medical history was otherwise unremarkable.

Her initial laboratory evaluation revealed: WBC 6300/mm^3, hemoglobin 12.4 g/dl, platelet 128×10^3/mm^3, albumin 3.2 g/dL, AST 126 IU/L, ALT 102 IU/L, alkaline phosphatase 234 IU/L, total bilirubin 1.4 mg/dL, lipase 58 IU/L, amylase 96 IU/L, and PT/INR 12.8/1.0 s. Urinalysis was negative for urine protein and WBC. She was admitted to the obstetric antepartum service.

What Is the Differential Diagnosis of Abdominal Pain and Elevated Liver Function Tests During Pregnancy?

The differential diagnosis of abdominal pain and increased LFTs during pregnancy is broad; clinical presentation, diagnostic imaging, and laboratory findings can help to discern the various causes. The presenting features of biliary disease may include abdominal pain, nausea, vomiting, jaundice, pruritus, and liver biochemical test abnormalities. Presentation of gallstone disease in pregnancy is similar to nonpregnant patients. However, other complications that may occur during pregnancy should be considered as they can mimic the clinical presentations of biliary disease [12]. The differential diagnoses can be categorized according to the trimester of the pregnancy and specific abnormal laboratory findings as outlined below (Table 19.1).

Hyperemesis gravidarum usually occurs during early pregnancy and resolves before 20 weeks gestation. Elevations in the serum transaminases occur in more than half of the cases and are typically less than 1000 IU/L with serum ALT usually higher than AST. Intrahepatic cholestasis of pregnancy is characterized by pruritus and should be considered in pregnant patients during the 2nd or 3rd trimester. High levels of serum transaminases up to 500 IU/L and serum bile acids (4–10 times normal) with a normal GGTP are the usual laboratory findings. The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) is characterized by abdominal pain and occurs during late pregnancy or shortly thereafter. Transaminase elevations can occur in the several thousand ranges but the prothrombin time is normal unless complicated by disseminated intravascular coagulation. Acute fatty liver of pregnancy also usually presents in the 3rd trimester of pregnancy. Elevation of serum transaminases up to 1000 IU/L and hepatic synthetic dysfunction, such as elevated prothrombin time and hypoglycemia in severe cases, are observed. Preeclampsia can occur in both HELLP syndrome and acute fatty liver of pregnancy, but the pathophysiology is different and sometimes it is difficult to differentiate among these conditions. Preeclampsia presents with hypertension and proteinuria and elevated transaminases signifies severe disease and usually occurs in the third trimester. Acute viral hepatitis (A, B, C) and hepatitis E (in endemic countries) should always be considered in any pregnant patient with elevated serum transaminases. A prospective

Table 19.1 Differential diagnoses of abnormal liver function tests in pregnant patients

Disease	Pregnancy trimester	Laboratory abnormalities
Hyperemesis gravidarum	First	Elevated AST, ALT
Intrahepatic cholestasis of pregnancy	Second and third trimester and postpartum	Elevated serum bile acids Elevated AST, ALT, Bilirubin Normal GGTP
Acute fatty liver of pregnancy	Third trimester and postpartum	Elevated AST, ALT, Bilirubin Elevated PT/INR Hypoglycemia
HELLP syndrome	Second half of pregnancy and postpartum	Elevated AST, ALT Decreased PLT Increased LDH
Preeclampsia	Third trimester and immediate postpartum	Elevated AST, ALT HTN, proteinuria
Viral hepatitis	Any trimester	Elevated AST, ALT, bilirubin

study from the UK revealed liver dysfunction in 3% of the deliveries during a 15-month period. Preeclampsia was the most common abnormality (48%) followed by HELLP syndrome (22%), intrahepatic cholestasis of pregnancy (16%), hyperemesis gravidarum (8%), and acute fatty liver of pregnancy (4%) [13].

It is important to remember that a slight increase or decrease in some liver function tests may be seen during a normal pregnancy and may not be clinically significant. Serum protein concentrations decrease due to hemodilution in pregnancy; and therefore, serum albumin levels are significantly lower during all three trimesters. Serum alkaline phosphatase levels usually increase late in pregnancy due to production of the placental isoenzyme and an increase in the bone isoenzyme. Serum ALT, AST, and total bile acids level usually remain the same but total serum bilirubin levels decrease during pregnancy [14].

Biliary Colic

Biliary colic is characterized by recurrent postprandial episodes of abdominal pain in the epigastrium or right upper quadrant. It is caused by contraction of the gallbladder against an obstructed outlet due to a stone. The stone may fall back from the cystic duct and the pain resolves temporarily. During pregnancy, 28−31% of the patients may experience biliary colic [1, 2]. Almost two thirds of the patients who experience pain have stones larger than 10 mm in diameter [2]. Biliary pain is significantly more frequent among women with gallstones (5 of 17 patients, 29%) than among women with biliary sludge (2 of 42 patients, 5%). Disappearance of biliary sludge and stones after delivery is common and occurs in about two-thirds and one-third of women, respectively [1, 2]. Pre-pregnancy obesity and elevated serum leptin have been shown to be risk factors for development of gallbladder disease during pregnancy [3]. Biliary colic without bile duct stones is usually not associated with abnormal liver function tests.

Acute Cholecystitis

Acute cholecystitis is an inflammatory process with infection of the gallbladder as a result of cystic duct obstruction and bile stasis. The incidence of acute cholecystitis is between 1 and 8/10,000 pregnancies [8, 11]. Severe right upper quadrant pain in addition to other symptoms such as fever, tachycardia, nausea, vomiting, anorexia, and Murphy's sign should raise the suspicion for acute cholecystitis. The diagnosis is usually confirmed with ultrasonography findings. Uncomplicated cholecystitis is not often associated with hyperbilirubinemia. However, mild elevation of serum aminotransferases and amylase, along with hyperbilirubinemia, is seen in the setting of the passage of small stones and/or sludge. Marked elevation of the liver function tests indicates the possibility of a common bile duct stone, cholangitis, or Mirizzi's syndrome.

Acute Cholangitis

Acute cholangitis is a clinical syndrome characterized by fever, jaundice, and abdominal pain that develops as a result of stasis and infection in the biliary tract.

Laboratory tests typically reveal an elevated white blood cell count with neutrophil predominance, and a cholestatic pattern of liver test abnormalities with elevations in the serum alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin (primarily conjugated) concentration [15–17]. However, a pattern of acute hepatocyte necrosis can occur with aminotransferases as high as 2000 IU/L [18]. Cholangitis can be a common indication for ERCP during pregnancy.

Acute Pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas, which is associated with severe epigastric abdominal pain, elevated serum

amylase, and/or lipase three times greater than the upper limit of normal. Any significant elevation of serum pancreatic enzymes should be considered clinically relevant since serum amylase and/or lipase do not normally increase during the course of a normal pregnancy [18].

When uncertain, the diagnosis may be established by further radiologic findings such as focal or diffuse enlargement of the pancreas and/or peripancreatic inflammatory changes seen on contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI). The incidence of acute pancreatitis during pregnancy is fortunately uncommon (<10 in 10,000) [19]. In a 5-year study of over 46,000 pregnancies, the frequency of acute pancreatitis was 0.07% at one institution [9]. Acute pancreatitis in pregnancy is most often associated with gallstones, which are responsible for over 70% of the cases [8, 9, 19, 20]. Elevation in serum ALT to more than three times the upper limit of normal has been reported to be a very sensitive biomarker of biliary pancreatitis [21]. The pathogenesis of biliary pancreatitis is related to impaction or passage of a stone or crystals via the ampulla of Vater with pancreatic ductal obstruction causing activation of intra-acinar trypsinogen to trypsin. Biliary pancreatitis can occasionally be severe and associated with significant maternal morbidity [22]. Fetal loss is not uncommon (7%) in biliary pancreatitis and is as high as 30% when associated with recurrent pancreatitis [23, 24].

The second most common cause of acute pancreatitis during pregnancy is hypertriglyceridemia. In the third trimester, serum triglyceride levels rise three-fold, likely due to estrogen-induced increase in triglyceride synthesis [25]. Treatment of hyperlipidemic acute pancreatitis during pregnancy is mostly supportive.

What Are the Diagnostic Imaging Options?

Ultrasonography

Ultrasonography is a safe initial step for identifying gallbladder stones and sludge in pregnancy. Despite its high sensitivity for detection of cholelithiasis, it lacks sensitivity for identifying CBD stones. Dilated biliary ducts in the setting of abnormal liver function tests or pancreatitis raise the suspicion for choledocholithiasis.

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Cholangiopancreatography (MRCP)

MRI and magnetic resonance cholangiopancreatography (MRCP) provide large field view images of the body with excellent soft-tissue contrast and images of the pancreatobiliary system [19]. Gallstone pancreatitis is often associated with small stones and sludge, which can be missed even by MRCP especially if located in the distal CBD and smaller than 5–6 mm [26–28]. MRCP is an accepted alternative imaging modality for pregnant women when more information is needed about the biliary system. Because no contrast is given during MRCP, there is no risk of renal injury. It is important to examine several views as different projection images may provide complementary information as shown in Fig. 19.1. Based on the American College of Radiology (ACR) guidance document for safe MR practice published in 2013, MRI is only indicated during pregnancy if the information cannot be acquired through other nonionizing diagnostic imaging studies, and the data will potentially affect the care of the patient or fetus during pregnancy [26]. There are no special considerations regarding performing MRI in the first compared to any other trimester of pregnancy.

Endoscopic Ultrasonography (EUS)

Endoscopic ultrasonography is highly sensitive (89–94%) and specific (94–95%) for detecting CBD stones [29, 30]. EUS has high diagnostic accuracy for detecting CBD stones; however, compared to other imaging modalities it requires sedation, an expert endoscopist, and specialized equipment. Although EUS does not allow therapeutic intervention, it is generally safe and does

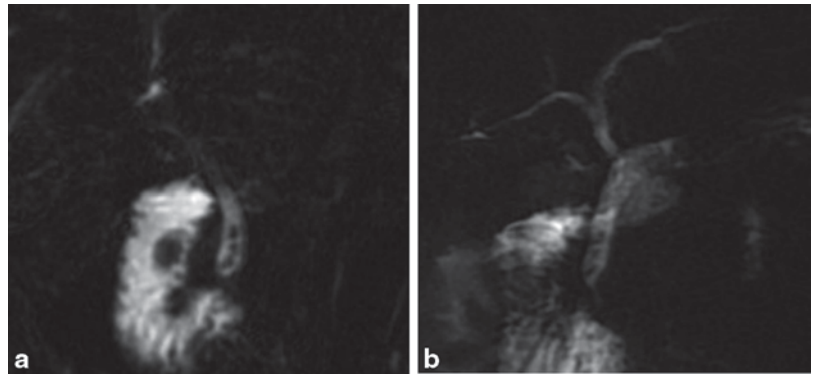

Fig. 19.1 A 21-year-old at 8 weeks gestation was referred for evaluation of suspected biliary colic due to RUQ pain, nausea, vomiting, and increased LFTs. MRCP showed several stones in the distal bile duct that are best appreciated when examining different projected images as shown here. ERCP was performed without fluoroscopy with sphincterotomy and removal of stones

not involve radiation exposure. Performing EUS prior to ERCP in patients with suspected CBD stones can help to avoid unnecessary ERCP and its complications in near two thirds of the patients [31, 32]. If a common bile duct stone is detected by EUS (Fig. 19.2), an ERCP with sphincterotomy can be performed during the same session [33, 34].

Case Continued

Abdominal ultrasonography showed cholelithiasis and moderate extrahepatic biliary duct dilation. There was no evidence of cholecystitis. A subsequent MRCP showed a dilated bile duct to 1.3 cm in diameter and multiple stones in the common bile duct. Based on the imaging findings, elevated transaminases, and her symptoms of abdominal pain and nausea, the likely diagnosis was biliary colic due to choledocholithiasis. The decision was made to proceed with ERCP.

What Are the Indications for ERCP in Pregnancy?

Choledocholithiasis and its complications are far and away the most common indication for performing ERCP during pregnancy. It is most important to understand that ERCP should only be considered when there is absolute certainty that endotherapy is necessary. The indications for performing an ERCP during pregnancy are

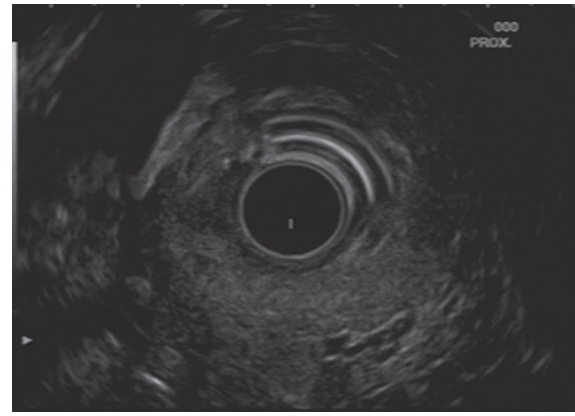

Fig. 19.2 A 26-year-old at 8 weeks gestation was referred for suspected choledocholithiasis based on increased ALT and dilated bile ducts on transabdominal ultrasonography. Endoscopic ultrasound showed a hyperechoic shadowing stone (*arrow*) in the bile duct that was removed at the same session during ERCP

Table 19.2 Indications for ERCP during pregnancy

Urgent
Acute cholangitis
Biliary pancreatitis with suspected impacted stones
Elective
Suspected symptomatic choledocholithiasis
Post-operative complications, e.g., bile leak
Relapsing pancreatitis
Pancreatic duct disruption

similar but more restricted when compared to the nonpregnant state (Table 19.2). Furthermore, if possible, ERCP should be postponed until the second trimester or postpartum.

Development of biliary disease during the pregnancy, especially in the first trimester, can result in maternal and fetal physiologic dysfunction leading to adverse pregnancy outcome such as preterm labor or low birth weight. It is important to identify complications of choledocholithiasis early during pregnancy and determine if there is a need for intervention as promptly as possible.

Not surprisingly, early reports of ERCP during pregnancy were performed for urgent indications. Baillie et al. reported the first case series of five patients in 1990. The indications were acute cholangitis in four and gallstone pancreatitis in one patient. All five patients delivered healthy babies at term [35]. Since then, ERCP during pregnancy is still almost always performed for biliary indications, but sometimes under more elective settings.

Historically, the care of pregnant patients with acute biliary related disease entailed conservative management with the hope of delaying intervention until after pregnancy or the second trimester when organogenesis is completed. While this still remains true, currently, urgent ERCP with sphincterotomy and clearance of bile duct stones is indicated in patients with cholangitis and in those with severe acute pancreatitis and evidence of persistent biliary obstruction. Elective ERCP with biliary sphincterotomy +/− stenting may be indicated when there is evidence of symptomatic CBD stones and cholecystectomy needs to be delayed due to the pregnancy or for less common reasons such as postoperative complications like bile leak (Fig. 19.3). Rarely, it may be reasonable to consider ERCP for management of pancreatitis that is not due to a biliary etiology. In the report by Jamidar et al., only 2 of the 23 pregnant patients underwent ERCP to treat a purely pancreatic indication including pancreas divisum and pancreatic duct stricture [36].

Pre-Procedure Considerations

Informed Consent

Performing ERCP in a pregnant patient is appropriate only when there are clear indications for endotherapy. The benefits and risks of the procedure should be clarified for the patient, spouse, and any other relevant family members.

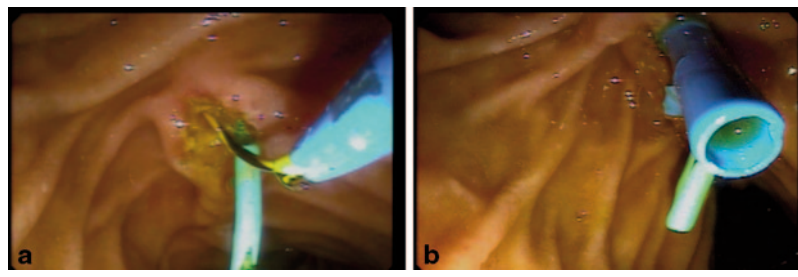

Fig. 19.3 A 42-year-old with a 21-week gestation underwent open cholecystectomy for gangrenous cholecystitis. Due to the persistent bile drainage via a percutaneous drain, she was referred for ERCP for treatment of a suspected bile leak. **a** Biliary access was obtained without use of fluoroscopy after a needle-knife access sphincterotomy over a pancreatic stent. **b** A bile duct stent was placed to ensure drainage. A postpartum ERCP was normal and the bile duct stent was extracted

The risks include not only those to the mother but also to the fetus. Complications of ERCP in general are pancreatitis, hemorrhage, perforation, infections (cholangitis, cholecystitis), cardiopulmonary complications (arrhythmia, hypoxemia, aspiration), stent-related complications (stent migration, stent occlusion, liver abscess, bile duct or pancreatic duct injury, and subsequent duct stricture), and death [37]. The fetus is sensitive to maternal hypoxia and hypotension, which can lead to fetal distress and demise. Other risks to the fetus include teratogenicity from medications and/or radiation exposure and premature birth. A full review of radiation issues will be discussed below. An informed consent for ERCP during pregnancy should include a discussion of potential risks of radiation, methods to reduce risk as well as an alternative for ERCP without any radiation. It should be clarified that ERCP without use of fluoroscopy is more difficult and therefore potentially associated with more risk from a technical aspect. Whether or not the endoscopist is comfortable with no radiation techniques (see below) should also be discussed. If patient and family are completely opposed to use of any radiation, then it is appropriate to discuss options for transfer to another expert center, if conditions allow.

Patient Positioning

Patient positioning for ERCP during pregnancy is typically different from the customary prone position used in the nonpregnant state. During pregnancy, the patient's position for ERCP depends on the trimester of her pregnancy and whether or not fluoroscopy is planned. Maintaining a prone position may be difficult during the second and third trimester, so a left lateral position with the use of a pelvic wedge, if needed, is preferable. It is generally recommended that the patient should not be completely supine since the gravid uterus can compress the vena cava or the aorta causing maternal hypotension and decreased placental perfusion [10, 38, 39]. Nonetheless, outcome of the pregnancy was not adversely affected in a study of all patients who underwent ERCP in a supine position.[38] If ERCP is performed without any fluoroscopy, then all patients regardless of pregnancy stage can remain in the left lateral position.

When monopolar electrocautery is anticipated for purposes of sphincterotomy, the return electrode (cautery pad) should be placed on the trunk or upper abdomen. This is to ensure that the uterus is not between the active and return electrodes to avoid fetal effects [40–42].

Patient Monitoring

Standard American Society of Anesthesiologists (ASA) monitoring should be utilized throughout the procedure. In the setting of a viable fetus, fetal heart rhythm should be monitored continuously or at a minimum before and after general anesthesia depending on the gestational age. Before 24 weeks, Doppler can be used to document the presence of fetal heart rate before and after the procedure. Continuous fetal heart and uterine contraction monitoring before, during, and after the endoscopy should be performed for fetuses older than 24 weeks. This should be discussed and coordinated with the obstetric team who should be consulted in all cases involving pregnant patients.

Sedation

There are potential risks to the fetus from the use of specific medications for sedation (Table 19.3). None of the medications that are used for sedation during ERCP are in category A of Food and Drug Association of the United States (FDA), so category B or C drugs may be used [10]. Category B medications are considered relatively safe while category C drugs are likely safe and category D medications should be avoided unless absolutely needed with no safer alternatives. Most ERCPs are performed using a combination of benzodiazepine and opiates or propofol and opiates. Meperidine is a category B drug and does not appear teratogenic. However, meperidine can be considered as category D when used for long periods (>36 h) in high doses at term due to concerns

Table 19.3 Medication Safety in ERCP during pregnancy

Medications	FDA category	Comment
Meperidine	B	Safe in pregnancy, avoid use at term
Propofol	B	Safe in pregnancy
Fentanyl	C	Safe at low doses
Morphine	C	Crosses fetal blood–brain barrier rapidly
Naloxone	B	Use with caution, one reported case of neonatal fatality
Flumazenil	C	Use only if clearly indicated
Benzodiazepines (diazepam)	D	Possible association with mental retardation and congenital anomalies
Midazolam	D	Preferred over diazepam, no reports of congenital anomalies, avoid in 1st trimester
Glucagon	B	Safe in pregnancy

about accumulation of its mildly toxic metabolite, normeperidine. During routine endoscopy, the maximum suggested dose for meperidine is 75 mg. Fentanyl is a category C drug as it has embryocidal effects in rats, but appears safe in humans at low doses. Propofol is classified as category B, but its use in the first trimester has been inadequately studied [7]. Benzodiazepines, including midazolam and diazepam, are category D drugs. Midazolam has not been associated with congenital abnormalities like cleft palate malformations and is preferred over diazepam when sedation with meperidine is inadequate, but if possible it should be avoided in the first trimester due to the potential fetal harm at that time. Glucagon and lidocaine are considered category B, whereas flumazenil and simethicone are rated as category C [10].

Endotracheal intubation is generally recommended for any upper endoscopy procedure due to the potential concern for aspiration as well as to maintain the airway and for a potentially prolonged, complicated procedure. Physiologic changes during pregnancy include swelling of the oropharyngeal tissue and narrower glottis opening [43].

Antibiotics

An appropriate antibiotic should be administered in cases with evidence for acute cholangitis or cholecystitis; however, selecting the right antibiotic during pregnancy can be complicated (Table 19.4). There are potential concerns regarding the transplacental passage of antibiotics leading to possible teratogenic effects on the fetus. Initial antibiotic choice is empiric and should be subsequently modified based on the organisms found in the blood and bile cultures. Most of the penicillin derivatives (amoxicillin, ampicillin, ampicillin-sulbactam, piperacillin-tazobactam), clindamycin, erythromycin, and cephalosporins are classified as category B drugs and are safe during pregnancy [19]. Metronidazole crosses the placenta and should be avoided in the first trimester [43]. Imipenem, which belongs to carbapenem class, is a category C drug, and while animal studies showed no teratogenic risks, there are no available human data [19]. Quinolones are category C with reports of adverse effects to the fetus, therefore their use should be avoided during pregnancy.

Case Continued

The decision of proceeding with ERCP was discussed with the patient's obstetrician, and we were assured of staff availability during the procedure in case of fetal distress or pregnancy related complications. Informed consent was obtained after the risks, benefits, and alternatives of the procedure were thoroughly explained. She and her husband wished to have the ERCP performed without any fluoroscopy, if possible. Standard ASA monitors were placed with the addition of fetal heart monitoring. A labor and delivery nurse was present before, during, and after the ERCP to monitor fetal heart rate and rhythm, and to monitor for uterine contractions. Preoxygenation and rapid sequence

Table 19.4 Antibiotic safety in ERCP during pregnancy

Antibiotics	FDA category	Comment
Penicillins	B	Safe in pregnancy
Cephalosporines	B	Safe in pregnancy
Erythromycin	B	Safe in pregnancy
Clindamycin	B	Safe in pregnant patients with penicillin allergy
Ampicillin- sulbactam	B	Safe in pregnancy
Piperacillin-tazobactam	B	Safe in pregnancy
Metronidazole	B	Avoid in first trimester
Quinolone	C	Avoid in pregnancy
Imipenem	C	Avoid in pregnancy
Tetracycline	D	Avoid in pregnancy
Sulfonamide	C	Avoid in third trimester

induction was then performed followed by a standard general endotracheal anesthetic. The patient was positioned in the left lateral position.

Radiation and Pregnancy

What Are the Potential Effects of Fluoroscopy During Pregnancy?

Use of fluoroscopy and spot radiography is inherent to standard ERCP procedures. Any ERCP during pregnancy that utilizes fluoroscopy will expose the fetus to potential risks of ionizing radiation with the greatest risk during 8–15 weeks gestation. There are a number of excellent and comprehensive reviews on the topic [7, 10, 38, 39, 41, 44–46].

X-ray exposure or the amount of ions per unit mass of air is measured in roentgens (R). The radiation dose of energy deposited in tissue is measured in gray (Gy) that is equal to 1 J of energy per kilogram of tissue. An equivalent of approximately 0.01 (Gy) is generated by 1 R. Ionizing radiation is measured in radiation absorbed dose (rads) and radiation equivalent man (rem), and in the international units as gray (Gy) and seivert (Sv) (1 rad = 1 rem = 0.01 Gy = 0.01 Sv).

Radiation damage is classified into stochastic and deterministic effects. The stochastic (carcinogenic) effects include childhood cancer, leukemia, and genetic effects. The probability, but not the severity, of stochastic effects increases with dose and does not have a threshold value. Conceptus dose radiation up to 1 mGy is considered insignificant but doses higher than 10 mGy (1 rad or 0.01 Sv) will require measurement of associated risks. The National Council on Radiation Protection (NCRP, 1977) raised this threshold and suggested that fetal radiation doses up to 50 mGy (5 rad) would still be considered a minor teratogenic factor and did not, by itself, justify therapeutic abortion [47].

Deterministic effects, such as growth and mental retardation depend on gestational age and conceptus radiation dose. The threshold dose is 100 mGy, above which fetal growth retardation and malformations may develop, and the severity of the effects varies with the dose. Below this level there is no risk of deterministic effects. It is recommended that fetal radiation dose should not exceed 0.5 mSv per month or 1 mSv during the first trimester with 5 mSv being the maximum permitted over the entire gestation.

Factors that can affect fetal radiation dosage depend on the energy and size of the x-ray beam, the skin surface exposure to the mother, the depth of fetus, and the size of the mother. It is estimated that the fetal dose may range between 10 and 30 % of the mother's exposure. However, fetal radiation exposure may be underestimated due to an inability to detect scatter radiation. Samara et al. developed a method for assessing the conceptus dose from ERCP procedures based on mathematical and physical phantom models. Their study revealed that the conceptus dose from ERCPs might occasionally exceed 10 mGy, the limit above which an accurate determination of conceptus dose is required by placing a dosimeter on the abdomen over the uterus. They

emphasized that the main source of radiation to the fetus during an ERCP is scattered radiation that is absorbed within the mother's body; therefore, they concluded that external shielding is unnecessary since the dose reduction is trivial. The normalized dose data derived from this study may be used for accurate estimation of conceptus dose from an ERCP performed on a pregnant patient, regardless of body size, gestational age, operating parameters, and equipment used [41]. Kahaleh et al. found a linear relationship between fluoroscopy time and fetal radiation exposure although there was up to a three-fold difference in the estimated exposure for a given fluoroscopy time. This difference makes the estimation of radiation exposure based on fluoroscopy time difficult. They concluded that fetal exposure to ionizing radiation must be kept to the absolute minimum [38]. Consultation with a radiation physicist who can provide assistance in protecting the fetus and estimating fetal exposure is helpful.

What Are the General Principles for Safe and Effective Fluoroscopy in Pregnancy?

The following strategies and general techniques to minimize radiation and maximize safety should be considered for fluoroscopy use during ERCP (Table 19.5) [40]. Short taps of fluoroscopy instead of continuous operation will limit x-ray beam exposure. Use of the last-image-hold or fluoroscopy loop-recording feature for image study, instruction, etc. will also decrease radiation exposure. The number of recorded images should be minimal or even avoided all together. Collimate the x-ray beam to the smallest field possible. This technique will decrease the amount of scatter radiation striking the fetus in proportion to the exposure area. The image quality will also improve by reducing the amount of scatter radiation reaching the image receptor. The x-ray tube should be placed as far as possible from the patient with the image receptor as close as possible to the patient. This action will not only improve image quality but also decrease patient dose. Magnification mode should be used sporadically and if absolutely necessary. Placing a lead shield over the uterus can prevent direct fetal exposure. However, because the fetus is exposed to scatter radiation, this will provide only a diminutive amount of dose reduction [41]. If digital fluoroscopy is available, it is preferred over film-screen radiography because it requires significantly lower dose of radiation during image acquisition. The fluoroscopy store feature to save the last-image-hold images instead of acquiring a separate digital image should be used. A low-dose-rate setting is recommended with digital fluoroscopy. Advances in ERCP cannulation techniques are probably most important toward the goal of minimizing or eliminating risk of radiation (see next section).

Table 19.5 Techniques to reduce radiation exposure during ERCP in pregnancy

Use short taps of fluoroscopy instead of continuous operation
Use digital fluoroscopy if available
Collimate the x-ray beam to the smallest field possible
Avoid magnification of fluoroscopic image
Use fluoroscopic videotaping for documentation when needed instead of spot radiographs
Position patient as close as possible to the image receptor and as far as possible from the x-ray tube
Adjust patient position and use shielding to minimize fetal radiation exposure
If possible delay ERCP from first trimester to second trimester to avoid fetal radiation exposure during organogenesis
Minimize procedure time

ERCP Strategies and Techniques in Management of Pregnant Patients

Normally, fluoroscopy is used during ERCP to evaluate biliary anatomy, confirm, and monitor stone(s) and guidewire, catheter, or sphincterotome positions in the bile duct, and document ductal clearance. Some modified ERCP strategies and techniques are required in the setting of pregnancy as outlined in the algorithm (Fig. 19.4). Such techniques are focused on limiting or eliminating the use of fluoroscopy and replacing it with alternative means of confirming biliary access and duct clearance.

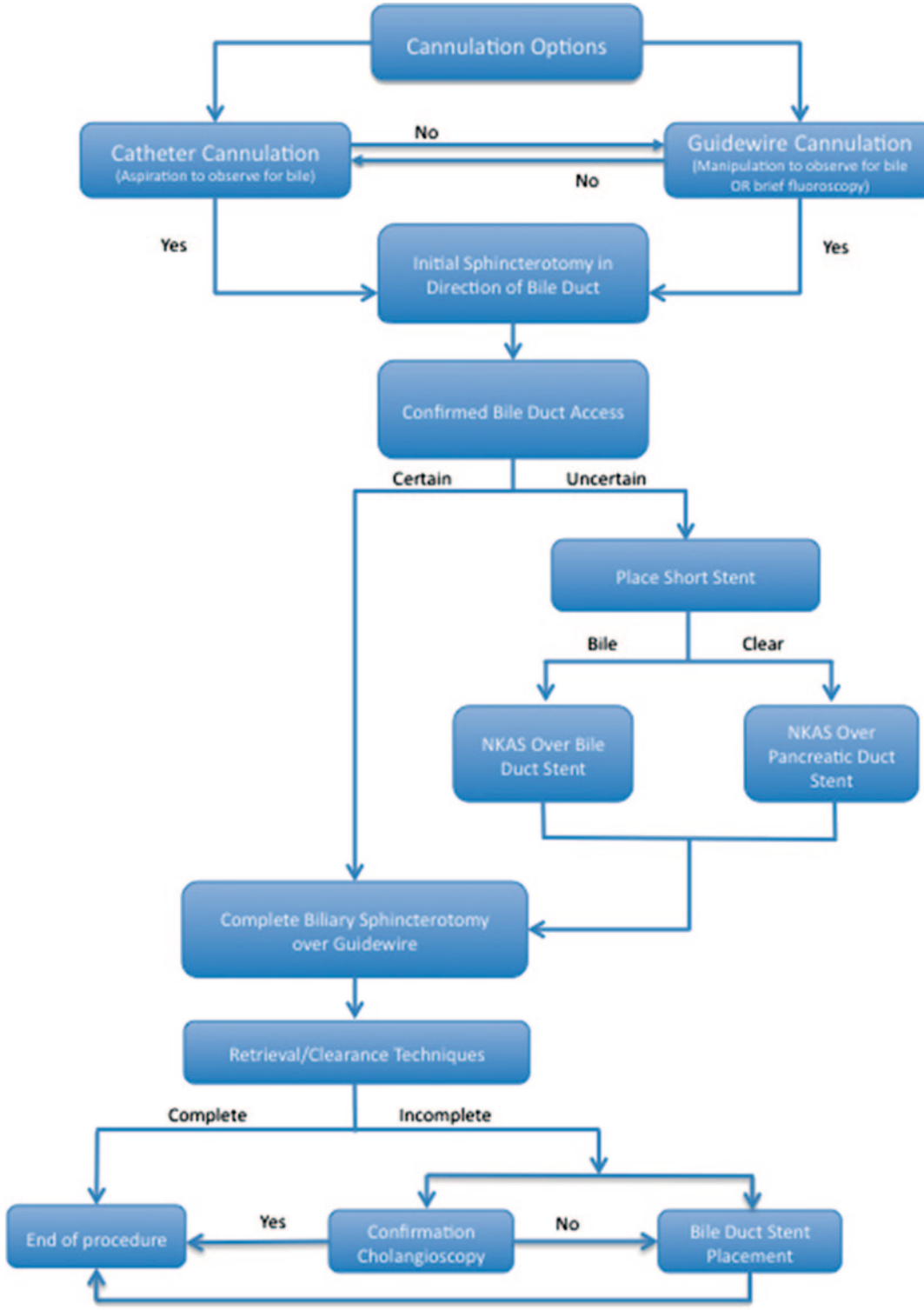

Fig. 19.4 Suggested algorithm for cannulation and confirmation of biliary access and ductal clearance for ERCP during pregnancy. *NKAS*: needle-knife access sphincterotomy

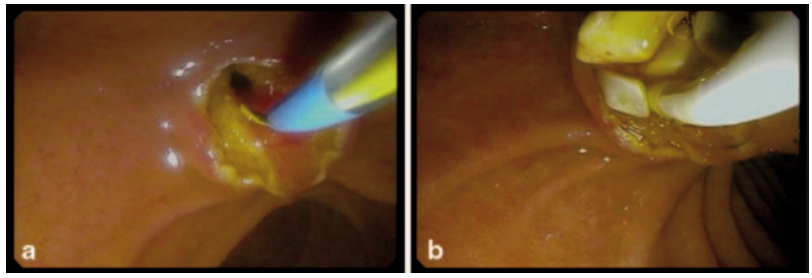

Fig. 19.5 A 27-year-old at 21 weeks gestation presented with jaundice and numerous stones were noted on MRCP. ERCP was performed without fluoroscopy with sphincterotomy and removal of stones. Biliary access and drainage becomes obvious after a complete biliary sphincterotomy (**a**) and then stone retrieval (**b**) can be accomplished

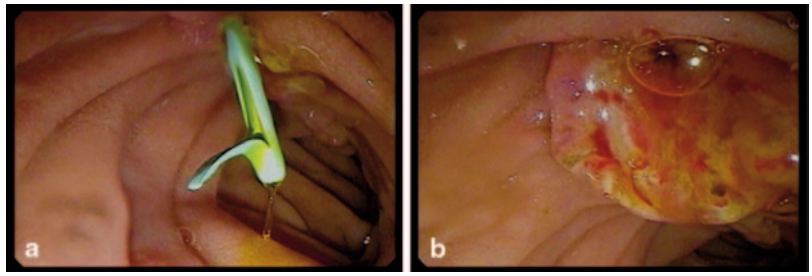

Fig. 19.6 A 29-year-old at 9 weeks gestation presented with her second attack of biliary pancreatitis in 2 weeks. The papilla was prominent and biliary cannulation could not be confirmed after manipulation of the guidewire. **a** A short 5F stent was placed, which appeared to angle in the direction of the bile duct, and bile was observed draining from the stent. **b** Sludge was noted to drain after completing the biliary sphincterotomy

As almost all ERCP procedures during pregnancy are therapeutic with interventions that include sphincterotomy, most endoscopists begin cannulation attempts using a sphincterotome preloaded with a guidewire. Usually wire-guided cannulation is performed without contrast injection, and the wire is carefully advanced to an observed distance of approximately 10–15 cm over which the sphincterotome is introduced into the duct. [48] Alternatively, cannulation can be performed by advancing the sphincterotome with or without a guidewire several centimeters into the duct. The standard method to confirm biliary cannulation is by applying manual suction using a syringe attached to the sphincterotome and observing for bile. An alternative approach to confirm bile duct cannulation entails manipulation of the guidewire to open the sphincter and promote bile drainage around the guidewire [34]. If biliary cannulation is confirmed, then sphincterotomy can be started along the intraduodenal segment in the direction of the bile duct (Video 19.1 and Fig. 19.5).

If biliary cannulation is uncertain after either guidewire access or manipulation or an initial sphincterotomy, then we typically place a short (2–3 cm) 5F stent over the guidewire and observe the stent direction and color of drainage via the tip and side flaps. The stent may or may not have proximal flaps. If the stent does not have proximal flaps, it may migrate out during the procedure. If the stent angles in the direction of the bile duct and/or bile clearly drains from the stent, then biliary access is certain (Fig. 19.6). Biliary sphincterotomy can be initiated with a sphincterotome after cannulating alongside the indwelling stent with a guidewire or with a needle knife using the stent as a guide. The biliary stent can be removed following guidewire access if it has not already migrated out spontaneously.

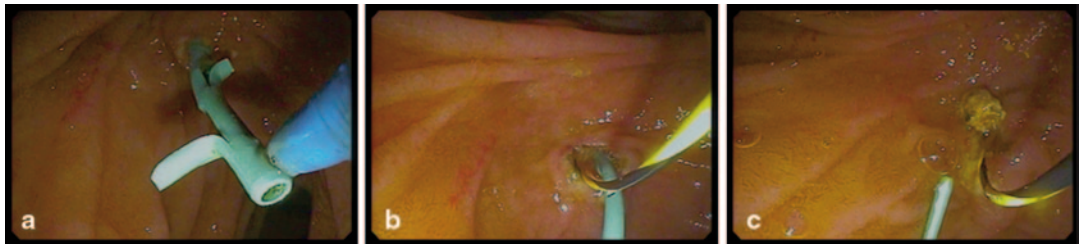

Fig. 19.7 A 21-year-old at 8 weeks gestation was referred for evaluation of suspected biliary colic due to RUQ pain, nausea, vomiting, and increased LFTs. MRCP showed several stones in the distal bile duct (See Fig. 19.1). Guidewire cannulation was obtained without any fluoroscopy. **a** A short 5F stent without internal flaps was placed, which appeared to angle in the direction of the pancreatic duct and drained clear fluid. **b** A needle knife access biliary sphincterotomy was performed, **c** followed by stone extraction. The pancreatic stent migrated out spontaneously while extracting stones

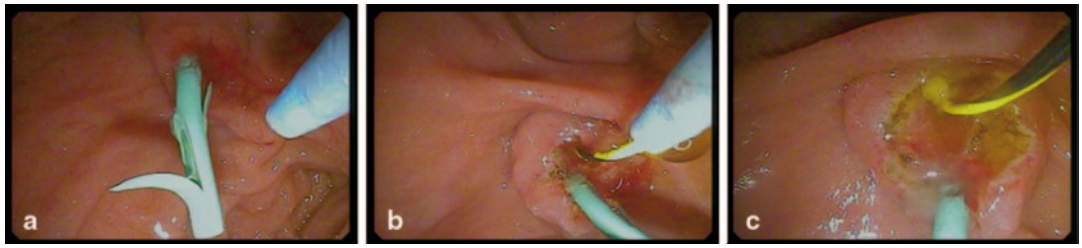

Fig. 19.8 A 16-year-old with a 6-week intrauterine pregnancy presented with biliary colic, marked elevations in LFTs, and an MRCP showing a distal bile duct stone. Guidewire cannulation was obtained without fluoroscopy and a short 5F stent without internal flaps was placed. **a** The stent appeared to angle in the direction of the bile duct but only drained clear fluid from the side flap. **b** Biliary access was obtained after needle knife sphincterotomy over the pancreatic stent. **c** The biliary sphincterotomy was completed with a papillotome followed by stone extraction

If the stent angles in the direction of the pancreatic duct and/or only clear fluid or no fluid drains from the stent, then biliary access should be considered unlikely, and instead, one should assume that the pancreatic duct has been entered (Fig. 19.7). Sometimes the stent may appear to angle in the direction of the bile duct but with clear and not bilious fluid draining (Fig. 19.8). Again, one should assume that the pancreatic duct has been accessed. In this situation, biliary cannulation can be attempted with a guidewire over the stent. An experienced operator may consider performing an access biliary sphincterotomy with a needle knife using the pancreatic stent as a guide. The stent can be removed at the end of the procedure if it has not already migrated out, and if not, left in place to reduce the risk of post-ERCP pancreatitis. If the endoscopist does not have the expertise to proceed with a high-risk access sphincterotomy, an alternative would be to discontinue the procedure and consider repeat ERCP by another operator. The pancreatic stent may remain in situ if the repeat ERCP is planned within the next few days.

When there is evidence of an impacted stone, a needle-knife access sphincterotomy over the stone is reasonable. After biliary access and initial sphincterotomy are achieved by one of the methods described above, the sphincterotomy may be completed, if necessary, followed by stone retrieval and any other necessary maneuvers.

Ensuring ductal clearance can be difficult when performing ERCP with limited or even no fluoroscopy. Without fluoroscopy one cannot document location of the stones, balloon catheter manipulations, and confirmation of clearance.

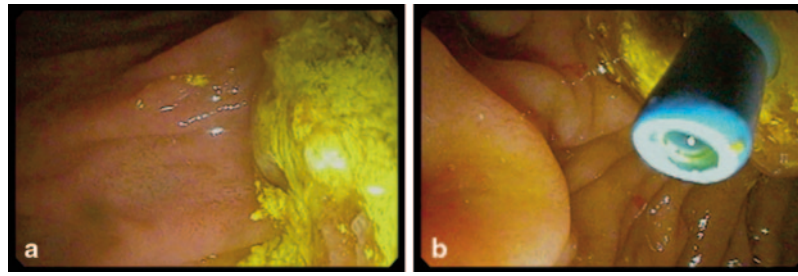

Fig. 19.9 A 23-year-old at 29 weeks gestation presented with biliary colic and multiple stones seen on MRCP. **a** An ERCP was performed without fluoroscopy and abundant stones and sludge were repeatedly removed with a balloon catheter. Cholangioscopy with a Spyglass catheter showed residual stones and sludge. **b** A 7 cm long 7F biliary stent was placed to ensure drainage. An ERCP was performed 1 month after delivering a healthy boy at which time the biliary stent and multiple stones were removed

Prior imaging can provide a reasonable estimate of the number of stones allowing some confidence of ductal clearance by observing the number of stones retrieved into the duodenum. We typically perform several "negative" balloon sweeps after stone extraction(s) before considering the procedure complete.

Cholangioscopy allows direct visualization of the biliary tree and provides an alternative to fluoroscopy for stone visualization without apparent adverse outcomes during pregnancy [33, 34, 49, 50]. Limitations include the need for proper equipment and operator expertise and prolonged procedures with longer sedation times. A mother–daughter system may require two operators [33]. The single operator SpyGlass system (Boston Scientific, Marlborough, MA) can be used as designed with the SpyGlass optical catheter inserted into the SpyScope [50, 51]. We typically use only the SpyGlass catheter [34] via a standard ERCP catheter, sphincterotome, or needle knife accessory (Video 19.2). Imaging by this method may be adequate but often inferior due to the limited ability to achieve directional control of the optical catheter.

There are some reports of bile duct stent placement to ensure drainage if uncertainty remains over stone clearance [34, 48]. This is reasonable if prior imaging demonstrated significant stone burden, repeated balloon sweeps continue to retrieve stones, and/or many stones are seen on cholangioscopy (Fig. 19.9). Because stent occlusion remains a potential complication, follow-up ERCP must be performed postpartum for stent removal and further endotherapy (Fig. 19.10).

Case Continued

A duodenoscope was introduced through the mouth and advanced to the second portion of the duodenum. Brief endoscopic survey of the stomach and duodenum was normal. The major papilla was notable for evidence of an impacted stone. The common bile duct was successfully cannulated using a straight-tipped guidewire technique (Video 19.1). Bile was noted to drain from around the guidewire, confirming biliary cannulation. Biliary sphincterotomy was performed using a papillotome over the guidewire. Following sphincterotomy, sludge drained spontaneously. No fluoroscopy was used, and neither pancreatography nor cholangiography was attempted. One bile duct stone was extracted using a balloon catheter. Several balloon sweeps were performed. Cholangioscopy using Spyglass catheter showed biliary sludge without evidence of residual stones or Mirizzi syndrome (Video 19.2).

The following day, her abdominal pain, nausea, and vomiting, had subsided. There was no concern for post-ERCP pancreatitis, and her diet was advanced without difficulty.

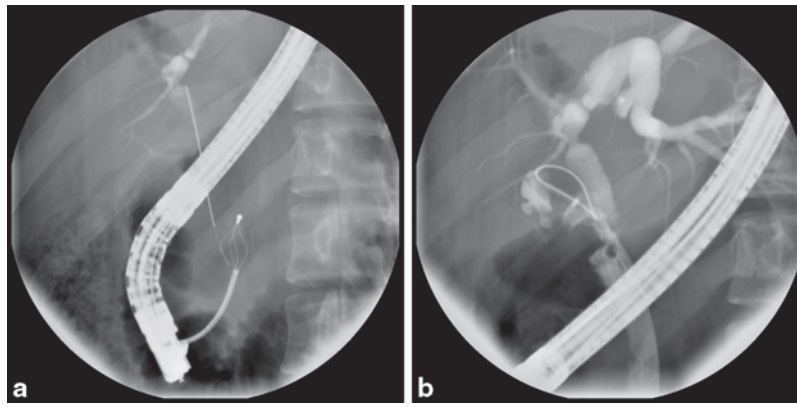

Fig. 19.10 A 22-year-old at 34 weeks gestation was referred for jaundice and suspected bile duct stones due to persistently elevated LFTs. An MRCP prior to referral showed dilation of the gallbladder, cystic duct, and bile duct with a very obvious distal filling defect. An ERCP without fluoroscopy was performed with removal of a bile duct stone. The duct did not appear clear of debris on cholangioscopy so a 7 cm long 7F biliary stent was placed. She had an uneventful delivery and underwent cholecystectomy and ERCP postpartum. **a** Following stent extraction, mechanical lithotripsy was required to remove a distal bile duct stone. **b** A second stone was removed with a balloon catheter from the cystic duct remnant

Outcomes After ERCP During Pregnancy

Technical Aspects

Many reports on ERCP during pregnancy represent anecdotal experiences from expert centers, and there are no established guidelines on the topic. As mentioned earlier, Baillie et al. published the first reported case series in 1990 of five pregnant patients who all underwent ERCP with sphincterotomy using fluoroscopy and delivered healthy babies at term. Fluoroscopy time was under 10 s, no spot radiographs were obtained, radiation exposure was measured with dosimetry badges to document fetal exposure, and lead shields were utilized [35]. In 1990, the first reported ERCP without using fluoroscopy and using needle-knife papillotomy for an impacted CBD stone in a pregnant patient was published [52]. The actual first non-radiation ERCP was performed in 1988, but reported in 1991 [53]. Gall bladder stent placement during pregnancy in addition to bile duct stone removal was reported in 1993; this procedure required about 4 min of fluoroscopy [54]. In 1994, two reports of successful ERCP without fluoroscopy described the bile aspiration technique to confirm biliary access [55, 56].

A relatively large multicenter experience described the first reported case of post-ERCP pancreatitis during pregnancy, albeit in a patient with a primary pancreatic indication [36]. In the only prospective study, ten patients underwent biliary stenting without sphincterotomy [57]. One patient needed a second ERCP during pregnancy to remove an impacted stone after sphincterotomy. The remaining patients required postpartum ERCP for stent extractions, two of which were complicated by proximal stent migrations. Radiation exposure was carefully reported (range 30–90 s, mean 45 sec, 18 mrad). The authors proposed that this strategy might be safer than sphincterotomy with initial attempts at ductal clearance and may require less radiation exposure. This approach, however, has not become popular likely due to need for repeat procedures and potential stent-related complications.

About 10-years-ago, a single center experience reported on the safety of ERCP in 15 pregnant patients [58]. Although fluoroscopy and spot radiographs were used and more than half the patients underwent diagnostic ERCP only, the authors concluded that ERCP during pregnancy

should be performed using safety measures and only when there is a therapeutic intent. This report spurred two letters describing small series of non-radiation ERCP during pregnancy with therapy performed in all cases [59, 60]. Since then, experience with ERCP during pregnancy has dramatically expanded in the last decade.

The largest series published by Tang et al. involved 65 patients who underwent 68 ERCPs during pregnancy [11]. Nearly half the ERCPs occurred during the third trimester with a calculated rate of ERCP in pregnancy of 1 per 1415 births. Median fluoroscopy time was 1.45 min. Nearly all patients underwent biliary sphincterotomy and biliary stenting was performed in 15 patients (22%) for biliary strictures or concern for retained stone. Post-ERCP pancreatitis was diagnosed in 11 patients (17%) with one patient graded as severe, which is a higher rate than reported in other studies.

Maternal Risks

Pregnant patients are exposed to the same general risks of ERCP as nonpregnant patients. These include acute pancreatitis, cholangitis, post-sphincterotomy bleeding, and perforation. Pancreatitis is the most feared complication with isolated reports of over 10% rate of post-ERCP pancreatitis [11, 61]. Cappell pooled data on 296 patients from 46 studies of ERCP during pregnancy [44]. Fortunately, the overall rate of post-ERCP pancreatitis (6.4%) was similar to nonpregnant patients. The risk for maternal bleeding after sphincterotomy (1%) was also within the expected range. None of the cases required surgical intervention to stop bleeding. No biliary or gastrointestinal perforation occurred after sphincterotomy.

Fetal Risks

Development of hepatobiliary diseases may lead to adverse pregnancy outcome such as prematurity, fetal loss, and low birth weight. Use of ionizing radiation during ERCP will add to the fetal risks of teratogenicity and carcinogenesis, which may take years to appear. Based on several animal studies and human observational studies of atomic bomb survivors, radiation exposure in the first trimester during which organogenesis occurs has the highest risk of adverse effects on the fetus. The average reported radiation exposures from available ERCP series range from 4 to 310 mrad [35, 38, 57, 58], which falls within the acceptable range. In a study that included 17 first trimester patients who underwent ERCP, 15 patients were followed to delivery. Preterm delivery occurred in 20% of this group compared to 5% in the 44 patients who completed ERCP during the second or third trimesters [11]. None of the 59 patients who were followed until delivery had spontaneous fetal loss, perinatal death, stillbirth, or fetal malformation. In an Indian study by Gupta et al., the longest follow-up of fetal outcome with a mean of 6 years postpartum was reported in 11 patients who all had healthy babies. [62]. Fetal outcomes from 254 patients were described in a review by Cappell [44]. Healthy term babies were delivered by 234 patients. There were 11 preterm births, 3 late spontaneous abortions, 2 infant deaths after birth, 1 voluntary abortion, and no associated congenital malformations observed.

Back to Our Case

The patient was discharged and cholecystectomy with intraoperative cholangiogram in the postpartum period was recommended.

Indications for Cholecystectomy During Pregnancy or Postpartum

Patients with biliary colic should initially be managed with supportive care but those with recurrent symptoms during pregnancy will often need consideration for cholecystectomy. Indications for surgery in pregnancy also include severe symptoms, obstructive jaundice, acute cholecystitis intractable to medical management, and peritonitis [19]. More than 50% of the patients have recurrent biliary symptoms with a higher rate of fetal loss (up to 12%) in patients

managed conservatively [63, 64]. Similarly, from a study of 9714 pregnant patients who underwent cholecystectomy, those who underwent surgery had significantly lower maternal (4.3 vs. 16.5 %) and fetal (5.8 vs. 16.5 %) complications compared to patients treated nonoperatively [65]. For patients with biliary pancreatitis, the relapse rate exceeds 70 % when not treated surgically before delivery [9]. If surgery is necessary during pregnancy, the second or early third trimester are generally considered the safest. During this period, organogenesis has been completed and the uterus is not large enough to occupy the operative field. An early study from the 1980s reported that spontaneous abortion was nearly twice as likely in patients undergoing surgery during early pregnancy compared to nonpregnant patients [66]. More recent experience suggested that cholecystectomy and even common duct explorations can occur safely at any time during pregnancy although this is a minority opinion [67]. Retrospective studies comparing open and laparoscopic cholecystectomy reported no significant difference in maternal or fetal outcomes [23].

Postpartum cholecystectomy is indicated in patients who had evidence of complications of choledocholithiasis including a passed common bile duct stone or biliary pancreatitis. Since gallstones and sludge frequently resolve after pregnancy, the decision to proceed with surgery should include further imaging to confirm the presence of stones and the patient's desire for having subsequent pregnancies.

Key Points

- Pregnancy associated hormonal changes increase the risk of gallstone formation.
- Complications related to gallstones during pregnancy may benefit from therapeutic ERCP.
- Consultation from the obstetrics team should be obtained to help manage pregnant patients.
- ERCP should be performed only when there is a strong indication for endotherapy to treat choledocholithiasis and its complications, such as biliary colic, acute biliary pancreatitis, or acute cholangitis.
- Endoscopic ultrasonography and magnetic resonance cholangiography are appropriate diagnostic options in pregnant patients with suspected biliary tract disease because of their accuracy in detecting common bile duct stones and lower morbidity than ERCP.
- If possible, ERCP should be postponed to the second trimester or postpartum.
- Efforts should be taken during ERCP to minimize or completely avoid using fluoroscopy to prevent possible radiation exposure to the fetus.
- ERCP is overall a safe and successful therapeutic option in the management of gallstone-related complications in pregnant patients.

Video Captions

Video 19.1 In this pregnant patient with confirmed choledocholithiasis on MRCP, ERCP shows a stone at the biliary orifice. Guidewire cannulation is performed with bile seen subsequently emanating from the papilla. The wire is advanced into the bile duct, biliary sphincterotomy performed, and balloon extraction of the stone performed. No fluoroscopy was used during the ERCP

Video 19.2 In the same patient, cholangioscopy using the optical fiber of Spyglass preloaded into a cannula shows biliary sludge without evidence of residual stones

References

1. Maringhini A, Ciambra M, Baccelliere P, et al. Billiary sludge and gallstones in pregnancy: incidence, risk factors, and natural history. Ann Intern Med 1993;119:116–20.
2. Validivieso V, Covarrubias C, Siegel F, Cruz F. Pregnancy and cholelithiasis: Pathogenesis and natural course of gallstones diagnosed in early puerperium. Hepatology 1993;17:1–4
3. Ko CW, Beresford SA, Schulte SJ, et al. Incidence, natural history, and risk factors for biliary sludge and stones during pregnancy. Hepatology 2005;41:359–65.

4. Mendez-sanchez N, Chavez- Tapia NC, Uribe M. Pregnancy and gallbladder disease. Annals of Hepatology 2006;5:227–30
5. Kern Jr F, Everson GT, DeMark B, et al. Biliary lipids, bile acids, and gallbladder function in the human female. Effects of pregnancy and the ovulatory cycle. J Clin Invest. 1981;68:1229–42
6. Melnick DM, Wahl WL, Dalton VK. Management of general surgical problems in the pregnant patient. The American Journal of Surgery 2004;187:170–80
7. Chan CH, Enns RA. ERCP in the management of choledocholithiasis in pregnancy. Curr gastroenterol Rep 2012;14:504–10.
8. Ramin KD, Ramsey PS. Disease of the gallbladder and pancreas in pregnancy. Obstet Gynecol Clin North Am. 2001;28:571–80.
9. Swisher SG, Hunt KK, Schmit PJ, Hiyama DT, et al. Management of pancreatitis complicating pregnancy. Am Surg 1994;60:759–62
10. Al-Hashem H, Muralidharan V, Cohen H, Jamidar PA. Biliary disease in pregnancy with an emphasis on the role of ERCP. J Clin Gastroenterol 2008;43:58–62.
11. Tang S, Mayo MJ, Rodriguez-Frias E, et al. Safety and utility of ERCP during pregnancy. Gastrointest Endosc 2009;69:453–61.
12. Riely CA. Liver disease in the pregnant patient. Am J Gastroenterol 1999;94:1728.
13. Ch'ng CL, Morgan M, Hainsworth I, Kingham J G. Prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut 2002;51:876–80.
14. Bacq Y, Zarka O, Bréchot JF, et al. Liver function tests in normal pregnancy: a prospective study of 102 pregnant women and 102 matched controls. Hepatology. 1996;23:1030
15. Kimura Y, Takada T, Kawarada Y, Nimura Y. Definitions, pathophysiology, and epidemiology of acute cholangitis and cholecystitis: Tokyo guidelines. J Hepatobiliary Pancreat Surg 2007;14:15–26.
16. Mosler P. Diagnosis and management of acute cholangitis. Current Gastroenterol Reports. 2011;13:166–72.
17. Attasaranya S, Fogel EL, Lehman GA. Choledocholithiasis, ascending cholangitis, and gallstone pancreatitis. Med Clin North Am. 2008;92:925–60.
18. Karsenti D, Bacq Y, Bréchot JF, et al. Serum amylase and lipase activities in normal pregnancy: a prospective case-control study. Am J Gastroenterol. 2001;96:697
19. Pitchumoni CS, Yegneswaren B. Acute pancreatitis in pregnancy. World J Gastroenterol 2009;15:5641–6.
20. Mckay AJ, O'Neil J, Imrie CW. Pancreatitis, pregnancy and gallstones. Br J Obstet Gynaecol 1980;87:47–50.
21. Tenner S, Dubner H, Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. Am J Gastroenterol. 1994;89(10):1863.
22. Robertson KW, Stewart IS, Imrie CW. Severe acute pancreatitis and pregnancy. Pancreatology 2006;6:309–15.
23. Date RS, Kaushal M, Ramesh A. A review of the management of gallstone disease and its complications in pregnancy. Am J Surg 2008;196:599.
24. Scott LD. Gallstone disease and pancreatitis in pregnancy. Gastroenterol Clin North Am 1992;21:803–15.
25. Lippi G, Albiero A, Montagnana M, Salvagno GL. Lipid and lipoprotein profile in physiological pregnancy. Clin Lab. 2007;53(3–4):173–7.
26. Kanal E, Barkovich AJ, MD, Bell C. ACR Guidance Document on MR Safe Practices: 2013. J of Magn Reson Imaging. 2013;37:501–30.
27. Venneman NG, Renooij W, Rehfeld JF, VanBerge-Henegouwen GP. Small gallstones, preserved gallbladder motility, and fast crystallization are associated with pancreatitis. Hepatology. 2005 Apr;41(4):738–46.
28. Scheiman JM, Carlos RC, Barnett JL, Elta GH, Nostrant TT, Chey WD, Francis IR, Nandi PS. Can endoscopic ultrasound or magnetic resonance cholangiopancreatography replace ERCP in patients with suspected biliary disease? A prospective trial and cost analysis. Am J Gastroenterol. 2001;96(10):2900–4.
29. Garrow D, Miller S, Sinha D, Conway J, Hoffman BJ, Hawes RH, Romaqnuolo J. Endoscopic ultrasound: a meta-analysis of test performance in suspected biliary obstruction. J Clin Gastroenterol Hepatol. 2007;5(5):616.
30. Tse F, Liu L, Barkun AN, Armstrong D.EUS: a meta-analysis of test performance in suspected choledocholithiasis. Gastrointest Endosc. 2008;67(2):235.
31. Petrov MS, Savides TJ. Systematic review of endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis. Br J Surg. 2009;96(9):967.
32. Lee YT, et al. Comparison of EUS and ERCP in the investigation with suspected biliary obstruction caused by choledocholithiasis: a randomized study. Gastrointest Endosc. 2008;67:660–8
33. Vohra S, Holt EW, Bhat YM, Kane S, Shah JN, Binmoeller K. Successful single-session endosonography-based endoscopic retrograde cholangiopancreatography without fluoroscopy in pregnant patients with suspected choledocholithiasis: a case series. J Hepatobiliary Pancreat Sci. 2014;21(2):93–7
34. Shelton J, Linder JD, Rivera-Alsina ME, Tarnasky PR. Commitment, confirmation, and clearance: new techniques for non-radiation ERCP during pregnancy (with videos). Gastrointest Endosc. 2008;67:364–8.
35. Baillie J, Cairns SR, Putnam WS, Cotton PB. Endoscopic management of choledocholithiasis during pregnancy. Surg Gynecol Obstet 1990;171:1–4.
36. Jamidar PA, Beck GJ, Hoffman BJ, et al. Endoscopic retrograde cholangiopancreatography in pregnancy. Am J Gastroenterol. 1995;90:1263
37. Anderson MA, et al. Complications of ERCP. ASGE guidelines. Gastrointest Endosc. 2012;75:467–73
38. Kahaleh M, Hartwell GD, Arseneau KO, et al. Safety and efficacy of ERCP in pregnancy. Gastrointest Endosc 2004;60:287–92.

39. Menees S, Elta G. Endoscopic retrograde cholangiopancreatography during pregnancy. Gastrointest Endosc Clin N Am. 2006;16:41–57
40. Baron TH, Schueler BA. Pregnancy and radiation exposure during therapeutic ERCP: time to put the baby to bed? Gastrointest Endosc. 2009;69:832–4.
41. Samara ET, Stratakis J, Enele Melono JM, et al. Theraputic ERCP and pregnancy: is the radiation risk for the conceptus trivial? Gastrointest Endosc. 2009;69:824–31.
42. Tokar JL, et al. Electrosurgical generators. Gastrointest Endosc. 2013;78:197–208
43. Shergill AK, et al. Guidelines for endoscopy in pregnant and lactating women. ASGE guidelines. Gastrointest Endosc. 2012;76:18–24
44. Cappell MS. Risks versus benefits of gastrointestinal endoscopy during pregnancy. Nat Rev Gastroenterol Hepatol 2011;8:610–34.
45. International Commission on Radiological protection. Biological effects after prenatal irradiation (embryo and fetus). Publication 90. Oxford: Pergamon; 2004
46. Campbell N, Sparrow K, Fortier M, Ponich T. Practical radiation safety and protection for the endoscopist during ERCP. Gastrointest Endosc. 2002;55:552–7.
47. NCRP (National Council on radiation Protection and Measurements). Medical Radiation Exposure of Pregnant and Potentially Pregnant Women, NCRP reports no. 54. National Council on Radiation Protection and Measurements, Washington, D.C. 1977
48. Akcakaya A, Ozkan OV, Okan I, Kocaman O, Sahin M. Endoscopic retrograde cholangiopancreatography during pregnancy without radiation. World J Gastroenterol 2009;15:3649–52
49. Fishman DS, Tarnasky PR, Patel SN, Rajiman I. Management of pancreatobiliary disease using a new intra-ductal endoscope: the Texas experience. World J Gastroenterol. 2009;15:1353–8
50. Girota M, Jani N. Role of endoscopic ultrasound/spy scope in diagnosis and treatment of choledocholithiasis in pregnancy. World J Gastroenterol. 2010;16:3601–2
51. Uradomo L, Pandolfe F, Aragon G, Borum ML. SpyGlass cholangioscopy for management of choledocholithiasis during pregnancy. Hepatobiliary Pancreat Dis Int. 2011;10:107.
52. Binmoeller KF, Katon RM. Needle knife papillotomy for an impacted common bile duct stone during pregnancy. Gastrointest Endosc 1990;36:607–9
53. Prada AA, Goncalves MO, Tafner E, et al. Endoscpic papillotomy under ultra-sonographic control. Int Surg 1991;76:75–6
54. Goldschmiedt M, Wolf L, Shires T. Treatment of symptomatic choledocholithiasis during pregnancy. Gastrointest Endosc 1993;39:812–4
55. Uomo G, Manes G, Picciotto FP, Rabitti PG. Endoscopic treatment of acute biliary pancreatitis in pregnancy. J Clin Gastroenterol 1994;18:250–2.
56. Rahmin MG, Hitscherich R, Jacobson IM. ERCP for symptomatic choledocholithiasis in pregnancy. Am J Gastroenterol 1994;89:1601
57. Farca A, Aguilar M, Rodriguez G, et al. Biliary stents as temporary treatment for choledocholithiasis in pregnant patients. Gastrointestin Endosc. 1997;46:99–101
58. Tham TC, Vandervoort J, Wong RC, et al. Safety of ERCP during pregnancy. Am J Gastroenterol 2003;98:308–11
59. Savas MC, Kadayifei A, Koruk M. Safety for ERCP during pregnancy (comment). Am J Gastroenterol 2003;98:2331–2
60. Tarnasky PR, Simmons DC, Schwartz AG, et al. Safe delivery of bile duct stones during pregnancy. Am J Gastroenterol 2003;98:2100–1
61. Barthel JS, Chowdhury T, Miedema BW. Endoscopic Sphincterotomy for the treatment of gallstone pancreatitis during pregnancy. Surg Endosc 1998;12:394–9
62. Gupta R, et al. Safety of therapeutic ERCP in pregnancy- an Indian experience. Indian J Gastroenterol.2005;24:161–3
63. Jelin EB, Smink DS, Vernon AH, et al. Management of biliary tract disease during pregnancy: a decision analysis. Surg Endosc. 2008;22:54–60
64. Dixon NP, Faddis DM, Silberman H. Aggressive management of cholecystitis during pregnancy. Am J Surg. 1987;154:292–4
65. Kuy S, Roman SA, Desai R, Sosa JA. Outcomes following cholecystectomy in pregnant and nonpregnant women. Surgery. 2009;146:358–66.
66. Brodsky JB, Cohen EN, Brown BW, Wu ML, Witcher C. Surgery during pregnancy and fetal outcome. Am J of Obstet Gyne. 1980;138:1165–7
67. Cosenza CA, Saffari B, Jabbour N, et al. Surgical management of biliary gallstone disease during pregnancy. Am J of Surg. 1999;178:545–8

Pediatric Endoscopic Retrograde Cholangiopancreatography

20

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Special Considerations for Pediatric ERCP

Special considerations must be taken into account when preparing and performing ERCP in infants and small children. These considerations include issues with sedation, duodenoscope selection, and endoscope accessories. Due to the limited accessories that are compatible with the pediatric duodenoscope, the standard adult duodenoscope is preferred when performing therapeutic ERCP even in small children. A standard adult duodenoscope (outer diameters ranging from 10.8 to 12.1 mm) can usually be used to perform therapeutic ERCP in children weighing 10 kg or more. In small children and infants who cannot tolerate a standard adult duodenoscope, pediatric duodenoscopes with outer diameters ranging from 7.5 to 7.6 mm are available from Pentax Medical and Olympus, and have been successfully used in ERCP [1–6]. The working channel in pediatric duodenoscopes is only 2.0–2.2 mm in diameter, which limits options for accessories to those that will pass down a 2 mm diameter channel (Table 20.1) [7].

A relatively large diameter of standard adult duodenoscope can cause tracheal compression and compromise with the cardiopulmonary status of a small child. Prone position in small children may more easily result in hypoventilation compared to adults in this position. As in adults, ERCP in supine position can be considered for small children. General anesthesia with endotracheal intubation should be considered to maintain a safe and patent airway during ERCP for small children and infants [8].

Although special technical considerations must be taken into account when performing ERCP on infants and small children, ERCP in this patient population has been shown to be technically feasible, safe, and therapeutically effective [9–12]. Post-procedure admission is usually recommended after therapeutic ERCP, especially when sphincterotomy or sphincteroplasty has been performed to monitor the post-ERCP complications. The incidence of adverse events following ERCP in the pediatric population for both biliary and pancreatic indications appears similar to the rates in adults undergoing ERCP [13, 14]. The availability of ERCP as a diagnostic and therapeutic tool is essential in the evaluation and treatment of children with certain congenital or acquired pancreaticobiliary diseases.

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Table 20.1 Accessories for endoscope with a 2 mm channel. (Adapted from [7])

Device	Manufacturer	Comments
ERCP cannulation catheters	Boston Scientific, ConMed, Mediglobe, Telemed	Curved, straight, or tapered tip, 0.018–0.035 in wire
Sphincterotomes	Cook Medical, Mediglobe, Olympus	Limited to double lumen, cannot take 0.035 in wire
Needle knife papillotome	Cook Medical, Mediglobe, Olympus	–
Stone retrieval balloons	Boston Scientific, Horizons International, Mediglobe, Olympus	–

Case 1

Initial Presentation

A 2-year-old boy presents to the emergency department with a 2-day history of persistent emesis, abdominal pain, and decreased urine output. He is afebrile, but tachycardic and responds to fluid resuscitation. Past medical history reveals that the patient has congenital heart disease (Shone's complex), which was surgically repaired with aortic arch augmentation during the neonatal period accompanied by prolonged total parental nutrition during his perioperative recovery. On physical examination, the patient's sclera are icteric, abdomen is soft and non-tender with no masses palpable. Laboratory values reveal a total bilirubin level of 7 mg/dL, AST 145 U/L, ALT 314 U/L, and alkaline phosphatase 547 U/L. Abdominal ultrasonography revealed a slightly enlarged liver measuring 11 cm, a gallstone in the gallbladder, dilation of the intrahepatic bile duct, and dilation of the proximal common bile duct up to 1 cm.

What is the Differential Diagnosis for Children with Obstructive Jaundice?

Although the etiology of conjugated hyperbilirubinemia in the pediatric population can be similar to adults, one must have a higher consideration for congenital biliary anomalies, such as choledochal cyst, accessory bile duct, and biliary atresia, when evaluating the neonatal or pediatric patient. Although malignancy of the bile duct is rare in the pediatric population, botryoid rhabdomyosarcoma can present with obstructive biliary disease, and a hepatic infiltrative process can resemble biliary obstruction in laboratory values. When evaluating the pediatric patient, the differential diagnosis must also include diseases seen in adults, such as choledocholithiasis, primary sclerosing cholangitis, and infectious etiologies (Table 20.2).

Choledocholithiasis

Previously considered uncommon in children, cholelithiasis and choledocholithiasis are being diagnosed with increasing frequency in children

Table 20.2 Biliary indications and therapeutic options for pediatric ERCP

Indications	Endoscopic/therapeutic maneuvers
Neonatal cholestasis/biliary atresia	Flush biliary plugs
Bile leak	Stent placement
Biliary stricture (e.g., bile duct anastomosis in duct-duct orthotopic liver transplant)	Stricture dilation, stent placement, choledochoscopy
Choledochal cyst	Sphincterotomy, stone removal, stent placement, preoperative assessment
Choledocholithiasis	Sphincterotomy, stone removal, choledochoscopy with lithotripsy
Malignancy (botryoid rhabdomyosarcoma)	Biopsy, stent placement
Sclerosing cholangitis	Stricture dilation, stent placement
Sphincter of Oddi dysfunction	Sphincterotomy

and adolescents (Figs. 20.1, 20.2, and 20.3) [15, 16]. Obstructive biliary disease occurs in 28% of the patients requiring cholecystectomy

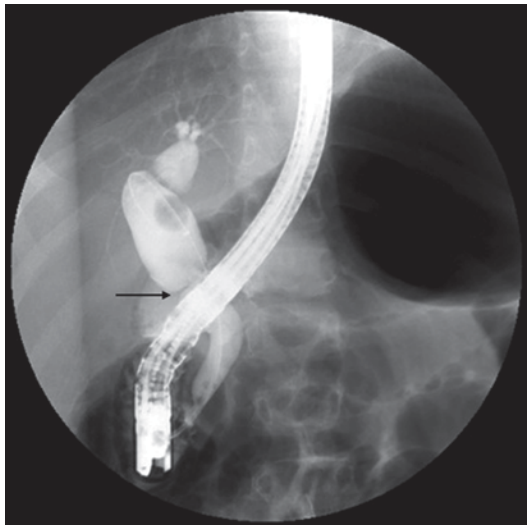

Fig. 20.1 Cholangiogram of a stone-induced stricture (*arrow*) with proximal saccular dilation mimicking a choledochal cyst in a child with autoimmune hemolytic anemia. (Note inflated 15 mm biliary stone extraction balloon in proximal bile duct)

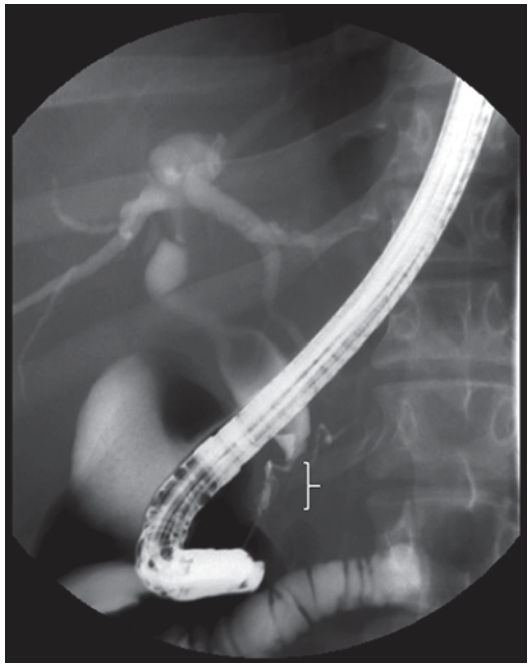

Fig. 20.2 Common bile duct stone and distal biliary stricture (*bracket*) in a child with Down syndrome and duodenal atresia repair

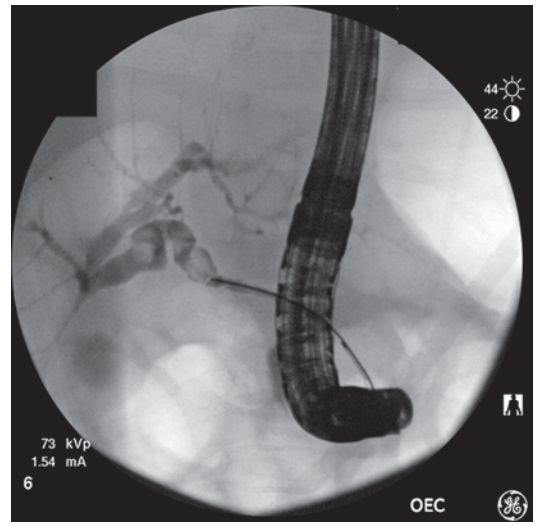

Fig. 20.3 Choledocholithiasis secondary to TPN in a 6-week-old infant

[16]. Risk factors for stone disease encompass those commonly seen in adults, such as obesity especially during puberty or post-pubescence, as well as diseases often associated with the pediatric population including hematologic disorders, prolonged total parental nutrition, and cystic fibrosis. Patients usually present with acute epigastric or right upper quadrant abdominal pain, tenderness, elevated liver transaminases, and hyperbilirubinemia suggestive of an obstructing biliary stone. The American Society of Gastrointestinal Endoscopy (ASGE) published guidelines stratifying the likelihood of choledocholithiasis based on patient clinical symptoms, imaging studies, and laboratory values [17]. Fishman et al. have adapted these guidelines for the pediatric population and showed that substituting conjugated bilirubin for total bilirubin increased the specificity for identifying choledocholithiasis in children. In addition, the combination of conjugated bilirubin and identification of a common bile duct stone increased the odds of identifying a stone at ERCP. However, transabdominal ultrasonography (US) alone had poor sensitivity for identification of CBD stones and even when identified, may pass prior to ERCP [18].

Choledochal Cyst

Choledochal cysts are congenital abnormal dilations of the biliary tree. Most present during childhood with some manifesting in adulthood. Several types of choledochal cysts exit as described in Chap. 10. Choledochal cysts must be considered in young children presenting with a dilated bile duct with or without a bile duct stone. They can vary in size; and in children, a type 1B fusiform choledochal cyst can be difficult to distinguish from a dilated bile duct resulting from an obstructing bile duct stone. Stones can be present secondarily in the choledochal cyst on initial presentation making it more difficult to determine if the patient has a primary choledochal cyst, or if the obstructing stone led to the dilated, fusiform-like bile duct. What appears to be stone in choledochal cysts may actually be proteinaceous plugs [19, 20]. Differentiating a choledochal cyst from a secondarily dilated bile duct due to an obstructing stone is important because of the increased risk of biliary malignancy associated with choledochal cysts [21, 22]. Prior imaging studies of the biliary system before a patient's presentation with biliary symptoms can be essential to determine if the patient's abnormal biliary dilatation is congenital or acquired. In addition, if the patient undergoes ERCP with sphincterotomy, decompression of the biliary system following this is supportive of an acquired rather than congenital etiology.

In a young child without risk factors for cholelithiaisis, magnetic resonance cholangiopancreatography (MRCP) should be performed with and without contrast to differentiate a tumor from a stone as a tumor will be enhanced on T2-weighted imaging. ERCP may be appropriate when there is concern for obstruction (elevated LFTs, abnormal MRCP) to differentiate obstructing stone disease from a choledochal cyst. However, definitive treatment for a choledochal cyst is surgical resection.

Associated with choledochal cysts are anomalous pancreaticobiliary junction (APBJ) in which the common channel from the ampulla to the pancreaticobiliary junction is abnormally long, typically greater than 1.5 cm. One etiologic theory proposes that in APBJ, pancreatic enzymes reflux into the biliary tree, leading to injury of the bile duct and the formation of a choledochal cyst [23]. Similarly, APBJ is believed to predispose a patient to pancreatitis from bile refluxing back into the pancreatic duct and causing pancreatic irritation (Figs. 20.4, 20.5, 20.6, 20.7, and 20.8).

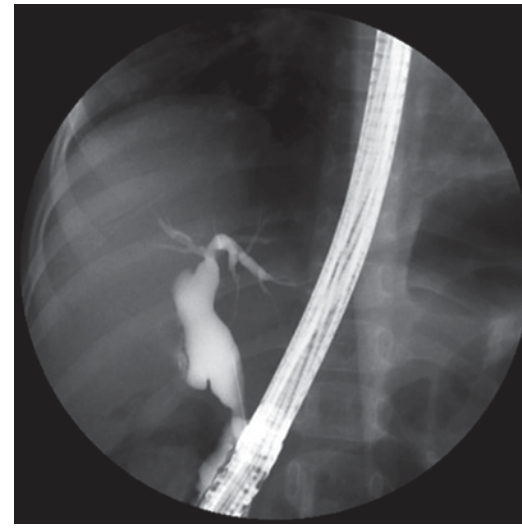

Fig. 20.4 Choledochal cyst in a 5-year-old male Pacific Islander treated with hepaticojejunostomy

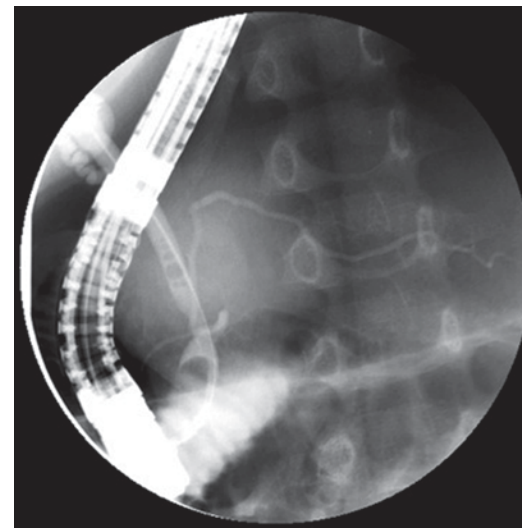

Fig. 20.5 Long common channel in a 3-year-old male with recurrent pancreatitis and obstructive jaundice. Inflated 9 mm stone extraction balloon in distal bile duct

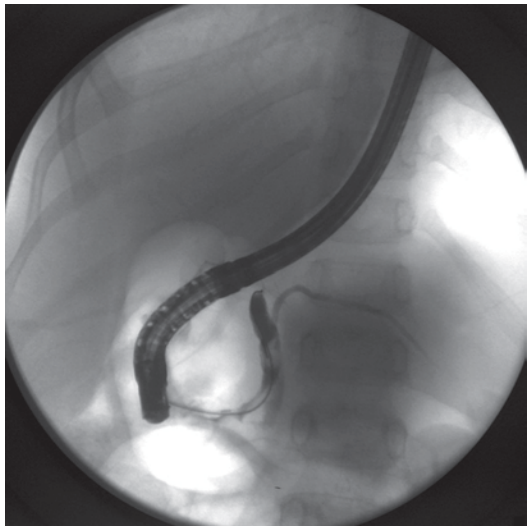

Fig. 20.6 Anomalous pancreaticobiliary union in a 12-year-old male with obstructive jaundice. Filling defect identified in common channel

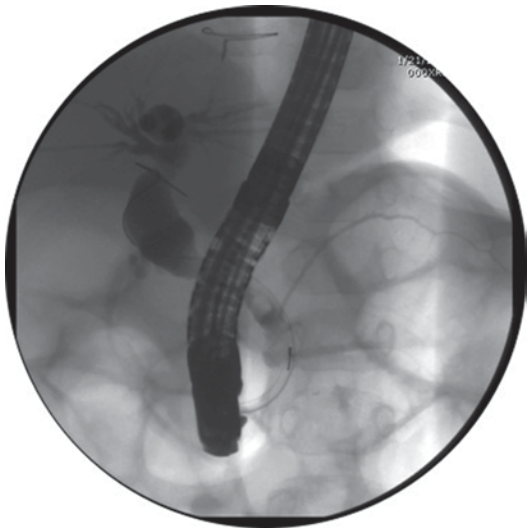

Fig. 20.7 Choledochal cyst and anomalous pancreaticobiliary union

Biliary Atresia

Biliary atresia is an inflammatory process leading to localized obliteration of the extrahepatic bile ducts. This process likely begins prenatally and worsens during the first 1–2 months of life. Early and accurate diagnosis is essential as delayed surgical intervention is associated with poor outcomes [24, 25]. Although biliary atresia is extremely high on the differential diagnosis when evaluating the patient with neonatal cholestasis, outside the neonatal period, it is extremely unlikely as certain mortality occurs, if not surgically addressed.

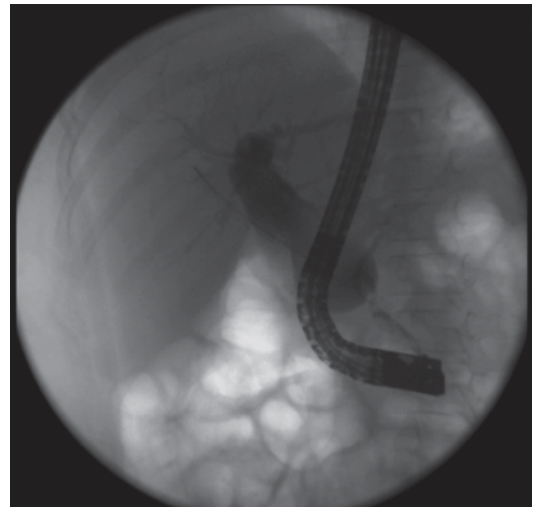

Fig. 20.8 Choledochal cyst with typical saccular appearance

The gold standard for diagnosis of biliary atresia is an intraoperative cholangiogram although the diagnosis is usually suggested by the patient's clinical picture, imaging studies, and liver biopsy. Familial Intrahepatic Cholestasis Type 3 can present similarly, and MRCP has been used to help diagnose biliary atresia [26]. Non-invasive imaging and liver biopsy will fail to diagnose about 14% of the infants with neonatal cholestasis [27]. ERCP can exclude biliary atresia as a diagnosis in infants with neonatal cholestasis if a normal cholangiogram is visualized; and therefore, can spare the infant from a surgical intraoperative cholangiogram [5, 6, 28–30]. However, ERCP is not widely performed in the evaluation of biliary atresia in most pediatric liver centers due to lack of availability and less invasive alternatives.

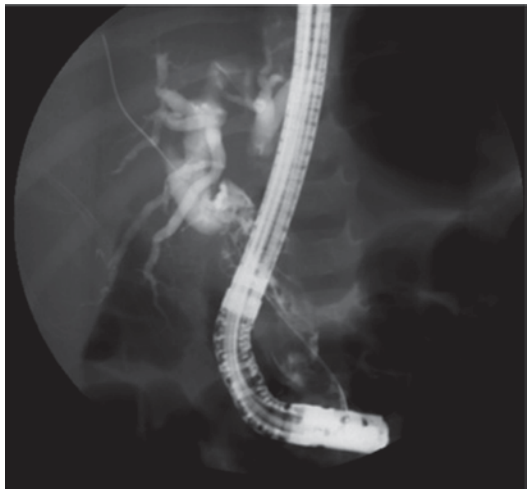

Fig. 20.9 Biliary rhabdomyosarcoma in a 4–year-old male with obstructive jaundice. Extensive irregular filling defects in mid to distal common bile duct

Tumor–Botryoid Rhabdomyosarcoma

Obstructive jaundice secondary to biliary tumor and malignancy is rare in children. While botryoid rhabdomyosarcoma is the most common biliary tumor in children, overall it is rare with mostly case reports in the literature and accounts for only 0.8% of all rhabdomyosarcomas [31]. Treatment usually consists of surgical resection and chemoradiation; although, Himes et al. reported the role of ERCP in the diagnosis and management of biliary rhabdomyosarcoma with stenting followed by chemotherapy and radiation therapy (Fig. 20.9) [32].

What Diagnostic Tools Are Available for Children with Obstructive Jaundice?

US is usually the first radiographic tool to evaluate the biliary system for obstructing stones or lesions and the gallbladder for cholelithiasis. US sensitivity for detecting bile duct stones ranges from 45 to 55% [33, 34]. In addition, US may not be able to evaluate the entire bile duct due to anatomy and bowel gas that can obstruct the sonographic signals.

Computed tomography (CT), which is readily available, can provide valuable anatomical details of the pancreaticobiliary system in children with biliary obstruction. There are concerns that children are more radiosensitive than adults, and that increased exposure to ionizing radiation can potentially raise malignancy risk [35, 36]. Therefore, MRCP is usually recommended instead of an abdominal CT in the pediatric population for detailed imaging of the pancreaticobiliary system.

MRCP is the diagnostic study of choice after abdominal ultrasonography due to its ability to define the pancreaticobiliary anatomy well in a non-invasive manner. MRCP with and without contrast can evaluate for the presence of a choledochal cyst and for filling defects concerning obstructing lesions such as choledocholithiasis, or biliary neoplasms such as rhabdomyosarcoma. MRCP correlates highly with ERCP in the pediatric population [37]. Practically, one must consider whether the child can lay motionless for an MRCP over an extended period of time. Therefore, with infants and young children, sedation is usually required to ensure optimal MRCP image quality.

Endoscopic ultrasound (EUS) can image the entire pancreaticobiliary anatomy in detail while providing the opportunity to perform fine-needle aspiration and needle biopsy of concerning lesions. EUS is technically feasible and safe while adding valuable diagnostic information in the care of children [38–40]. Similar to ERCP, EUS can be limited in children mainly due to the relatively large outer diameters of the echoendoscopes. Currently, echoendoscope diameters range from 11.8 to 12.8 mm, which precludes its use in infants and small children. The variation in size of duodenoscopes makes ERCP easier than EUS in some cases as EUS can be difficult in small children and infants due to the relatively large outer diameter and stiffness of the tip of the echoendoscope.

Case Continued

The patient was admitted from the emergency department and rehydrated. Repeat laboratory values showed persistent conjugated hyperbilirubinemia and elevated markers of liver inflammation. The obtained MRCP confirmed a dilated biliary tree of the patient's left and right intrahepatic bile ducts to the mid common bile duct with the largest diameter of up to 1 cm. The MRCP also revealed a filling defect in the distal bile duct, suggestive of a bile duct stone.

What Are the Management and Therapeutic Options for a Child with Obstructive Jaundice from a Biliary Stone or Choledochal Cyst?

As the patient had persistent obstructive jaundice and radiographic findings suggestive of obstructing biliary stone, ERCP is a treatment option that can both further confirm the diagnosis and treat the biliary obstruction. ERCP with sphincterotomy and stone extraction can relieve the acute obstruction, treat potential ascending cholangitis, and reestablish bile flow. Larger stones may require more advanced techniques including mechanical, electrohydraulic, or laser lithotripsy. The latter two are performed under direct endoscopic visualization via a choledochoscope advanced into the bile duct (Video 20.1). As stated earlier, therapeutic ERCP in the pediatric population has been shown to be safe and effective for pancreaticobiliary diseases [8–12]. In cases of potential choledochal cyst, ERCP has an established role to better define the biliary anatomy, assess for the presence of an anomalous pancreaticobiliary junction, and aid the surgical planning for cyst resection [19, 41–46].

Case Continued

Due to persistent hyperbilirubinemia and high suspicion for obstructive jaundice suggested by MRCP, the patient underwent ERCP. Cholangiogram was consistent with MRCP showing dilated common hepatic, left, and right intrahepatic bile ducts. A 5 mm-filling defect was seen in the distal bile duct. Biliary sphincterotomy was performed and balloon sweep retrieved a bile duct stone. The patient recovered from the ERCP without complications and his laboratory values normalized. Repeat imaging 6 months post-ERCP and sphincterotomy showed persistent dilation of the common hepatic duct and intrahepatic ducts with normal liver laboratory values. As the biliary system remained dilated despite adequate drainage of his biliary system, the patient was diagnosed with a choledochal cyst and referred for surgical resection. After multidisciplinary discussion, it was decided that the patient complete all stages of his planned cardiac surgeries prior to the biliary cyst resection to optimize his cardiopulmonary status. There would also be little immediate risk of biliary complications, such as biliary obstruction with his biliary sphincterotomy providing adequate bile flow, and his risk of biliary malignancy was not immediate given his young age.

Miscellaneous Biliary Procedures

ERCP, EUS, and choledochoscopy are utilized for both, diagnosis and treatment in children after orthotopic liver transplant (OLT) and other abdominal organ transplants [47]. ERCP may be performed in the first days of transplant, although ideally after two weeks in patients with choledochocholedochostomy (duct-to-duct) or related anastomoses. Although the most common reason for transplant is biliary atresia (which requires Roux-en-Y anastomoses), in other infants and children, duct-to-duct anastomoses may be performed. Most commonly, ERCP is used in this population to diagnose and treat strictures or leaks at the anastomosis or vascular insufficiency leading to ischemic strictures (Figs. 20.10 and 20.11, Chap. 9) [48]. Cast-syndrome and other stone and sludge formations can occur in the setting of a stricture and should be treated at the same session. Balloon dilation of anastomotic or ischemic-induced strictures (using 4–8 mm diameter balloons) with or without stent placement (5F–10F with upsizing as appropriate) is fre-

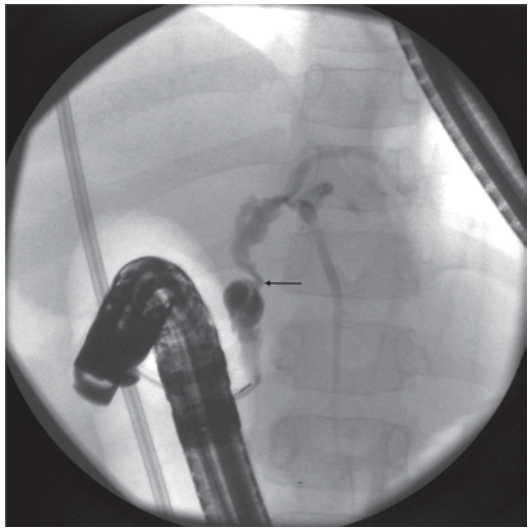

Fig. 20.10 Anastomotic biliary stricture (*arrow*) in a 3-year-old following OLT for metabolic disease

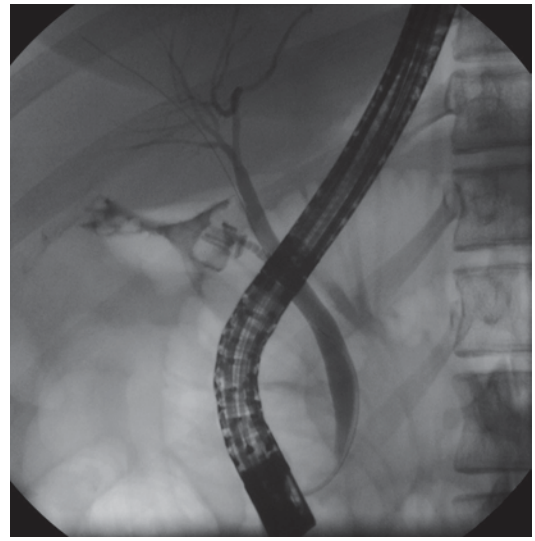

Fig. 20.12 Bile leak from cystic duct stump in a 16-year-old female after cholecystectomy

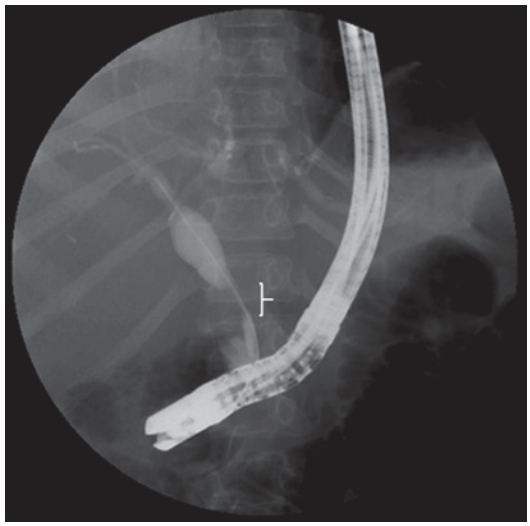

Fig. 20.11 Anastomotic biliary stricture (*bracket*) in a teenager 8 days after OLT for autoimmune hepatitis

quently performed. Sphincterotomy with removal of stone and debris from the biliary tree can also be safely performed [47]. Direct visualization with choledochoscopy may be used to improve diagnostic yield in pediatric liver transplant patients [49, 50]. During ERCP, choledochoscopy has been used for a variety of indications to provide direct visualization and offer therapeutic options with subsequent change in management in over 60 % of the patients [50]. Percutaneous transhepatic cholangiography should be considered if ERCP is unsuccessful, and is usually the first option in children with Roux-en-Y anastomoses.

Traumatic leaks from blunt or penetrating injury as well as postoperative leaks are treated with combined sphincterotomy and stent or stent therapy alone (Fig. 20.12) [48]. Spontaneous bile duct perforation has been reported in an infant and ERCP with stent placement was used successfully [51]. Sphincter of Oddi manometry can also be performed to evaluate and treat patients with either suspected abnormal biliary or pancreatic types of sphincter of Oddi dysfunction. There is limited published data on normal pediatric sphincter pressure values, and larger pediatric series are usually grouped with other therapeutic ERCP procedures [52–54].

Case 2

A 4-year-old boy with autism presented to the emergency department with acute onset of vomiting and abdominal pain and laboratory investigation notable for a lipase of 19,000 U/L. These symptoms had been ongoing for 2 years, but

pancreatic enzymes were normal during a prior clinic visit. He was hospitalized for the first time with pancreatitis, and MRCP demonstrated normal pancreatic anatomy without strictures, dilation, or stones. He then had several additional episodes of documented pancreatitis. Genetic analysis confirmed a mutation encoding cationic trypsinogen (PRSS1).

Pancreatic Endoscopy in Children

It is generally accepted that ERCP is not necessary for the first episode of pancreatitis in a child, unless therapy is indicated from an auxiliary study, such as CT or MRCP. Improved imaging modalities have shifted the indications for ERCP from diagnostic to mainly therapeutic. The evaluation of recurrent pancreatitis typically involves a battery of labs, transabdominal ultrasound, and usually an MRCP (Table 20.3) [55]. ERCP is often considered at this point and recurrent pancreatitis is the most common indication for pancreatic ERCP in children (Table 20.4). While gallbladder or stone-related disease can be identified in patients of all ages, an anatomic cause is more likely in younger children. Multiple centers have reported their experience with pancreatic ERCP in children with recurrent pancreatitis, but there are limited recommendations to guide patient selection regarding pediatric-specific endotherapies [53, 54, 56–58].

Therapeutic ERCP for Treatment of Acute Recurrent and Chronic Pancreatitis in Children

ERCP is commonly used in the treatment of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) for children. The diagnosis of ARP and CP may be difficult in children, but recent pediatric working groups have begun to clarify definitions of ARP and CP. For example, chronic pancreatitis is defined by the INSPPIRE consortium as requiring at least one of the following three: (1) abdominal pain consistent with pancreatic origin and imaging findings suggestive

Table 20.3 What are the common tests performed in children with recurrent and chronic pancreatitis?

Labs
Liver panel (AST, ALT, alkaline phosphatase, GGT, and fractionated bilirubin)
Serum calcium
Triglycerides
Sweat (Cl^-) testing
Genetic analysis (PRSS1, CFTR, SPINK1, and CTRC)
Imaging
Abdominal ultrasound
Vas deferens ultrasound in patients when CF is considered
CT scan
MRCP
ERCP
EUS

Table 20.4 What are the common pediatric indications for pancreatic ERCP?

Idiopathic recurrent pancreatitis
Chronic calcific pancreatitis (pancreatic sphincterotomy, stone removal, stent placement)
Pancreas divisum (minor sphincterotomy, stent placement)
Anomalous pancreaticobiliary junction
Pancreatic pseudocyst (cystgastrostomy)
Pancreatic leak secondary to trauma, tumor, pancreatitis (stent placement)
Sphincter of Oddi dysfunction (manometry with or without sphincterotomy)
Autoimmune pancreatitis

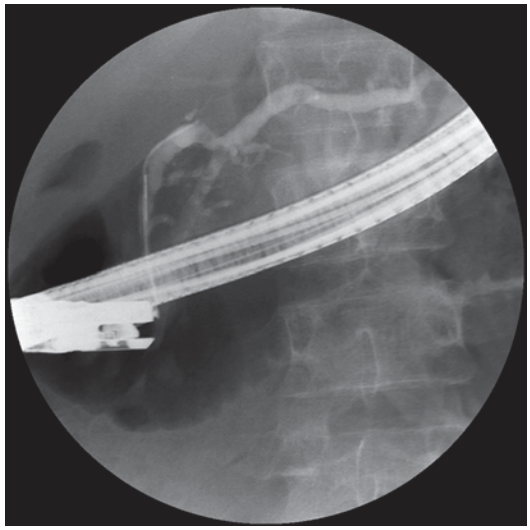

Fig. 20.13 Chronic pancreatitis with small filling defects, dilated main pancreatic duct, and clubbed accessory branches in a 14-year-old male with mutation in cationic trypsinogen

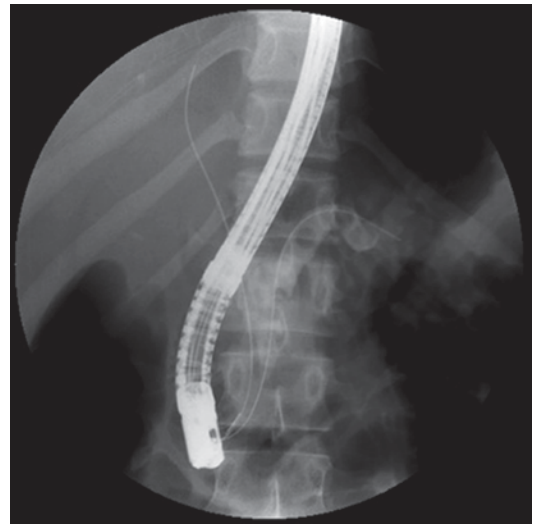

Fig. 20.14 Chronic pancreatitis with several filling defects in a dilated main pancreatic duct of a teenager with cystic fibrosis-related pancreatic disease

of chronic pancreatic damage, (2) evidence of exocrine pancreatic insufficiency and suggestive pancreatic imaging findings, and/or (3) evidence of endocrine pancreatic insufficiency and suggestive pancreatic imaging findings [55].

Several large series have investigated the role of ERCP in ARP and CP in children [52, 59, 60]. Otto et al. reported a series of 231 ERCPS, of which 148 ERCPs were performed for pancreatitis; 106 (71.6%) had either ARP or CP as the indication and identified an etiology in 60% (41 of 68) with ARP. A recent study from India reported on 221 ERCP procedures in 172 children with pancreatic disease of whom 143 (83%) had CP and 19 (11%) had ARP. The ductal changes noted on pancreatogram in the CP patients included dilated and irregular main pancreatic duct (MPD) in 64%, PD calculi in 53% (84% in the head), dominant MPD stricture in 16% (69.3% in the head), and PD leak in 4.9% (Figs. 20.13 and 20.14). There are no pediatric-specific EUS features for chronic pancreatitis, thus EUS diagnosis of CP is based on extrapolation of adult criteria.

The endoscopic treatment options in children with ARP and CP are similar to adults and include major and minor papillotomy, stent placement, stone removal, and lithotripsy (Chaps. 13–14). In the Agarwal series, nearly 90% of them underwent pancreatic sphincterotomy for CP (67% major papillotomy and 22% minor papillotomy) with 4–7 French pancreatic stents in 55%, and extracorporeal shock wave lithotripsy (ESWL) in 35%. ESWL is infrequently performed in US pediatric centers. During mean follow-up of 61 months after endoscopic therapy in pediatric patients with CP, 71% of the patients reported improvement in pain with 57% being pain free [56, 59].

In patients with ARP, these etiologies were detected by ERCP: pancreas divisum in 37%, biliary pancreatitis in 11%, mildly dilated MPD suggestive of possible early CP in 21%, and 26% with no obvious etiology [56]. Pancreatic sphincterotomy was performed in 58% (11 of 19 patients) with ARP. During follow-up, 63% of ARP patients reported pain relief. Overall complication rate for all ERCPs was 5% with 1.5% mild acute pancreatitis and 3.4% with abdominal pain requiring hospitalization.

In CP, a discussion with patients and their families regarding alternatives to ERCP (e.g., ESWL, surgery, or islet cell transplant) is important. Judicious patient selection should guide the use of sphincterotomy and stents in children. In a patient with idiopathic ARP following an

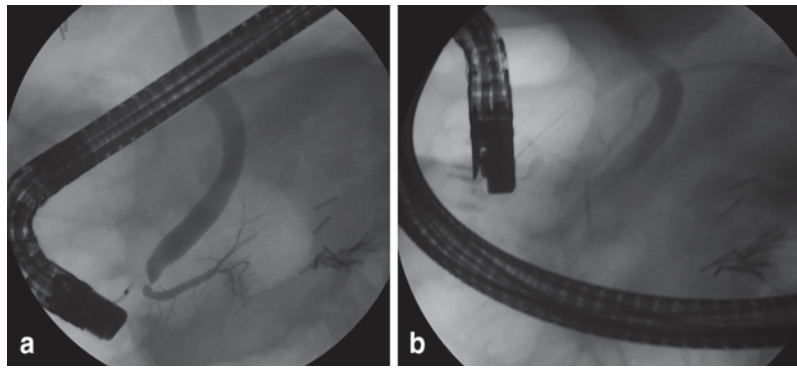

Fig. 20.15 ERCP with injection through major papilla into normal common bile duct and diminutive ventral duct consistent with complete pancreas divisum (**a**). Injection through minor papilla shows dorsal pancreatic duct consistent with complete pancreas divisum (**b**). (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

exhaustive evaluation for biliary disease, we would consider ERCP in the setting of a normal MRCP after the second attack of pancreatitis, but typically only if the episodes are prolonged. A rule of thumb is to consider ERCP if the patient has had three or more attacks in 6 months or more than five episodes in a year. With limited data to guide endoscopic management, a young child with numerous episodes of pancreatitis, a normal MRCP, and no identifiable cause might receive either a trial of stent therapy or a pancreatic sphincterotomy, although data to support this practice is lacking. A child with metabolic disease induced recurrent pancreatitis (e.g., hypertriglyceridemia) is unlikely to benefit from endoscopic therapy in the absence of other findings.

What is the Role of ERCP in Congenital Anomalies of the Pancreas?

Although its significance is debated, recurrent pancreatitis in children is commonly linked to congenital anomalies of the pancreas. Pancreas divisum and its variants are frequently present in up to 25% of the pediatric ERCP performed for acute or chronic pancreatitis [53, 56, 58]. Agarwal et al. reported 30 of 143 (21%) patients with CP and 7 of 19 (37%) patients with ARP had pancreas divisum, while Otto et al. found 20 of 106 (19%) patients with abnormal anatomic variations [52, 56].

Pancreas divisum is a congenital anomaly caused by abnormal fusion of the ventral and dorsal pancreatic buds (Chap. 15). Occurring in up to 14% of the general population, this may lead to abnormal drainage of the ventral pancreas via the duct of Wirsung with the predominant drainage from the dorsal (duct of Santorini) section. Pancreas divisum may lead to either stenosis or a functional obstruction. Minor papilla sphincterotomy with or without stent improves symptoms in 30–50% of the pediatric patients [54, 56]. Other anatomic variations have been described, but their role in pediatric disease is less characterized.

While MRCP may support a diagnosis of pancreas divisum, ERCP is necessary to confirm the diagnosis in a symptomatic patient for whom therapy is being considered (Fig. 20.15). Smaller caliber wires (e.g., 0.018, 0.021, or 0.025 in.) may be necessary due to the relatively small size of the minor ampulla and presence of stenosis. In addition, secretin (ChiRhoStim®, Burtonsville, MD, USA) may assist in the identification of the minor papilla and subsequent cannulation in children with pancreas divisum.

Case Continued

After discussion with family and primary care physician, ERCP was performed during a prolonged hospitalization for acute recurrent pancre-

atitis. The pancreatic duct was cannulated with a 0.025 in. wire, and pancreatogram demonstrated a dilated main pancreatic duct to 6 mm with a stricture at the genu and multiple filling defects despite a previously normal MRCP from a prior admission. It may be helpful to repeat MRCP if there has been a significant amount of time between the last imaging and planned ERCP to assess for any changes. Secretin-enhanced MRCP has been demonstrated to be useful in the adult population and may offer improved visualization of the pancreatic duct in children as well. Multiple small-stone fragments were removed following pancreatic sphincterotomy and a 5F 7 cm stent was placed across the stricture to the junction of the body and tail. The patient did well and had dramatic improvement in symptoms during stent replacement over the next 6 weeks.

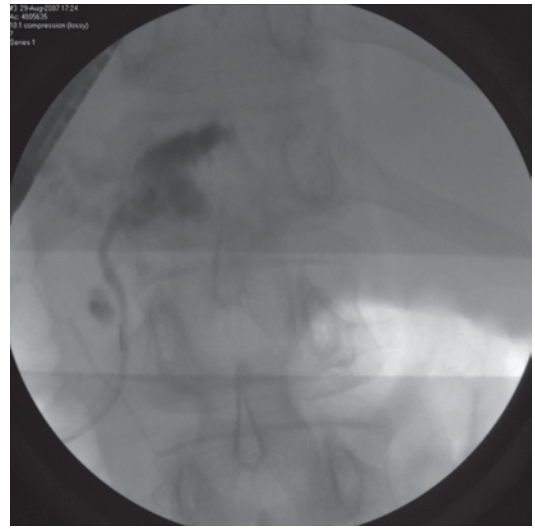

Fig. 20.17 Pancreatic duct leak in the neck of pancreas of a child with acute pancreatitis after Pegylated L-asparaginase

How Are Pancreatic Leaks and Pseudocysts Managed Endoscopically in Children?

Pancreatic duct leaks can occur in acute pancreatitis or due to traumatic injury (Figs. 20.16, 20.17, and 20.18). Blunt trauma (classically, a handlebar

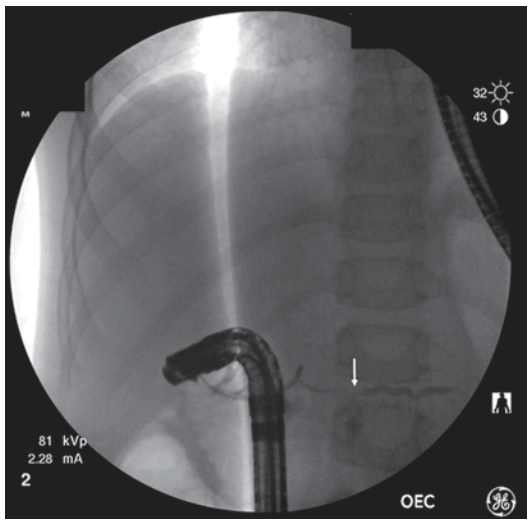

Fig. 20.16 Pancreatic trauma from falling off a bicycle with small leak in midbody with stricture (*arrow*) and mild upstream main pancreatic duct dilation, all treated with stent therapy (not shown) to bridge the leak and stricture

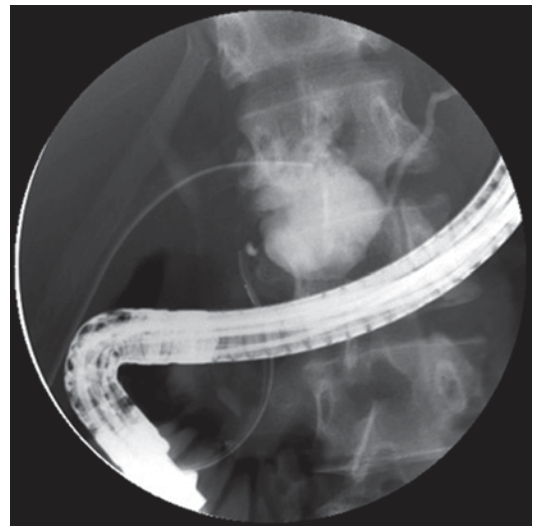

Fig. 20.18 Pancreatic trauma secondary to motorized cart injury with leak and continuity with the upstream component of a normal appearing main pancreatic duct

or seatbelt injury) is the most common mechanism, but penetrating injury can occur. Although CT and MRCP can assist in diagnosis, ERCP is probably most useful for combined diagnosis and therapy in a patient with either a Grade III (distal transection or parenchyma and duct injury) or

Table 20.5 Grading of pancreatic injury. (Adapted from [61])

Grade	Pancreatic injury
I	Minor contusion
II	Major contusion
III	Distal transection or parenchyma and duct injury
IV	Proximal transection or parenchyma and duct injury
V	Massive disruption of pancreatic head

Grade IV (proximal transection or parenchyma and duct injuries) injury (Table 20.5) [61, 62]. Pancreatic stenting across a disruption may allow for ductal recommunication. If the stent cannot be advanced across the injury, a short stent may be placed across the sphincter; although this has a lower success rate of 20–40% (Chap. 12). In children, 3F or 5F stents are commonly used and upsized as needed.

Depending on the location as well as other factors outlined in Chap. 12, endoscopic management of pancreatic pseudocysts and walled-off necrosis is more commonly utilized given the morbidity of percutaneous and surgical drainage. Endoscopic drainage can be performed via transpapillary stent placement, cystgastrostomy, or necrosectomy. Several centers have reported their experience using ERCP or EUS, or a combination of both, for diagnosis and management of pseudocysts in children [54, 56, 57, 63, 64]. In majority of the cases this is a highly effective procedure, but pseudocysts can recur.

Training in Pediatric ERCP

As outlined in Chap. 1, rigorous training is necessary to master ERCP in a patient of any age. Depending on the available expertise, pediatric ERCP is most often performed by either an adult pancreaticobiliary endoscopist or a pediatric gastroenterologist with focused ERCP training. A growing number of pediatric gastroenterologists perform ERCP and receive training under the mentorship of an adult gastroenterologist or by completing an advanced endoscopy fellowship to achieve requisite skills. As pediatric gastroenterology fellows perform fewer endoscopies overall compared to their counterparts in adult gastroenterology fellowships, advanced endoscopy training for pediatric gastroenterologists need to account for this. To date, there are no specific recommendations for maintenance of skill in those performing pediatric ERCP, whether a pediatric or adult gastroenterologist. Given the significant variation in patient size (i.e., neonates to obese teenagers), equipment needs, and case distribution compared to adult patients, unique competencies may be needed to assess proceduralists in the future.

Future Directions

Pancreaticobiliary endoscopy in children is becoming more commonplace as an alternative to surgery or interventional radiology. Future studies should be directed at establishing guidelines for specific therapies (e.g., choledocholithiasis or recurrent pancreatitis). We would encourage a pediatric registry to collect data regarding outcomes and adverse events. In addition, technical modifications of current equipment, including duodenoscopes, echoendoscopes, and papillotomes, should be tailored towards pediatric-sized patients and their disorders. Continued collaboration between pediatric and adult gastroenterologists is critical in advancing the field of pediatric ERCP and EUS.

Key Points

- ERCP in neonates and children has been shown to be safe and effective for treatment of, both, biliary and pancreatic diseases.
- In younger children, anatomic abnormalities and tumors should be considered in those with biliary obstruction or recurrent pancreatitis.
- Choledochal cyst must be considered in the differential of a child with a significantly dilated bile ducts and stones due to the increased risk of cholangiocarcinoma.

- Early diagnosis in biliary atresia is a key to improved surgical outcomes, and ERCP can help in the evaluation of exclusion of the disease in neonatal cholestasis.
- MRCP and ultrasonography are preferred for initial assessment of pediatric pancreatic and biliary diseases to spare children from ionizing radiation associated with CT scans.
- Pancreatic leaks and pseudocysts can be managed endoscopically in children using transpapillary or transgastric methods.

Conflict of Interest The authors declare no conflict of interest.

Financial Disclosures None

Video Caption

Video 20.1 16-year-old with large CBD stone pulverized with Yag-Holmium laser using single operator choledochoscopy

References

1. Aabakken L, Aagenaes I, Sanengen T, Aasen S, Emblem R, Bjornland K. Utility of ERCP in neonatal and infant cholestasis. J Laparoendosc Adv Surg Tech A. 2009;19(3):431–6.
2. Guelrud M, Jaen D, Torres P, Mujica C, Mendoza S, Rivero E, et al. Endoscopic cholangiopancreatography in the infant: evaluation of a new prototype pediatric duodenoscope. Gastrointest Endosc. 1987;33(1):4–8.
3. Kato S, Kamagata S, Asakura T, Ozawa K, Nio M, Ohi R, et al. A newly developed small-caliber videoduodenoscope for endoscopic retrograde cholangiopancreatography in children. J Clin Gastroenterol. 2003;37(2):173–6.
4. Ohnuma N, Takahashi T, Tanabe M, Yoshida H, Iwai J. The role of ERCP in biliary atresia. Gastrointest Endosc. 1997;45(5):365–70.
5. Petersen C, Meier PN, Schneider A, Turowski C, Pfister ED, Manns MP, et al. Endoscopic retrograde cholangiopancreaticography prior to explorative laparotomy avoids unnecessary surgery in patients suspected for biliary atresia. J Hepatol. 2009;51(6):1055–60.
6. Shanmugam NP, Harrison PM, Devlin J, Peddu P, Knisely AS, Davenport M, et al. Selective use of endoscopic retrograde cholangiopancreatography in the diagnosis of biliary atresia in infants younger than 100 days. J Pediatr Gastroenterol Nutr. 2009;49(4):435–41.
7. Barth BA, Banerjee S, Bhat YM, Desilets DJ, Gottlieb KT, Maple JT, et al. Equipment for pediatric endoscopy. Gastrointes Endosc. 2012;76(1):8–17.
8. Fox VL, Werlin SL, Heyman MB. Endoscopic retrograde cholangiopancreatography in children. Subcommittee on endoscopy and procedures of the patient care committee of the North American society for pediatric gastroenterology and nutrition. J Pediatr Gastroenterol Nutr. 2000;30(3):335–42.
9. Jang JY, Yoon CH, Kim KM. Endoscopic retrograde cholangiopancreatography in pancreatic and biliary tract disease in Korean children. World J Gastroenterol. 2010;16(4):490–5.
10. Otto A, Neal M, Slivka A, Kane T. An appraisal of endoscopic retrograde cholangiopancreatography (ERCP) for pancreaticobiliary disease in children: our institutional experience in 231 cases. Surg Endosc. 2011;25(8):2536–40.
11. Rocca R, Castellino F, Daperno M, Masoero G, Sostegni R, Ercole E, et al. Therapeutic ERCP in paediatric patients. Dig Liver Dis. 2005;37(5):357–62.
12. Varadarajulu S, Wilcox CM, Hawes RH, Cotton PB. Technical outcomes and complications of ERCP in children. Gastrointest Endosc. 2004;60(3):367–71.
13. Iqbal CW, Baron TH, Moir CR, Ishitani MB. Post-ERCP pancreatitis in pediatric patients. J Pediatr Gastroenterol Nutr. 2009;49(4):430–4.
14. Troendle DM, Barth BA. ERCP can be safely and effectively performed by a pediatric gastroenterologist for choledocholithiasis in a pediatric facility. J Pediatr Gastroenterol Nutr. 2013;57(5):655–8.
15. Rescorla FJ. Cholelithiasis, cholecystitis, and common bile duct stones. Curr Opin Pediatr. 1997;9(3):276–82.
16. Mehta S, Lopez ME, Chumpitazi BP, Mazziotti MV, Brandt ML, Fishman DS. Clinical characteristics and risk factors for symptomatic pediatric gallbladder disease. Pediatrics. 2012;129(1):e82–8.
17. Maple JT, Ben-Menachem T, Anderson MA, Appalaneni V, Banerjee S, Cash BD, et al. The role of endoscopy in the evaluation of suspected choledocholithiasis. Gastrointest Endosc. 2010;71(1):1–9.
18. Fishman DS, Chumpitazi BP, Raijman I, Gilger MA. 227 Choledocholithiasis in Children: Can We Use Adult Guidelines? Gastrointestinal Endoscopy. 2011; 73(4, Supplement):AB117.
19. Tsuchiya H, Kaneko K, Itoh A, Kawashima H, Ono Y, Tainaka T, et al. Endoscopic biliary drainage for children with persistent or exacerbated symptoms of choledochal cysts. J Hepatobiliary Pancreat Sci. 2013 Mar;20(3):303–6. doi: 10.1007/s00534-012-0519-5.
20. Kaneko K, Ando H, Ito T, Watanabe Y, Seo T, Harada T, et al. Protein plugs cause symptoms in patients with choledochal cysts. Am J Gastroenterol. 1997;92(6):1018–21.
21. Benjamin IS. Biliary cystic disease: the risk of cancer. J Hepatobiliary Pancreat Surg. 2003;10(5):335–9.
22. Kobayashi S, Asano T, Yamasaki M, Kenmochi T, Nakagohri T, Ochiai T. Risk of bile duct car-

cinogenesis after excision of extrahepatic bile ducts in pancreaticobiliary maljunction. Surgery. 1999;126(5):939–44.
23. Miyano T, Suruga K, Suda K. Abnormal choledochopancreatico ductal junction related to the etiology of infantile obstructive jaundice diseases. J Pediatr Surg. 1979;14(1):16–26.
24. Davenport M, Kerkar N, Mieli-Vergani G, Mowat AP, Howard ER. Biliary atresia: the King's College Hospital experience (1974–1995). J Pediatr Surg. 1997;32(3):479–85.
25. Mieli-Vergani G, Howard ER, Portman B, Mowat AP. Late referral for biliary atresia–missed opportunities for effective surgery. Lancet. 1989;1(8635):421–3.
26. Takaya J, Nakano S, Imai Y, Fujii Y, Kaneko K. Usefulness of magnetic resonance cholangiopancreatography in biliary structures in infants: a four-case report. Eur J Pediatr. 2007;166(3):211–4.
27. Manolaki AG, Larcher VF, Mowat AP, Barrett JJ, Portmann B, Howard ER. The prelaparotomy diagnosis of extrahepatic biliary atresia. Arch Dis Child. 1983;58(8):591–4.
28. Keil R, Snajdauf J, Rygl M, Pycha K, Kotalova R, Drabek J, et al. Diagnostic efficacy of ERCP in cholestatic infants and neonates–a retrospective study on a large series. Endoscopy. 2010;42(2):121–6.
29. Shteyer E, Wengrower D, Benuri-Silbiger I, Gozal D, Wilschanski M, Goldin E. Endoscopic retrograde cholangiopancreatography in neonatal cholestasis. J Pediatr Gastroenterol Nutr. 2012;55(2):142–5.
30. Vegting IL, Tabbers MM, Taminiau JA, Aronson DC, Benninga MA, Rauws EA. Is endoscopic retrograde cholangiopancreatography valuable and safe in children of all ages? J Pediatr Gastroenterol Nutr. 2009;48(1):66–71.
31. Stocker J. Hepatic tumors. In Balistreri W, editor. Pediatric hepatology. New York: Hemisphere Publ. Co.; 1990. p. 399–488.
32. Himes RW, Raijman I, Finegold MJ, Russell HV, Fishman DS. Diagnostic and therapeutic role of endoscopic retrograde cholangiopancreatography in biliary rhabdomyosarcoma. World J Gastroenterol. 2008;14(30):4823–5.
33. O'Connor HJ, Hamilton I, Ellis WR, Watters J, Lintott DJ, Axon AT. Ultrasound detection of cholocholithiasis: prospective comparison with ERCP in the postcholecystectomy patient. Gastrointest Radiol. 1986;11(2):161–4.
34. Cronan JJ. US diagnosis of choledocholithiasis: a reappraisal. Radiology. 1986;161(1):133–4.
35. National Research C. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press; 2006.
36. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012;380(9840):499–505.
37. Tipnis NA, Dua KS, Werlin SL. A retrospective assessment of magnetic resonance cholangiopancreatography in children. J Pediatr Gastroenterol Nutr. 2008;46(1):59–64.
38. Al-Rashdan A, LeBlanc J, Sherman S, McHenry L, DeWitt J, Al-Haddad M. Role of endoscopic ultrasound for evaluating gastrointestinal tract disorders in pediatrics: a tertiary care center experience. J Pediatr Gastroenterol Nutr. 2010;51(6):718–22.
39. Attila T, Adler DG, Hilden K, Faigel DO. EUS in pediatric patients. Gastrointest Endosc. 2009;70(5):892–8.
40. Cohen S, Kalinin M, Yaron A, Givony S, Reif S, Santo E. Endoscopic ultrasonography in pediatric patients with gastrointestinal disorders. J Pediatr Gastroenterol Nutr. 2008;46(5):551–4.
41. Ando H, Ito T, Nagaya M, Watanabe Y, Seo T, Kaneko K. Pancreaticobiliary maljunction without choledochal cysts in infants and children: clinical features and surgical therapy. J Pediatr Surg. 1995;30(12):1658–62.
42. Houben CH, Chiu PW, Lau J, Lee KH, Ng EK, Tam YH, et al. Preoperative endoscopic retrograde cholangiopancreatographic treatment of complicated choledochal cysts in children: a retrospective case series. Endoscopy. 2007;39(9):836–9.
43. Miyano T, Ando K, Yamataka A, Lane G, Segawa O, Kohno S, et al. Pancreaticobiliary maljunction associated with nondilatation or minimal dilatation of the common bile duct in children: diagnosis and treatment. Eur J Pediatr Surg. 1996;6(6):334–7.
44. De Angelis P Foschia F Romeo E Caldaro T Rea F di Abriola GF, et al. Role of endoscopic retrograde cholangiopancreatography in diagnosis and management of congenital choledochal cysts: 28 pediatric cases. J Pediatr Surg. 2012;47(5):885–8.
45. Komi N, Takehara H, Kunitomo K, Miyoshi Y, Yagi T. Does the type of anomalous arrangement of pancreaticobiliary ducts influence the surgery and prognosis of choledochal cyst? J Pediatr Surg. 1992;27(6):728–31.
46. Sharma AK, Wakhlu A, Sharma SS. The role of endoscopic retrograde cholangiopancreatography in the management of choledochal cysts in children. J Pediatr Surg. 1995;30(1):65–7.
47. Otto AK, Neal MD, Mazariegos GV, Slivka A, Kane TD. Endoscopic retrograde cholangiopancreatography is safe and effective for the diagnosis and treatment of pancreaticobiliary disease following abdominal organ transplant in children. Pediatr Transplant. 2012;16(8):829–34.
48. Enestvedt BK, Tofani C, Lee DY, Abraham M, Shah P, Chandrasekhara V, et al. Endoscopic retrograde cholangiopancreatography in the pediatric population is safe and efficacious. J Pediatr Gastroenterol Nutr. 2013;57(5):649–54.
49. Siddique I, Galati J, Ankoma-Sey V, Wood RP, Ozaki C, Monsour H, et al. The role of choledochoscopy in the diagnosis and management of biliary tract diseases. Gastrointest Endosc. 1999;50(1):67–73.

50. Harpavat S, Raijman I, Hernandez JA, Fishman DS. Single-center experience of choledochoscopy in pediatric patients. Gastrointest Endosc. 2012;76(3):685–8.
51. Barnes BH, Narkewicz MR, Sokol RJ. Spontaneous perforation of the bile duct in a toddler: the role of endoscopic retrograde cholangiopancreatography in diagnosis and therapy. J Pediatr Gastroenterol Nutr. [Case Reports]. 2006;43(5):695–7.
52. Otto AK, Neal MD, Slivka AN, Kane TD. An appraisal of endoscopic retrograde cholangiopancreatography (ERCP) for pancreaticobiliary disease in children: our institutional experience in 231 cases. Surg Endosc. 2011;25(8):2536–40.
53. Guelrud M, Mujica C, Jaen D, Plaz J, Arias J. The role of ERCP in the diagnosis and treatment of idiopathic recurrent pancreatitis in children and adolescents. Gastrointest Endosc. 1994;40(4):428–36.
54. Graham KS, Ingram JD, Steinberg SE, Narkewicz MR. ERCP in the management of pediatric pancreatitis. Gastrointest Endosc. 1998;47(6):492–5.
55. Morinville VD, Husain SZ, Bai H, Barth B, Alhosh R, Durie PR, et al. Definitions of pediatric pancreatitis and survey of present clinical practices. J Pediatr Gastroenterol Nutr. 2012;55(3):261–5.
56. Agarwal J, Nageshwar Reddy D, Talukdar R, Lakhtakia S, Ramchandani M, Tandan M, et al. ERCP in the management of pancreatic diseases in children. Gastrointest Endosc. 2014 Feb;79(2):271–8.
57. Kozarek RA, Christie D, Barclay G. Endoscopic therapy of pancreatitis in the pediatric population. Gastrointest Endosc. 1993;39(5):665–9.
58. Hsu RK, Draganov P, Leung JW, Tarnasky PR, Yu AS, Hawes RH, et al. Therapeutic ERCP in the management of pancreatitis in children. Gastrointest Endosc. [Clinical Trial]. 2000; 51(4 Pt 1):396–400.
59. Li ZS, Wang W, Liao Z, Zou DW, Jin ZD, Chen J, et al. A long-term follow-up study on endoscopic management of children and adolescents with chronic pancreatitis. Am J Gastroenterol. [Research Support, Non-U.S. Gov't]. 2010;105(8):1884–92.
60. Agarwal J, Nageshwar Reddy D, Talukdar R, Lakhtakia S, Ramchandani M, Tandan M, et al. ERCP in the management of pancreatic diseases in children. Gastrointest Endosc. 2014;79(2):271–8.
61. Moore EE, Cogbill TH, Malangoni MA, Jurkovich GJ, Champion HR, Gennarelli TA, et al. Organ injury scaling, II: Pancreas, duodenum, small bowel, colon, and rectum. J Trauma. [Guideline]. 1990;30(11):1427–9.
62. Houben CH, Ade-Ajayi N, Patel S, Kane P, Karani J, Devlin J, et al. Traumatic pancreatic duct injury in children: minimally invasive approach to management. J Pediatr Surg. 2007;42(4):629–35.
63. Jazrawi SF, Barth BA, Sreenarasimhaiah J. Efficacy of endoscopic ultrasound-guided drainage of pancreatic pseudocysts in a pediatric population. Dig Dis Sci. 2011;56(3):902–8.
64. Makin E, Harrison PM, Patel S, Davenport M. Pancreatic pseudocysts in children: treatment by endoscopic cyst gastrostomy. J Pediatr Gastroenterol Nutr. [Evaluation Studies]. 2012;55(5):556–8.

Part V
EUS – Overview

Training in Endoscopic Ultrasound

21

Rahul Pannala and Douglas O. Faigel

Introduction

Endoscopic ultrasound (EUS) has evolved to become an established endoscopic technique in the diagnosis and treatment of a variety of gastrointestinal disorders including but not limited to pancreatic cysts, mucosal and subepithelial tumors, chronic pancreatitis, and various gastrointestinal malignancies. EUS has a particularly important role in the diagnosis and staging of gastrointestinal and pancreaticobiliary cancers. Several studies have demonstrated the superiority of EUS compared to conventional abdominal computed tomography (CT) in the staging of esophageal, gastric, and pancreatic cancers [1–4]. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is in many instances a preferred alternative to traditional percutaneous biopsies obtained under CT or ultrasound guidance; an additional benefit is the ability to diagnose and stage the tumor in a single procedure. For pancreatic tumors, EUS-FNA has a sensitivity ranging between 85 and 90 % and a specificity of 100 % [5, 6]. More recently, in addition to the staging and diagnostic capabilities of EUS, there are several therapeutic interventions of EUS that have been developed including gaining access to and stenting the bile and pancreatic ducts, draining fluid collections, treating bleeding, injecting tumor suppressing agents, and placement of fiducials for stereotactic radiotherapy [7]. In many ways, the introduction of EUS into clinical practice has transformed the field of gastroenterology, in particular gastrointestinal oncology, with potential applications, especially therapeutic interventions, continuing to evolve.

With the increasing use and availability of EUS, ensuring adequate training of practicing endosonographers has become a priority for the American Society for Gastrointestinal Endoscopy (ASGE), as evidenced by the guidelines and core curriculum set forth on advanced training in EUS [8, 9]. The aims of this chapter are to cover current guidelines for individual trainees and practitioners, training programs, and credentialing in EUS. We will also discuss the merits of a formal year of advanced endoscopy training that includes training in EUS, evaluating trainees in their EUS proficiency, and educational resources available to complement clinical training. Although computer-based training simulators are in their infancy in endosonography, they represent an exciting adjunct to formal training and will also be briefly considered.

Training in EUS: An Extra Year

As EUS becomes increasingly applied in clinical practice, the demand for well-trained endosonographers has risen [8, 10]. Both the ASGE and the European Society of Gastrointestinal Endoscopy (ESGE) have recently published guidelines for EUS training [9, 11].

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The training landscape of EUS has changed substantially in the past few years. Initially, a relative lack of training centers and the extensive commitment required by the trainee limited the availability of skilled endosonographers. EUS is now available at most US academic medical centers and most gastroenterology trainees have exposure to EUS in their regular fellowship curriculum. This contact is usually limited to understanding the procedural indications and complications rather than hands-on experience.

Achieving proficiency in EUS typically requires additional training beyond the scope of a traditional 3-year Gastroenterology fellowship program. The limitations of incorporating advanced endoscopic skills into the 3-year fellowship curriculum have been the major impetus for establishing fourth-year fellowships in EUS. Currently in the USA, a 1-year Advanced Endoscopy fellowship following completion of an accredited gastroenterology training program is the most common training pathway for most endosonographers. Training during this year usually involves acquisition of other advanced endoscopic skills such as endoscopic retrograde cholangiopancreatography (ERCP) and luminal stenting in addition to learning EUS. As interventional EUS becomes more main stream and boundaries between EUS and ERCP blur, endosonographers will be expected to possess a wide array of interventional skills in addition to core EUS skills. Only a minority of traditional 3-year Gastroenterology fellowship programs provide adequate hands-on EUS and ERCP training, and therefore, a formal advanced endoscopy fellowship is generally considered mandatory for proficiency in EUS. While clinical workshops, short-term EUS apprenticeships with hands-on training, animal models, EUS teaching videos, and computer-based training simulators provide experience and offer an understanding of the indications and complications of EUS, they do not substitute for formal fellowship training and arguably do not adequately train individuals as independent endosonographers. At select institutions, there may be 1- to 2-week workshops in EUS allowing exposure to this technology. These teaching methods simply represent useful adjuncts to formal training and should not be used in lieu of a more formal supervised training experience. One retrospective study showed that endosonographers with formal supervised training experience in pancreaticobiliary EUS achieve a significantly higher sensitivity for EUS-FNA in diagnosing pancreatic malignancy compared to those without formal FNA training [12]. A general consensus by expert endosonographers suggests that luminal endosonography requires at least 3–6 months of intensive training to establish competency while pancreaticobiliary EUS and FNA may require up to 1 year [13]. In fact, one study suggested that the learning curve continues to develop after fellowship training because more procedures are needed to gain proficiency and efficiency with EUS-FNA of solid pancreatic masses [14, 15]. This is supported by a recent multicenter study of 12 EUS-naive advanced endoscopy fellows reporting sobering numbers that included only 2 trainees attaining competency by 225 and 245 upper EUS procedures. another 2 fellows trending towards acceptable performance by 289 and 355 cases and the other 8 fellows requiring ongoing training.

Currently, there are more than 50 Advanced Endoscopy training programs in the USA that participate in the fellowship match (www.asge.org/education/). Many of these programs provide training in ERCP and EUS while a few separate the training into either EUS or ERCP. A survey by Azad and colleagues found that the majority of gastroenterology fellowship programs in the USA have the necessary EUS volume to annually train at least one EUS fellow [16]. However, most 3-year and many advanced fellows receive insufficient EUS training according to ASGE guidelines. Among 3-year GI fellows, 55 % received less than 3 months of training with 43 % not receiving actual hands-on experience, and 61 % not learning EUS-FNA. Programs offering advanced training in EUS had a median advanced-trainee EUS volume of 200 procedures (range, 50–1100). Of the advanced fellows, 20 % failed to receive hands-on training while 52 % performed fewer than 200 procedures. Although there are limitations to this study, the findings highlight some of the inadequacies in training for EUS and demonstrate areas for improvement.

Training Program Requirements

While programs may vary in the design of their training experience, two critical components are necessary for a qualified training program: adequate patient volume and recognized faculty expertise. Not all training programs should offer EUS training due to limitations of patient volume and faculty interests. When considering advanced training in EUS, a trainee should investigate all aspects of the training program [17]. Arguably, the most important aspect to a training program is the reputation and expertise of the faculty endosonographers. Programs should have a minimum of one skilled endosonographer who is acknowledged as an expert by his/her peers and is committed to teaching EUS. Ideally, there is a roster of experienced faculty who can guide the trainee. In addition, the program should promote the interaction of the trainee with other faculty from the multidisciplinary teams for various disease states.

Unfortunately, the majority of EUS programs across the USA have limited, if any, extramural funding and may require additional clinical responsibilities from the trainee to help support the salary. While understanding the financial limitations of most institutions, training programs should strive to limit the clinical responsibilities unrelated to EUS when developing their core curriculum. Ideally, programs should provide protected research time and encourage academic pursuits such as designing research protocols, preparing manuscripts, writing grant proposals, and attending EUS courses. Creating an environment emphasizing endoscopic research and clinical investigation should be a fundamental goal for each training program. Trainees should be provided with the protected time and necessary funds to attend at least one scientific meeting during the course of their training, preferably one related to endosonography. A common goal for all committed trainees should be presenting their endoscopic research at either a national or international meeting. Many trainees in EUS may pursue future academic positions, and exposure to endoscopy unit management including scheduling, staffing, equipment maintenance, and management skills is also a valuable asset to any training program. These are invaluable skills to acquire early in an academic career. While development of future academic endosonographers is a common goal for most training programs, some trainees may express different career interests that conflict with the goals of the training program. Understanding and recognizing the program's expectations and trainee's career interests is crucial to an enjoyable and successful training experience.

Each program in EUS should have the ability to provide sufficient numbers of procedures that will substantially surpass those required for minimal competence (Table 21.1). Although a large procedure volume does not necessarily guarantee competence, it is highly unlikely that a low volume of cases will provide sufficient exposure to these highly complicated and technically challenging procedures to allow adequate assessment of competency. Requiring a large volume of cases is not an elitist attempt by tertiary centers

Table 21.1 Threshold numbers for EUS before competency can be assessed [2]

Site/Lesion	Number of cases required
Mucosal tumors (cancers of the esophagus, stomach, and rectum)	75
Subepithelial abnormalities	40
Pancreaticobiliary	75
EUS-FNA	50 (includes 25 pancreatic FNA)
Non-pancreatic FNA	25
Pancreatic FNA	25
Comprehensive competence	150[a]

[a] Including at least 75 pancreaticobiliary and 50 FNA

to exclude others from potential training opportunities, but rather an attempt to guarantee the delivery of skilled endosonographers into the workforce and answering the demand for endoscopic ultrasound. For these reasons, EUS training is concentrated in academic tertiary centers with highly skilled endosonographers and adequate patient volume to ensure successful training.

In addition to the hands-on learning, formal supervised EUS training should include reviews of cross-sectional anatomy, atlases of endoscopic or abdominal ultrasonography, videotaped teaching cases, and didactic courses in EUS. A combination of well-supervised EUS procedures and didactic teaching will aid in ensuring an adequate training experience as well as an overall understanding of endoscopic ultrasonography.

Training Evaluation: What Tools Are Available to Assess Competence?

Competency is defined as the minimum level of skill, knowledge, and/or expertise acquired through training and experience required to safely and proficiently perform a task or procedure [18]. Unfortunately, there have been few published reports regarding training of individuals in EUS or the number of procedures required to attain competence [12, 19–25]. A common goal for all gastroenterology training programs is the production of knowledgeable, experienced, and competent endoscopists. Although there exists a demand for qualified endosonographers, not all trainees should pursue advanced training due to both variations in individual skill level and regional manpower needs.

Competence in routine endoscopic procedures should be documented as it provides a vital foundation for advanced endoscopic training. Individuals wishing to pursue further training in EUS must have completed at least 24 months of a standard GI fellowship or demonstrate equivalent training [9].

Obviously, trainees in endoscopy develop skills at widely varying rates that can be evaluated by experienced endoscopists. Therefore, the use of an absolute or threshold number of procedures to demonstrate competence may be misleading and should be employed with caution in the evaluation of individual trainees. The minimum number of procedures required to achieve competency in EUS will vary based on the individual's skill level, understanding of ultrasound principles, and quality of the training experience. Performing an arbitrary number of procedures does not necessarily guarantee competency. Although the ASGE Standards of Practice Committee published a minimum number of procedures necessary to perform before assessing competency (Table 21.1), these numbers simply represent a minimum requirement and should serve only as a guide for evaluating individual trainees [26]. These numbers are derived from studies on training in EUS, published expert opinion, and consensus of the Ad Hoc EUS and Standards of Practice committees of the ASGE. Many if not most trainees will require procedure numbers in excess of these minimums. A prospective multicenter study of five advanced endoscopy trainees, without any previous EUS experience, evaluated the variation in learning curves for EUS [22]. This study showed substantial variability in achieving competency with some trainees requiring nearly double (or more in some cases) the minimum number of procedures required to achieve competency. Ideally, competency in both the technical and cognitive aspects of EUS should be gauged through direct observation by an experienced endosonographer.

A variety of tools and techniques have been proposed to assess competency in EUS. A recent study utilized a combination of a survey assessment tool designed to measure competence in EUS-FNA for mediastinal staging of non-small-cell lung cancer (NSCLC) in addition to direct expert observation and video-based performance review [25]. In this study, three advanced endoscopy trainees and three experienced endosonographers performed EUS-FNA on a total of 30 patients with proven or suspected NSCLC. The experienced endosonographers evaluated

the trainees by direct observation. Digital video recordings of these procedures were made and reviewed by the expert endosonographers in a blinded fashion 2 months later. They then completed a scoring sheet called the Endoscopic Ultrasound Assessment Tool (EUSAT). The EUSAT is a scoring sheet specifically created for the standardized assessment of EUS-FNA in mediastinal staging of NSCLC. The assessment consists of twelve items related to the techniques of endoscope insertion, identification and presentation of anatomical landmarks, and biopsy sampling. There was good intra-rater reliability for direct observation and blinded video recording, and the assessment tool provided an objective discrimination between trainees and expert physicians. These results suggest that objective assessment tools can be combined with direct supervision and video-based feedback to create a high-quality EUS training experience.

Areas of Competence for an Endosonographer

Competence in EUS requires both cognitive and technical skills [27], including an understanding of the appropriate indications for endoscopic ultrasound, conducting appropriate pre- and post-procedure evaluations, and managing procedure-related complications. Trainees must be able to perform the procedure in a safe and efficient manner while also recognizing and understanding the ultrasound images [28]. The ASGE recently published quality indicators for EUS summarized in Table 21.2.

Table 21.2 Quality Indicators for EUS by ASGE/ ACG Taskforce on Quality in Endoscopy [28]

Quality Indicator	Grade of recommendation	Goal (%)
Appropriate and documented indication	1C	>80
EUS-specific consent obtained and documented	3	>98
Appropriate antibiotics administered during FNA of cysts	2C	Not available
EUS performed by trained endosonographer	3	>98
Relevant structures as per indication documented	3	>98
*All gastrointestinal cancers staged with TNM staging system	3	>98
Size of pancreatic mass, vascular involvement, lymphadenopathy, and distant metastases documented	3	>98
EUS wall layers involved in subepithelial lesions documented	3	>98
EUS-FNA of distant metastases, ascites and lymph nodes and primary tumor when sampling both would alter management	1C	>98
Adequate sample for diagnosis in all solid lesions by EUS-FNA	3	≥85
*Adequate diagnostic rate and sensitivity for EUS-FNA of pancreatic mass	1C	Diagnostic rate ≥70 Sensitivity ≥85
Adverse events after EUS-FNA documented	3	>98
*Appropriate incidence of adverse events after EUS-FNA	1C	Acute pancreatitis <2% Perforation <0.5% Clinically significant bleeding <1%

*Priority indicators
ASGE: American Society for Gastrointestinal Endoscopy
ACG: American College of Gastroenterology
Definitions of grades of recommendation:
1C (clear benefit, based on observational studies, intermediate-strength recommendation, may change when stronger evidence available)
2C (unclear benefit, based on observational studies, very weak recommendation, alternative approaches likely to be better under some circumstances)
3 (unclear benefit, based on expert opinion only, weak recommendation, likely to change as data becomes available)

Cognitive Skills in EUS

Equally important as the technical training of endosonography is the cognitive training in EUS. The ASGE Training Committee recently published an EUS Core Curriculum summarizing the technical and cognitive aspects of training [8]. The curriculum should focus on a thorough understanding of the relevant anatomical and clinical aspects of EUS (Table 21.3). These include knowledge of the cross-sectional anatomy of the human body and understanding the principles of ultrasonography. The trainee must appreciate the basic principles by which ultrasound waves create an image through various media as well as the principles of Doppler imaging and how it is used to identify and differentiate vascular structures. EUS is used to stage malignancies, and the trainee must understand TNM staging and how staging is used to guide therapy. A thorough understanding of the indications, contraindications, individual risk factors, and benefit–risk considerations for individual patients must be demonstrated. Being able to clearly and accurately describe the procedure, its indications, and potential complications to patients and obtain informed consent is critical. The trainee should also understand the alternatives to EUS and their strengths and limitations. Acquiring skills in drafting an accurate, comprehensive, and easy-to-read EUS report is also important. The trainee must also demonstrate excellent interpersonal and communication skills. When EUS is used to diagnose and stage cancers, knowing how to communicate EUS findings in a compassionate and sensitive manner to the patient is imperative. Also, the trainee must be able to effectively communicate with the multidisciplinary team and participate in the coordination of patient care.

Table 21.3 EUS comprehensive curriculum [8]

Cross-sectional human anatomy
Principles of ultrasonography
Principles of oncology
TNM staging systems
Stage-directed therapy
Indications and risks of EUS
Alternatives to EUS
EUS terminology
EUS equipment: echoendoscopes and processors
Safe passage of the echoendoscope
EUS evaluation of structures
Interpretation of images and detection of pathology
Tissue sampling
Recognition and management of complications
Advanced techniques
Interpersonal and communication skills
System-based practice and improvement

Thorough knowledge of the technical features of the EUS processor, echoendoscopes, and accessories is vital to transition from training to future independent practice. The trainee must be agile enough to adapt to the EUS equipment that is available at the practice, which may be different from the equipment used during training. The sonographer should also be involved in decisions regarding EUS equipment purchase to ensure that appropriate equipment is available for a successful EUS practice, especially if EUS is being introduced into the practice for the first time.

Lastly, it is important for the trainee to understand and document quality measures of endosonography including the proper indication for performing EUS as well as adequate visualization and description of the anatomical structures relevant to the procedure's indication [8]. Evaluating quality measures such as the use of prophylactic antibiotics prior to FNA of a cystic lesion and the appropriate use of EUS-FNA is a necessary part of EUS training. Also, keeping a record of complication rates of EUS procedures (i.e. the incidence of pancreatitis, infection, or bleeding after FNA) is an essential part of EUS training and quality improvement.

Technical Skills in EUS

Technically, the trainee must be able to safely intubate the esophagus, pylorus, and duodenum to acquire the necessary images. EUS is performed in a variety of anatomical locations for various indications [29]. These indications include evaluation and staging of mucosally based neoplasms (esophagus, stomach, colon, and rectum), evaluation of subepithelial abnormalities, assessment

of the pancreas and pancreaticobiliary ducts, and performance of EUS-FNA.

Mucosal Tumors

A crucial component of an EUS training program is achieving proficiency in gastrointestinal tumor staging. Where available, EUS has become the standard of care in staging several gastrointestinal malignancies including esophageal, gastric, rectal, and pancreatic cancers. Accurate imaging of the lesion and recognition of surrounding lymphadenopathy, in particular the celiac axis region for upper tract cancers, are critical to the diagnosis and correct staging of mucosally based tumors. Evaluation of rectal cancers should include intubation of the sigmoid colon and identification of the iliac vessels. A prospective study reported competent intubation of the esophagus, stomach, and duodenum was achieved in 1–23 procedures (median 1–2), with visualization of the esophageal or gastric wall in 1–47 procedures (median 10–15) [19]. Adequate evaluation of the celiac axis region required 8–36 procedures (median 10–15).

Unfortunately, there are limited studies addressing the learning curve for staging mucosal tumors of the gastrointestinal tract. Only two studies have evaluated the learning curve in esophageal cancer staging. Fockens et al. [20] reported that adequate staging accuracy was achieved only after 100 examinations, while Schlick and colleagues [21] reported an 89.5 % T stage accuracy after a minimum of 75 cases. A survey of the American Endosonography Club in 1995 suggested an average of 43 cases for esophageal imaging, 44 for gastric, and 37 for rectal [19]. Once competence is achieved in one anatomic location, the threshold number of procedures for other anatomical locations may be reduced depending on the skill and training of the endosonographer. The ASGE currently recommends a minimum of 75 supervised cases, at least 2/3 in the upper GI tract, before competency for evaluating mucosal tumors can be assessed [26].

Determining the accuracy of tumor staging by a trainee is an important aspect of trainee evaluation as EUS staging potentially alters the clinical neoadjuvant/adjuvant treatment plan and surgical decisions. Studies in endosonographic staging of esophageal cancer suggested that at least 75–100 procedures were required before an acceptable level of accuracy was achieved [20, 21]. Ideally, the accuracy of EUS staging should be compared to a gold standard such as surgical pathology; however, surgical specimens are not always readily available, and any preoperative chemoradiation therapy may affect staging. In these circumstances, staging by a skilled and competent endosonographer should be considered the gold standard comparison for the trainee. The trainee should achieve accuracy in tumor staging comparable to published medical literature (Table 21.4) [8]. Appropriate documentation of all EUS procedures in a training log, along with review of surgical pathology results, will further assist in improving the accuracy of tumor staging. Furthermore, the implications of EUS findings in staging gastrointestinal malignancies must be incorporated into the whole treatment plan for each patient (i.e. surgical, medical, and/or radiation oncology referrals).

Table 21.4 Staging accuracy of EUS for common GI malignancies [3]

Indication	T stage (%)	N stage (%)
Esophageal cancer	85	79
Gastric cancer	78	73
Pancreatic cancer	90	75
Ampullary carcinoma	86	72
Rectal cancer	84	84

Subepithelial Abnormalities

Evaluation of subepithelial lesions has become a common indication for EUS. Discriminating between neoplasms, varices, enlarged gastric folds, and extrinsic compression from extramural masses can be performed with traditional echoendoscopes or catheter-based ultrasound probes. With the advent of the catheter-based probes, some practitioners have developed competency in subepithelial abnormalities without achieving competence in other indications for EUS. Although no studies are available for determining the threshold number of cases required to accurately assess subepithelial abnormalities, the ASGE Standards of Practice Committee current-

ly recommends a minimum of 40–50 supervised cases [30].

Pancreaticobiliary Imaging

Most endosonographers will agree that accurate imaging and interpretation of images of the pancreaticobiliary system including the gallbladder, bile duct, pancreatic duct, and ampulla are more technically challenging than evaluating mucosal and subepithelial lesions. For this reason, a larger volume of supervised pancreaticobiliary cases are required before competence can be adequately assessed. A multicenter, 3-year prospective study reported that adequate imaging of the pancreatic and bile ducts required 13–135 cases (median 55), while imaging of the pancreatic parenchyma required 15–74 cases (median 34) [31]. Adequate assessment of the ampulla required 13–134 cases (median 54). Although technical competence in pancreaticobiliary imaging may be achieved in less than 100 cases, a survey from the American Endosonography Club suggests that interpretive competence of pancreatic images may require additional procedures (120 cases) [19]. Other expert opinion suggests a higher threshold of 150 cases before assessing interpretative competence [27]. Currently, the ASGE Standards of Practice Committee recommends a minimum of 75 pancreaticobiliary cases before competency can be assessed [26].

EUS-FNA

EUS-FNA has emerged as an important diagnostic tool for obtaining tissue from intramural lesions, peri-gastrointestinal adenopathy, pancreatic lesions, and others [32]. Training in EUS-FNA requires knowledge of basic endoscopic ultrasound principles along with mastery of the skills necessary for obtaining and interpreting EUS images. Understanding and appreciating the complexity and risk that EUS-FNA adds to the procedure is critical for successful training. A recent study suggested that introducing trainees to EUS-FNA from the onset of training is a safe and feasible way to maximize exposure to FNA during training [24]. This is the first reported study evaluating the safety and diagnostic yield of EUS-FNA by attending supervised advanced endoscopy trainees. It found similar diagnostic yield comparing attending versus fellow FNA passes when the trainee is supervised. Unfortunately, the minimum number of FNA cases needed to achieve competence has not been studied. Due to the lack of literature supporting a threshold number for EUS-FNA, these numbers were adopted from the guidelines set forth for therapeutic ERCP. The similarities between EUS and ERCP including use of side-viewing instruments and combined endoscopic and radiologic imaging led to these recommendations. The current recommendation suggests that the trainee perform a minimum of 50 EUS-FNA procedures, split between non-pancreatic and pancreatic FNA [8]. It is generally agreed that EUS-FNA of pancreatic lesions carries higher complexity and risk for potential complications than other anatomical sites. Therefore, the number of pancreatic FNAs is considered separately from other anatomical locations. Competence in EUS-FNA of pancreatic lesions requires demonstrating proficiency in at least 75 pancreaticobiliary EUS cases in addition to 25 supervised FNA of pancreatic lesions. For non-pancreatic lesions (i.e. intramural lesions, lymph nodes, and ascites), the trainee should perform at least 25 supervised FNA cases before competency can be assessed [26]. Large clinical studies are needed to further assess the validity of these recommendations.

Advanced and Interventional EUS

In addition to the standard techniques used in EUS, a number of new advanced diagnostic and therapeutic EUS procedures have been described. EUS elastography has been used to analyze the tissue stiffness of solid pancreatic masses and may help differentiate benign and malignant lesions [32, 33]. When ERCP is unsuccessful, EUS-guided biliary and pancreatic access has been described as an alternative to percutaneous biliary drainage or surgery [34]. EUS has also been established in the drainage of symptomatic pancreatic fluid collections and walled-off pancreatic necrosis [35], and management of pancreatic pain by celiac plexus neurolysis and block [36]. EUS may also have a role in providing vascular access and therapy for conditions such as gastric variceal hemorrhage [37]. It is important to realize that many of these applications are still being

developed, and that there are no currently accepted training guidelines or competency criteria to allow for their evaluation during EUS training.

Comprehensive EUS Competence

Some practitioners may desire to acquire competence in only one or two areas of EUS and can therefore focus their efforts on specific anatomical locations as outlined above. However, for those practitioners aspiring to achieve competence in multiple areas of EUS, training must include exposure to a variety of procedures and clinical pathology. Once competence has been established in one area of EUS, the number of cases required to achieve competence in other areas is likely reduced. For trainees interested in only mucosal and subepithelial lesions, performing a minimum of 100 supervised cases is generally recommended [26]. Comprehensive EUS competence, including pancreaticobiliary imaging and FNA, requires a minimum of 150 cases, including 50 EUS-FNA and at least 75 pancreaticobiliary EUS although the recent study of learning curves amongst EUS-naive advanced endoscopy fellows suggests much greater numbers are necessary [15].

Credentialing in EUS

Credentialing is the process of assessing and validating the qualifications of a licensed independent practitioner to provide patient care. Determining qualifications for credentialing is based upon an assessment of the individual's current medical license, knowledge base, training and/or experience, current competence, and ability to independently perform the procedure or patient care requested. The ASGE has provided guidelines for credentialing and granting hospital privileges to perform routine gastrointestinal endoscopy [18]. Furthermore, the ASGE has also established guidelines for credentialing and granting privileges in EUS [26]. Credentialing for EUS should be determined separately from other endoscopic procedures such as sigmoidoscopy, colonoscopy, esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography, or any other endoscopic procedure. An endoscopist may be competent in one or more of these areas depending on his/her level of training and interest. Privileging in one or more of these areas may be considered separately, but training must be considered adequate in the areas for which privileging is requested. Determining competency and qualifications for credentialing can be challenging, as trained individuals possess varying degrees of skill in EUS along with recognized limitations. Nevertheless, providing a minimum number of procedures necessary prior to assessing competency (Table 21.1) creates some objective criteria for assessment in the credentialing process. As with credentialing in general gastrointestinal endoscopy, competency is ultimately assessed by the training director or other independent proctor.

Recredentialing and Renewal of EUS Privileges

Over time, physicians who have received appropriate privileges to perform EUS may change the scope of their clinical practice and subsequently reduce the frequency of performing endoscopic ultrasound procedures. It has been suggested that ongoing experience in advanced endoscopy is necessary to retain the technical skills required to safely and adequately perform these technically challenging procedures [38, 39]. The goal of recredentialing is to ensure continued clinical competence while promoting continuous quality improvement and maintaining patient safety. If ongoing experience is not maintained at some objective level, the quality of care provided to the patient may diminish, potentially leading to adverse events.

The ASGE has provided useful guidelines for renewing endoscopic privileges and assuring continued clinical competence in EUS [40]. However, it is the responsibility of each institution to develop and maintain individual guidelines for granting and renewing privileges. The threshold number of procedures necessary for recredentialing may vary among institutions; however, this threshold must be commensurate with the technical and cognitive skills required for advanced endoscopic procedures such as EUS.

Individual institutions must establish a frequency for the renewal process along with contingency plans when minimal competence cannot be assured. The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) has mandated that clinical endoscopic privileges be granted for no more than 2 years [41]. Endosonographers seeking renewal of privileges must document an adequate caseload over a set period of time in order to maintain the necessary skills required for EUS. This documentation may include procedure log books or patient records and should focus on objective measures such as number of cases, success rates, and complications. It is also important that endosonographers keep qualitative records of EUS, which may include indications for the procedure as well as any complication from FNA. Ongoing quality improvement efforts may be assessed as part of the recredentialing process and may include measurement of specific quality metrics and diagnostic yield of EUS-FNA [42] Continued cognitive training through participation in educational activities should also be a prerequisite for the renewal of privileges. New EUS procedures and clinical applications continue to emerge requiring a commitment to continued medical education within this specialized field.

Resources for Trainees and Continued Learning

There are several resources to complement the hands-on clinical training in EUS. Simulators can be very helpful in acquiring and practicing EUS skills and are discussed in detail below. In addition to several excellent traditional resources such as textbooks and journals, there is a plethora of potentially beneficial electronic resources. The ASGE maintains an Online Learning Center with various endoscopic videos and practice guidelines (https://www.extendmed.com/asge/) that are routinely updated. Several excellent EUS DVDs recorded by experts are also available from the ASGE through the Endoscopic Learning Library (http://www.asge.org/Education/). Of particular interest to the trainee or a practitioner new to EUS are the instructional videos that highlight the technique of examining a particular organ such as the pancreas or performing EUS-FNA. Similar resources are available through the United European Gastroenterology Society (www.e-learning.ueg.eu/home.html). In addition to the resources offered through the endoscopy societies, websites dedicated to the practice of endoscopy such as the Dave Project-Gastroenterology (daveproject.org) are also quite useful.

Simulators in Endoscopic Ultrasound

Endoscopic simulators have been developed for training in flexible sigmoidoscopy, EGD, colonoscopy, ERCP, and most recently EUS [43]. Since development of the first endoscopic mannequin simulator in the late 1960s [44], considerable technological advances have been made in endoscopic simulators. A variety of simulators are available today ranging from animal-based simulators (Erlangen Endo-Trainer; Erlangen Germany) to the computer-based simulators manufactured by CAE Healthcare (Endo VR Simulator; Montreal, Quebec, Canada) and Simbionix Corp. (GI Mentor II; Cleveland, OH) [45]. Validation studies and small, prospective, clinical trials assessing the utility of endoscopic simulators have been conducted for upper endoscopy, flexible sigmoidoscopy, and colonoscopy [46–52]. The benefits of simulator training have not been clearly demonstrated in EUS, emphasizing the need for further investigation with large, prospective trials. Nevertheless, this technology represents an exciting and potentially useful adjunct to formal endoscopic training.

Practicing EUS-FNA on a model prior to performing on a patient may potentially avoid safety and credentialing issues that would ordinarily limit the training endosonographer. Recently, a porcine training model for EUS-FNA of lymphadenopathy was reported [23]. The authors injected autologous blood admixed with carbon particles into the mediastinal lymph nodes of female pigs. After 2 weeks, the pigs were reexamined with EUS and demonstrated significant lymph node enlargement, thereby allowing

EUS-FNA of lymph nodes in various locations within the mediastinum. Training on this porcine model led to improved trainee performance in the accuracy, speed, and adequacy of sampling. This represents a potential in-vivo hands-on porcine model for future training in EUS-FNA.

Simbionix Corp. (www.simbionix.com) developed the first computer-based EUS simulator providing a platform for hands-on training and practice of EUS procedures (Fig. 21.1), [45]. The computer-based simulator generates ultrasound images in real time based on 3-dimensional anatomical models constructed from CT and MRI images from real patients. The trainee inserts a customized echoendoscope into the specially designed GI Mentor mannequin and simultaneously receives visual feedback from the monitor along with tactile sensation from scope maneuvering during the procedure. A highly sensitive tracking system translates position and direction of the camera into realistic computer-generated images. The EUS module enables the trainee to switch from endoscopic to ultrasound images in real time and also provides training in both radial and linear ultrasound. Split screen capability provides ultrasound images alongside three-dimensional anatomical maps further assisting in the interpretation and understanding of generated EUS images. The module also allows trainees to practice keyboard functions such as labeling of organs, magnifying images, changing frequencies, and measuring with calipers. Following completion of the examination, the computer software permits performance evaluation by reviewing all saved images (up to 50 frozen images per procedure) and indicating anatomy and landmarks that were improperly identified by the user.

Fig. 21.1 Simbionix GI-Mentor simulator

Although the Simbionix GI-Mentor II EUS training module presents an exciting approach to training in EUS, there are currently no published validation studies or clinical trials assessing EUS simulators. A small study was published on learning EUS using the new Erlangen Active Simulator for Interventional Endoscopy (EASIE-R) (ENDOSIM, LLC, Marlborough, MA) [53]. This simulator consists of a complete porcine gastrointestinal tract explant with surrounding structures including the bile duct and pancreas, all embedded in an ultrasound gel. Data were presented from a study examining the use of EASIE-R simulator during three EUS hands-on courses. A total of fifty-nine gastroenterologists who used the simulator completed a survey designed to assess the ease of using the simulator and provide initial evaluation data [54]. Over half the gastroenterologists surveyed had less than 1 year of experience with EUS. The simulator was described as realistic, easy to use, and useful for teaching EUS skills [55]. A novel 3-D printer generated polycarbonate dilated bile duct enabled ex vivo practice with EUS-guided biliary access. This model was judged as simulating real life by 71% of the experienced endosonographers and being at least suitable for all steps involved in EUS-guided biliary access except for stent placement. Although simulators represent useful educational tools, randomized controlled trials will be necessary to determine their validity in EUS training. Unfortunately, these simulators are not readily available at most training institutions due to cost restraints and regional needs.

Conclusion

EUS has become an important imaging tool for the evaluation of a variety of gastrointestinal disorders. It is a challenging endoscopic procedure

requiring both cognitive and technical skills beyond the general scope of traditional gastroenterology fellowship training. As the demand for skilled endosonographers continues to rise, training guidelines must be critically analyzed to assure the production of well-trained and competent future endosonographers. Although guidelines have been established for credentialing and granting privileges in EUS, additional studies of threshold numbers necessary to achieve competence are needed to fill existing gaps in the current literature. Endoscopists interested in learning EUS must recognize and appreciate the complexity of this procedure and risks for potential complications. Clearly, a 1- 2-week course in EUS is inadequate training and may potentially expose patients to unnecessary risks and poor quality of care. For those truly interested in mastering the skills required for EUS, a formal supervised Advanced Endoscopy fellowship training program is far superior to hands-on workshops, teaching videotapes, simulators, and inadequate exposure during a standard GI fellowship.

There are several traditional and electronic resources to complement hands-on clinical training, and it is recommended that trainees and practitioners utilize these resources for continued learning. Simulators for training in EUS represent an exciting and useful adjunct to supervised instruction. Although clinical trials investigating the efficacy of simulators in EUS training are lacking, the potential applications for this technology are promising. Unfortunately, these simulators are not readily available at most institutions due to cost restraints and regional needs. Further studies are necessary to determine the role of endoscopic simulators in EUS training.

Key Points

- Achieving proficiency in EUS typically requires additional training beyond the traditional 3-year Gastroenterology fellowship program. This most commonly involves an additional year of advanced endoscopy training.
- The American Society for Gastrointestinal Endoscopy (ASGE) has published minimum procedure numbers before competency can be assessed in EUS procedures and proposed an EUS core curriculum which can serve as a guide in the training process.
- Being expert in EUS involves achieving competency in both the technical and cognitive aspects, and this should ideally be gauged through direct observation by an experienced endosonographer.
- Pancreaticobiliary EUS is usually technically more challenging and may require a higher volume of cases to achieve proficiency.
- Several educational resources, including books and videos, are widely available as complements to supervised clinical training.
- Simulators, though in their infancy for EUS, are increasingly available and can be useful adjuncts to clinical training.

References

1. Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology. [Comparative Study]. 1994;190(3):745–51.
2. Eisen GM, Dominitz JA, Faigel DO, Goldstein JA, Petersen BT, Raddawi HM, et al. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc. [Guideline Practice Guideline]. 2001;54(6):811–4.
3. Van Dam J, Brady PG, Freeman M, Gress F, Gross GW, Hassall E, et al. Guidelines for training in electronic ultrasound: guidelines for clinical application. From the ASGE. American Society for Gastrointestinal Endoscopy. Gastrointest Endosc. [Guideline Practice Guideline Review]. 1999;49(6):829–33.
4. Palazzo L, Roseau G, Gayet B, Vilgrain V, Belghiti J, Fekete F, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. Results of a prospective study with comparison to ultrasonography and CT scan. Endoscopy. [Comparative Study]. 1993;25(2):143–50.
5. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology. [Clinical Trial Multicenter Study]. 1997;112(4):1087–95.
6. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Lehman GA. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. Gastrointest Endosc. 1997;45(3):243–50.

7. Hecht JR, Farrell JJ, Senzer N, Nemunaitis J, Rosemurgy A, Chung T, et al. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. Gastrointest Endosc. [Clinical Trial, Phase I Clinical Trial, Phase II Multicenter Study]. 2012;75(2):332–8.
8. DiMaio CJ, Mishra G, McHenry L, Adler DG, Coyle WJ, Dua K, et al. EUS core curriculum. Gastrointest Endosc. 2012;76(3):476–81.
9. Eisen GM, Dominitz JA, Faigel DO, Goldstein JL, Kalloo AN, Petersen BT, et al. Guidelines for advanced endoscopic training. Gastrointest Endosc. [Guideline Practice Guideline]. 2001;53(7):846–8.
10. Parada KS, Peng R, Erickson RA, Hawes R, Sahai AV, Ziogas A, et al. A resource utilization projection study of EUS. Gastrointest Endosc. [Multicenter Study Research Support, Non-U.S. Gov't]. 2002;55(3):328–34.
11. Polkowski M, Larghi A, Weynand B, Boustiere C, Giovannini M, Pujol B, et al. Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) technical guideline. Endoscopy. 2012;44(2):190–206.
12. Nayar M, Joy D, Wadehra V, Oppong K. Effect of dedicated and supervised training on achieving competence in EUS-FNA of solid pancreatic lesions. Scand J Gastroenterol. [Comparative Study]. 2011;46(7/8):997–1003.
13. Savides TJ, Fisher AH Jr, Gress FG, Hawes RH, Lightdale CJ. 1999 ASGE endoscopic ultrasound survey. ASGE Ad Hoc Endoscopic Ultrasound Committee. Gastrointest Endosc 2000;52(6):745–50.
14. Eloubeidi MA, Tamhane A. EUS-guided FNA of solid pancreatic masses: a learning curve with 300 consecutive procedures. Gastrointest Endosc. [Comparative Study]. 2005;61(6):700–8.
15. Wani S, Hall M, Keswani RN, Aslanian HR, Casey B, Burbridge R, Chak A Chen AM, Cote G, Edmundowicz SA, Faulx AL, Hollander TG, Lee LS, Mullady D, Murad F, Muthusamy VR, Pfau PR, Scheiman JM, Tokar J, Wagh MS, Watson R, Early D. Variation in aptitude of trainees in endoscopic ultrasonography based on cumulative sum analysis. Clin Gastroenterol Hepatol. 2014 Nov 14. Epub ahead of print.
16. Azad JS, Verma D, Kapadia AS, Adler DG. Can U.S. GI fellowship programs meet American Society for Gastrointestinal Endoscopy recommendations for training in EUS? A survey of U.S. GI fellowship program directors. Gastrointest Endosc. 2006;64(2):235–41.
17. Eloubeidi MA. Developing an academic EUS program: the University of Alabama at Birmingham experience. Gastrointest Endosc. 2007;65(7):1039–41. Discussion.
18. Eisen GM, Baron TH, Dominitz JA, Faigel DO, Goldstein JL, Johanson JF, et al. Methods of granting hospital privileges to perform gastrointestinal endoscopy. Gastrointest Endosc. [Guideline]. 2002;55(7):780–3.
19. Hoffman BJ, Hawes RH. Endoscopic ultrasound and clinical competence. Gastrointest Endosc Clin N Am. 1995;5(4):879–84.
20. Fockens P, Van den Brande JH, van Dullemen HM, van Lanschot JJ, Tytgat GN. Endosonographic T-staging of esophageal carcinoma: a learning curve. Gastrointest Endosc. 1996;44(1):58–62.
21. Schlick T, Heintz A, Junginger T. The examiner's learning effect and its influence on the quality of endoscopic ultrasonography in carcinoma of the esophagus and gastric cardia. Surg Endosc. 1999;13(9):894–8.
22. Wani S, Cote GA, Keswani R, Mullady D, Azar R, Murad F, 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(4):558–65.
23. Fritscher-Ravens A, Cuming T, Dhar S, Parupudi SV, Patel K, Ghanbari A, et al. Endoscopic ultrasound-guided fine needle aspiration training: evaluation of a new porcine lymphadenopathy model for in vivo hands-on teaching and training, and review of the literature. Endoscopy. 2013;45(2):114–20.
24. Cote GA, Hovis CE, Kohlmeier C, Ammar T, Al-Lehibi A, Azar RR, et al. Training in EUS-guided fine needle aspiration: safety and diagnostic yield of attending supervised, trainee-directed FNA from the onset of training. Diagn Ther Endosc. 2011;2011:378540.
25. Konge L, Vilmann P, Clementsen P, Annema JT, Ringsted C. Reliable and valid assessment of competence in endoscopic ultrasonography and fine-needle aspiration for mediastinal staging of non-small cell lung cancer. Endoscopy. [Validation Studies]. 2012;44(10):928–33.
26. Eisen GM, Dominitz JA, Faigel DO, Goldstein JA, Petersen BT, Raddawi HM, et al. Guidelines for credentialing and granting privileges for endoscopic ultrasound. Gastrointest Endosc. [Guideline Practice Guideline]. 2001;54(6):811–4.
27. Boyce HW Jr. Training in endoscopic ultrasonography. Gastrointest Endosc. 1996; 43(2 Pt 2):12–5.
28. Wani S, Wallace MB, Cohen J, Pike IM, Adler DG, Kochman ML, Lieb JG 2nd, Park WG, Rizk MK, Sawhney MS, Shaheen NJ, Tokar JL. Quality indicators for EUS. Gastrointest Endosc. 2015;81:67–80.
29. Chak A, Cooper GS. Procedure-specific outcomes assessment for endoscopic ultrasonography. Gastrointest Endosc Clin N Am. [Review]. 1999;9(4): 649–56, vii.
30. Adler DG, Bakis G, Coyle WJ, DeGregorio B, Dua KS, Lee LS, et al. Principles of training in GI endoscopy. Gastrointest Endosc. [Practice Guideline]. 2012;75(2):231–5.
31. Hoffman BJ, Wallace MB, Eloubeidi MA, Sahai AV, Chak A, van Velse A, et al. How many supervised

procedures does it take to become competent in EUS? Results of a multicenter three year study. Gastrointest Endosc. 2000;51:AB139.
32. American Society of Gastrointestinal Endoscopy. Technology Assessment status evaluation: tissue sampling during endosonography. 1998;47(6):576–8.
33. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology. 2010;139(4):1172–80.
34. 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. 48:80–7.
35. Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. Gastroenterology. 2013;145(3):583–90 e1.
36. Levy MJ, Topazian MD, Wiersema MJ, Clain JE, Rajan E, Wang KK, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct ganglia neurolysis and block. Am J Gastroenterol. [Comparative Study]. 2008;103(1):98–103.
37. Romero-Castro R, Pellicer-Bautista F, Giovannini M, Marcos-Sanchez F, Caparros-Escudero C, Jimenez-Saenz M, et al. Endoscopic ultrasound (EUS)-guided coil embolization therapy in gastric varices. Endoscopy. 2010;42(Suppl 2):E35–6.
38. Cass OW. Objective evaluation of competence: technical skills in gastrointestinal endoscopy. Endoscopy. 1995;27(1):86–9.
39. Jowell PS, Baillie J, Branch MS, Affronti J, Browning CL, Bute BP. Quantitative assessment of procedural competence. A prospective study of training in endoscopic retrograde cholangiopancreatography. Ann Intern Med. 1996;125(12):983–9.
40. Dominitz JA, Ikenberry SO, Anderson MA, Banerjee S, Baron TH, Cash BD, et al. Renewal of and proctoring for endoscopic privileges. Gastrointest Endosc. 2008;67(1):10–6.
41. Joint Commission on Accreditation of Healthcare Organizations. Comprehensive accreditation manual for hospitals: the official handbook, management of the environment of care chapter. (Revisions appear in italics and become effective Jan. 1, 1998.). Joint Commission perspectives Joint Commission on Accreditation of Healthcare Organizations. 1997;17(1):EC7–9.
42. Savides TJ, Donohue M, Hunt G, Al-Haddad M, Aslanian H, Ben-Menachem T, et al. EUS-guided FNA diagnostic yield of malignancy in solid pancreatic masses: a benchmark for quality performance measurement. Gastrointest Endosc. [Multicenter Study Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2007;66(2):277–82.
43. Desilets DJ, Banerjee S, Barth BA, Kaul V, Kethu SR, Pedrosa MC, et al. Endoscopic simulators. Gastrointest Endosc. 2011;73(5):861–7.
44. Markman HD. A new system for teaching proctosigmoidoscopic morphology. Am J Gastroenterol. 1969;52(1):65–9.
45. Gerson LB. Evidence-based assessment of endoscopic simulators for training. Gastrointest Endoscopy Clin N Am. [Review]. 2006;16(3):489–509, vii–viii.
46. Hochberger J, Maiss J. Currently available simulators: ex vivo models. Gastrointest Endosc Clin N Am. [In Vitro Review]. 2006;16(3):435–49.
47. Verdaasdonk EG, Stassen LP, Monteny LJ, Dankelman J. Validation of a new basic virtual reality simulator for training of basic endoscopic skills: the SIMENDO. Surg Endosc. [Multicenter Study Randomized Controlled Trial]. 2006;20(3):511–8.
48. Sedlack RE, Kolars JC, Alexander JA. Computer simulation training enhances patient comfort during endoscopy. Clin Gastroenterol Hepatol. [Comparative Study Research Support, Non-U.S. Gov't]. 2004;2(4):348–52.
49. Sedlack RE. The state of simulation in endoscopy education: continuing to advance toward our goals. Gastroenterology. 2013;144(1):9–12.
50. Kefalides PT, Gress F. Simulator training for endoscopic ultrasound. Gastrointest Endosc Clin N Am. [Review]. 2006;16(3):543–52, viii.
51. Gromski MA, Matthes K. Simulation in advanced endoscopy: state of the art and the next generation. Techniques Gastrointest Endosc. 2011;13:203–8.
52. Pawa R, Chuttani R. Benefits and limitations of simulation in endoscopic training. Techniques Gastrointest Endosc. 2011;13:191–8.
53. Yusuf TE, Matthes K, Lee Y, Goodman AJ, Robbins DH, Stavropoulos S, Gress FG. Evaluation of the EASIE-R simulator for the training of basic and advanced EUS. Gastrointest Endosc. 2009;69:S264.
54. Gromski MA, Brugge WR, Chuttani R, Sawhney M, Gress F, Matthes K. Development and evaluation of a novel endoscopic ultrasound (EUS) simulator. Digestive disease week, New Orleans, LA. 2010.
55. Dhir V, Itoi T, Fockens P, Perez-Miranda M, Khashab MA, Seo DW, Yang AM, Lawrence KY, Maydeo A. 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.

Equipment and Approach

22

Ali A. Siddiqui, Anna Strongin, Andrew Kistler and Mohamad A. Eloubeidi

Introduction

Over the past decade, endoscopic ultrasound (EUS) has evolved to be a first line modality for diagnostic and therapeutic procedures in managing gastrointestinal conditions. Among its many applications, EUS has been shown to be particularly effective for cancer staging, pseudocyst drainage, fine-needle aspiration (FNA), and celiac plexus neurolysis. Given the variety of indications for EUS, the technology has been adapted to perform multiple functions. Current echoendoscopes have the capacity for excellent resolution and are accompanied by a wide array of accessories, including needles and miniprobes. This chapter will discuss the various EUS equipment in detail, addressing how it works, when it should be used, and who makes it.

Echoendoscopes

General Echoendoscope Design: How Are Images Generated by EUS?

Endoscopic ultrasonography is an effective tool for accurate visualization of intra- and extraluminal structures within and around the gastrointestinal tract as well as for performing FNA. Currently, two types of echoendoscopes are commercially available: radial array and curved linear array. Although several differences exist between the two, both in terms of the technology and applications, the basic components are the same.

The most integral part of any echoendoscope is the ultrasound transducer, which generates the images. The transducer is composed of thousands of piezoelectric crystals. These crystals can vibrate at different frequencies, emitting sound waves that travel through space until they reflect off a given tissue back to the crystal. The returning sound wave (i.e., the echo) vibrates the crystal that emitted it in the first place and the vibration is converted into electrical current, which then travels to the processor and is converted into an image. Structures that have a higher density, such as solid organs or bone, will reflect more sound waves and appear brighter on ultrasound images, while lower density tissues, such as hollow organs or air-filled cavities, will reflect a smaller percentage of the sound waves, and appear darker. A single piezoelectric crystal would generate an image of a very thin line of tissue, but an array of thousands of these crystals together allows for many adjacent "lines" to be generated at the same time and summated into a complete image.

In order for this ultrasound technology to be effective, air interference between the probe and the tissue needs to be minimized. When using transcutaneous ultrasound, lubricating gel is applied to the body to address this problem. To

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achieve a similar effect during EUS, the scope is equipped with the ability to inflate and deflate a water-filled balloon around the transducer.

All echoendoscopes are equipped with a light source and a water irrigation system for cleaning the objective lens. A high-resolution video chip is also incorporated into every model. Its purpose is to electronically transmit the images visualized by the objective lens onto a monitor, creating real-time video footage of the gastrointestinal lumen as the scope is advanced. In addition, each scope has an instrument channel, which is used for introducing different equipment into the gastrointestinal lumen. The size of this channel varies depending on whether the echoendoscope is radial array or curved linear. The latter type tends to have larger diameter channels to accommodate the needles used in FNA, drainage, or other procedures. With the linear array echoendoscopes, the instrument channel also has an adjacent elevation function, which allows the adjustment of the needle position after it advances into the lumen without moving the scope itself. It is also worth noting that although these components are present in all of the scopes, the instrument channel, water nozzle, and light source are all located proximal to the transducer in the Olympus models and distal to the transducer, at the very tip of the scope, in the Pentax models.

What are the Differences Between Radial and Linear Echoendoscopes?

Radial Echoendoscopes

The radial echoendoscope has the capacity for very accurate and complete visualization of the gastrointestinal tract (Fig. 22.1). To achieve this effect, the ultrasound transducer is positioned perpendicular to the long axis of the scope, which allows for a 360° cross-sectional view, analogous to images obtained with cross-sectional computed tomography (CT) scans. However, since the transducer is unable to provide a longitudinal view, the scope cannot be used for performing FNA because there is no way to directly visualize the needle in real time as it is advanced out of the scope and into the lumen.

Fig. 22.1 Radial echoendoscope

Radial echoendoscopes can be subdivided into two types: mechanical and electronic (Table 22.1). The mechanical echoendoscope is the predecessor of the electronic technology and currently Olympus is the only company to produce a mechanical model. It contains a transducer with a single piezoelectric element that physically rotates perpendicular to the long axis of the scope generating circumferential, 2D (or B-mode) ultrasonographic images of the gastrointestinal mucosa and underlying structures. Earlier models designed the motor to be part of the operating handle, which made the equipment very heavy. However, more recent models have moved the motor to the base of the cord, which makes the echoendoscope lighter and easier to use.

The echoendoscope can operate at one of four frequencies, ranging from 5 to 20 mHz. Lower frequencies are ideal for viewing organs located further away from the scope, such as components of the pancreaticobiliary system, while higher frequencies can be used for up-close, detailed assessment of nearer structures, such as the gastrointestinal wall and its layers. Although the quality of these images is fairly good, the technology does create several disadvantages. First and foremost, the fact that the transducer is composed of multiple, mechanical parts makes the scope more prone to technical malfunctions and frequent repairs. In addition, since the transducer needs to physically rotate, it has a plastic cap filled with oil to lubricate and protect the mechanism. However, the oil and cap interfere with the ultrasound signals, creating ring-like artifacts that can impede visibility. Finally, mechanical radial echoendoscopes do not have Doppler or video

Table 22.1 Characteristics of current radial echoendoscopes

Radial echoendoscopes							
Brand	Model	Type	Field of view	Scanning range	Display mode	Frequency (MHz)	Channel diameter (mm)
Olympus	GF-UM160	Mechanical	100°	360°	B-mode	6/9/10/20	2.2
	GF-UE160-AL5	Electronic	100°	360°	B-mode, M-mode, D-mode, color Doppler, power Doppler	5/6/7.5/10	2.2
Pentax	EG-3670URK	Electronic	140°	360°	B-mode, color Doppler	5/7.5/10	2.4
Fujinon	EG-530UR2	Electronic	140°	360°	B-mode, M-mode, color Doppler, power Doppler	5/7.5/10/12	2.2

capabilities, which restricts the type of information that can be obtained from the images.

To overcome these limitations, an electronic radial echoendoscope was developed. Like its mechanical counterpart, this technology utilizes transducers that create a transverse view of the gastrointestinal tract. However, instead of the rotating technology, the scope's transducer has its crystals arranged in a fixed, circular array, which eliminates a lot of artifact and produces better quality images. In addition, the electronic echoendoscope is equipped with Doppler and tissue harmonic imaging (THI) capabilities. Power and color Doppler technology allows for accurate identification of the vasculature and evaluation of blood flow through tissue. THI is an ultrasound method that receives only second harmonic acoustic signals transmitted through the various tissues of the body, which are subsequently reconstructed into images. Multiple studies have shown that ultrasound systems utilizing the second harmonic increase the sound-to-noise ratio and reduce artifact, thus optimizing the resolution of the images created [1, 2].

Initially, the biggest disadvantage of the electronic radial echoendoscope was the ability to create only a 270° view, leaving behind a 90° "blind spot." However, this issue was resolved within the past several years with the development of a 360° scope. As a result of these technological advances, the electronic echoendoscope was consistently found superior to the mechanical echoendoscope for visualizing structures within the gastrointestinal tract, in both prospective and retrospective studies [3–5].

Curved Linear Echoendoscopes

The curved linear echoendoscope has imaging capabilities similar to those of the electronic radial echoendoscope, with the advantage of being able to perform procedures such as FNA, cystgastrostomy, and celiac plexus neurolysis (Fig. 22.2). The ultrasound transducer is oriented at an oblique angle to the long axis of the scope, which allows direct, real-time visualization of the needle as it emerges from the instrument channel at the same angle as the transducer. However, this advantage comes at the expense of the scanning range, which is limited to 120–180° at a time, depending on the model (Table 22.2). Therefore, the scope must be manually rotated by the operator to obtain a complete circumferential view.

Theoretically, this may create certain limitations for this type of echoendoscope, as it requires an operator with a more advanced level of experience and cannot generate complete, circumferential images. However, the clinical implications of the differences between the two scopes remain unclear. Several studies have compared the imaging capabilities of the linear and radial technologies in diagnosing and staging various gastrointestinal

Fig. 22.2 Linear echoendoscope with needle emerging from the tip

Table 22.2 Characteristics of current linear array echoendoscopes

Linear array echoendoscopes							
Brand	Model	Viewing direction	Field of view	Scanning range	Display mode	Frequency (MHz)	Channel diameter (mm)
Olympus	GF-UC160P-OL5	55° forward oblique	100°	150°	B-mode, color Doppler, power Doppler	7.5	2.8
	GF-UCT160-OL5	55° forward oblique	100°	150°	B-mode, color Doppler, power Doppler	7.5	3.7
	GF-UC140P-AL5	55° forward oblique	100°	180°	B-mode, M-mode, D-mode, color Doppler, power Doppler	5/6/7.5/10	2.8
	GF-UC140T-AL5	55° forward oblique	100°	180°	B-mode, M-mode, D-mode, color Doppler, power Doppler	5/6/7.5/10	3.7
	GF-UCT180	55° forward oblique	100°	180°	B-mode, M-mode, D-mode, color Doppler, power Doppler, flow mode	5/6/7.5/10	
Pentax	EG-3870UTK	50° forward oblique	120°	120°	B-mode, color Doppler	5/6//7.5/10	3.8
Fujinon	EG-530UT2	40° forward oblique	140°	124°	B-mode, M-mode, color Doppler, power Doppler	5/7.5/10/12	3.8

malignancies, but those have yielded mixed results, with the majority concluding that the two types of scopes were equivalent [6–10].

Although these oblique viewing echoendoscopes have proven both effective and efficient, a new class of forward viewing models is currently being developed to improve upon the original technology. The ultrasound transducer on these echoendoscopes faces straight forward and has a scanning angle of 90°. The instrument channel is positioned so that a needle advanced through it will emerge straight out, parallel to the long axis of the scope, rather than at an angle. The potential advantage of this setup is the ability to perform a targeted puncture of certain lesions, such as those in the uncinate or head of the pancreas, that may be difficult to access by a needle deployed at an angle. In addition, a needle that emerges in a straight line enables more efficient transmission of force compared to an angled needle when puncturing through tissue. And finally, a straight instrument channel without an adjacent elevator function allows for a bigger diameter, which, in turn, can accommodate larger bore needles or other devices.

However, these benefits must be weighed against the smaller scanning range of the forward viewing echoendoscope as well as the absence of the elevator function, which may decrease the accuracy during a needle puncture. To date, only several small studies with very small cohorts have evaluated the forward viewing linear echoendoscopes as the technology is still fairly new. Overall, all the studies seemed to conclude that the forward viewing and oblique viewing technologies are essentially equivalent, both in terms of imaging accuracy and success of therapeutic and diagnostic procedures [11–13]. However, more prospective, randomized controlled trials with larger cohorts are needed to assess more definitively the potential advantages of the newer forward viewing technology.

Endoscopic Ultrasound Processors

How Can We Adjust the Settings of the Echoendoscope Processors to Obtain Optimal Imaging?

As described above, echoendoscopes are equipped with multiple capabilities that can be

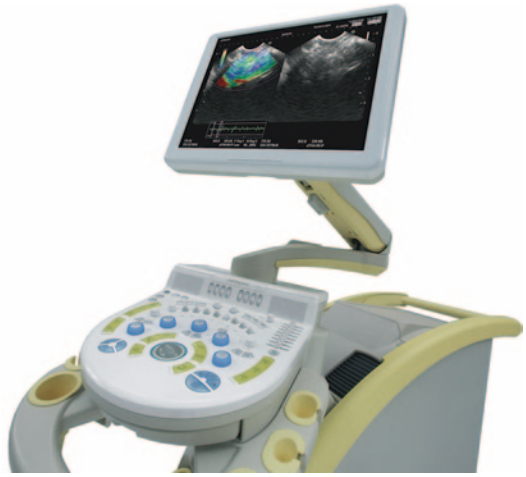

Fig. 22.3 EUS processor (Hi Vision Preirus, Hitachi Aloka Medical, Wallingford, CT)

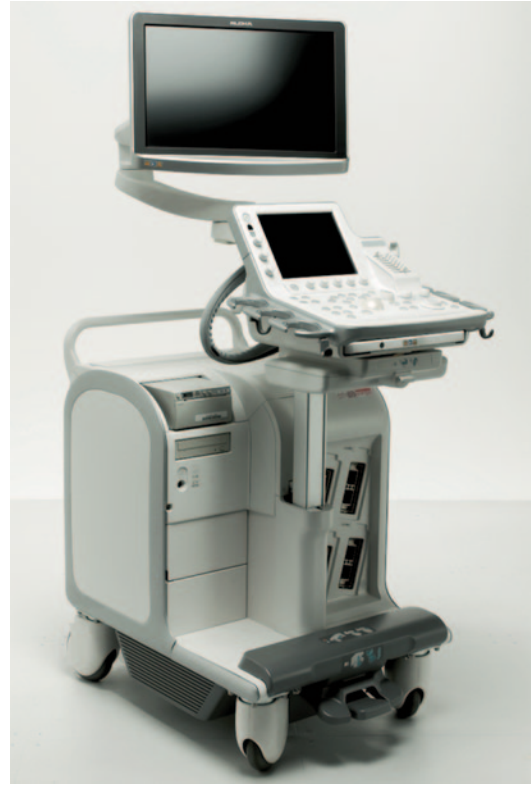

Fig. 22.4 EUS processor (ProSound F75, Hitachi Aloka Medical, Wallingford, CT)

manipulated by the available ultrasound processors. The endoscope companies have paired with ultrasound manufacturers to develop platforms for their echoendoscopes. Both Pentax and Olympus have partnered with Hitachi Aloka to generate different platforms for their own company's scopes (Hi Vision Preirus processor for Pentax scopes and ProSound F75 for Olympus scopes, Figs. 22.3 and 22.4). Fujinon also owns its own processor (SU-8000). The main goals when performing EUS are to minimize artifacts, optimize visibility of structures, and utilize the available Doppler technology. Most of the current echoendoscope processors have several different ultrasound modalities. The B-mode generates 2D images in rapid succession to create real-time imaging of anatomic structures.

When utilizing the B-mode, the GAIN knob can be used to change amplification of all echoes. By turning the gain higher or lower, the brightness of an image can be increased or decreased, respectively. Increasing the gain too high in order to brighten weak echoes can inadvertently brighten artifactual echoes as well, which decreases contrast between structures and blurs the image. The ultrasound processor also contains the time-gain compensation (TGC) function, which is used to improve image uniformity. As ultrasound waves travel through various tissues, they are attenuated due to absorption, scattering, and reflection. In general, the processor compensates for this phenomenon with amplification of echoes of deeper structures under the assumption of uniform attenuation. However, if the tissue has very low density, such as cysts, or very high density, such as blood or liver, this amplification effect can over- or undercompensate for the attenuation. TGC is composed of multiple sliding knobs, each corresponding to a different tissue depth that can be moved left to right to adjust the gain of inappropriately bright or dark portions of an image, creating a more uniform and accurate picture [14].

Evaluation of a particular target can be further optimized using the depth and frequency functions. The depth/range knob can increase or decrease the depth of the viewing field, while different frequencies can be used for finding a particular structure. Most of the current echoendoscopes operate at four different frequencies, 5,

6, 7.5, and 10 mHz. The lower frequencies allow better penetration to the deeper organs at the expense of resolution, which facilitates cursory scanning through multiple structures and organs at one time. Once a specific target is identified, a higher frequency mode can be selected to obtain finer resolution and further characterize the area of interest. The zoom function can be applied when the operator needs magnification. This may be particularly useful for evaluating small structures and distances, especially if they need to be measured accurately. The focus button can be used to converge the ultrasound beam onto a particular point in the image, which can improve lateral resolution. The freeze button allows the image to be frozen and a cine function allows the endosonographer to scroll back over the previous several seconds of images.

The EUS processor also has the capability to evaluate the vasculature. The color Doppler mode allows the assessment of blood flow direction and velocity. The red color generally represents blood flow toward the transducer, while the blue color represents blood flow away from the transducer. The angle between the US wave and the direction of the flow (also known as the insonation angle) should be less than 60° to create a good signal and maximize accuracy of blood flow measurement. If that angle is higher, and especially as it approaches 90°, the perpendicular orientation precludes any blood flow from being detected at all. The angle knob allows adjustments to the angle. When assessing very small vessels, the power Doppler is available. This setting can be very useful during FNA by assisting the endoscopist to avoid blood vessels during puncture, minimizing bleeding risk. Power Doppler, however, cannot provide information about direction of flow or velocity.

Velocity can be measured using the pulsed wave spectral Doppler (PW). A gate is placed inside the blood vessel of interest and flow through the gate is detected as the rate at which the frequency changes, which is subsequently converted into velocity by the fast Fourier transform. The range of the gate can be modified with the sample volume button. Decreasing the sample volume may be helpful when measuring flow in very small vessels or a specific portion of the vessel, while increasing it may be more optimal for evaluating flow in larger arteries and veins, where accurate velocity would be the mean of all the velocities in the vessel. When using larger sample volume, it is also important to appreciate the possibility of detecting artifactual flow information from adjacent vessels. This can be addressed by the Doppler filter function, which removes low-frequency noise. A low-filter setting can be used when analyzing low-flow structures within nonmoving tissue, but it does leave behind some wall noise. High-filter settings are better equipped for high-flow systems within tissue that has an element motion, but may fail to detect lower velocities along the walls of the vessel, which would result in calculating artificially high mean velocity.

What New Technologies Are Available to Improve Endoscopic Ultrasound Imaging?

Contrast-enhanced Ultrasonography

Contrast-enhanced ultrasonography (CE-EUS) is a newer accessory tool for electronic radial and linear echoendoscopes, which allows more accurate characterization of gastrointestinal tumors based on their microvascular patterns. This technique involves injecting a peripheral vein with a contrast agent composed of gas-filled microbubbles enveloped in an albumin or phospholipid shell [15]. After injection, the Doppler or THI functions of the echoendoscope can be used to assess vascular flow in the area of interest. Color or power Doppler accurately identifies hyper- and hypovascular structures, while harmonic imaging evaluates both the extent of the vasculature as well as parenchymal perfusion [16, 17]. In pancreaticobiliary tumors, CE-EUS has been shown to be superior to standard EUS in differentiating different types of neoplasms, distinguishing malignant from benign lymph nodes, and more accurately determining the depth of tumor invasion [18–23].

3D Endoscopic Ultrasound

3D ultrasonography is another relatively new tool for endoscopic imaging that reconstructs a sequence of 2D images into multiplanar structures. To ensure accuracy of the reconstruction, the angle and position of the echoendoscope during every acquired 2D image need to be known and the images must be obtained in a rapid sequence to minimize motion artifact [24]. This is easily accomplished with an electronic radial echoendoscope, because an axial view is generated without the need for manual rotation. With linear array echoendoscopes, obtaining an accurate 3D view can be more difficult, as manual rotation of the scope along its longitudinal axis can introduce artifact or error if certain areas are missed [25]. Therefore, operator experience is an integral part of generating accurate 3D representations of the anatomy. Once all the 2D images of interest are obtained, specialized software will import each digitized picture into its appropriate location within a 3D grid, ultimately creating a complete image of the area of interest. Currently, 3D imaging has been shown advantageous for characterizing rectal neoplasms, though this technology has yet to be utilized on a broad scale for evaluating other types of gastrointestinal malignancies, especially pancreatic cancer [26–28].

Endoscopic Ultrasound Elastography

Elastography is a method of determining real-time tissue stiffness, which is a property that can help distinguish malignant from benign lesions. Specialized software is used to measure stiffness by analyzing the changes in EUS images due to vascular pulsations and respiratory movements during tissue compression [29]. This information can then be translated into the degree of elasticity, either as a qualitative or quantitative measure. Qualitative elastography is based on the detection of the degree of tissue compressibility and converting that information into a color scheme overlying the B-image. In this setup, the color blue represents hard tissue, green/yellow is intermediately hard tissue, and red depicts soft tissue; harder tissue corresponds to a higher likelihood of a malignant lesion [30, 31]. Quantitative elastography is a more objective technique that involves converting the differences between tissue elasticity into a strain ratio, which may increase accuracy for differentiating benign from malignant lesions [32, 33]. To date, this software has been primarily employed in evaluating pancreatic masses and further studies are awaited to assess the value of this technique in assessing malignancies of the hepatobiliary tract.

Ultrasound Miniprobes

What Are the Advantages and Limitations of Echoendoscope Miniprobes?

As the applications of EUS continued to grow in the late 1980s, a more streamlined process along with higher resolution images was necessary [34, 35]. One important advancement in the world of EUS was the development of ultrasound miniprobes, also known as high frequency ultrasound sonography (HFUS) (Table 22.3, Fig. 22.5). Miniprobes were aimed at combining endoscopy and EUS in one continuous process, compared with what was considered “traditional” EUS, which encompassed two separate procedures with endoscopy followed by EUS. By passing the miniprobe down the accessory channel of the endoscope, it allowed the gastroenterologist to combine endoscopy and EUS into one procedure. In addition to providing this advantage, the technology behind miniprobes also focused on improving resolution in order to help discern between inflammatory and oncologic processes [36]. Miniprobes also gave gastroenterologists new access through tighter strictures and bile ducts, leading to a more detailed exploration of anatomy previously unavailable to EUS.

Miniprobes provide high-resolution radial images that can be used during upper endoscopy, enteroscopy, colonoscopy, and endoscopic retrograde cholangiopancreatography (ERCP). In addition to radial images, some miniprobes have dual reconstruction abilities, which provide both

Table 22.3 Ultrasound miniprobes. (Adapted from Liu et al. [37])

Company	Probe model #	Working length (meters)	Probe diameter (mm)	Frequencies (MHz)
Fujinon	PL 1726[a] PL 1926[a] PL 2226[a]	1.7, 1.9, 2.2	2.6	12, 15, 20
	PL 2220[a]	2.2	2.0	12, 15, 20
	PL 2226-7.5B	2.14	2.5	7.5
Olympus	UM-2R	2.14	2.5	12
	UM-3R	2.14	2.5	20
	UM-S20-20R	2.14	2.0	20
	UM-S30-20R	2.14	2.0	30
	UM-S30-25R	2.14	2.5	30
	UM-DP12-25R[a]	2.2	2.5	12
	UM-DP20-25R[a]	2.2	2.5	20
	UM-BS20-26R-3	2.14	2.6	20
	UM-G20-29R	2.14	2.9	20

[a] Radial/linear mode

radial and linear images. There are two basic types of catheters: electronic and mechanical [37, 38]. Mechanical catheters contain a single ultrasound transducer that produces a 360° image perpendicular to the longitudinal axis of the miniprobe catheter. The transducer cap holds oil, which provides an acoustic interface for the miniprobe. Electronic catheters contain a probe with several fixed ultrasound transducers at the tip, however they do not have a rotating system as found with the mechanical catheters.

There are two primary brands of miniprobes: Fujinon® and Olympus®. Miniprobes are available in a variety of diameters (2.2–2.9 mm), lengths (1.7–2.2 m), and frequencies (12–30 MHz) [39]. A list of available miniprobes is provided in Table 22.3. With higher frequencies between 12 and 30 MHz, resolution is possible between 0.07 and 0.18 mm [40, 41]. Higher resolution also allows identification of up to 9–11 layers of the gastrointestinal tract, whereas traditional EUS usually visualizes up to 5 layers [42, 43].

Fig. 22.5 Ultrasound miniprobe

A drawback of the higher resolution provided by miniprobes is the concomitant reduction in signal penetration. The depth of imaging decreases as frequency increases, ranging from 29 mm with 12 MHz, to 18 mm with 20 MHz, and 10 mm with 30 MHz [44–46]. Therefore, many gastroenterologists prefer the 20-MHz miniprobe, since it is between the extremes of resolution and depth of signal penetration.

Several acoustic coupling techniques are available for miniprobes. The first option includes a balloon sheath placed over the probe, which can be instilled with water to create an air–water interface [47, 48]. There is also a "condom" product available that is attached to the distal end of the endoscope, and requires air insufflations with a normal endoscope first followed by filling with water.

Miniprobes do have some limitations that should be considered prior to utilization. As discussed before, miniprobes provide higher resolution, but at the cost of limited depth of penetration, which may limit tumor, node, metastasis (TNM) staging due to incomplete visualization of surrounding lymph nodes. Miniprobes have a limited lifetime use, with most probes averaging up to 30 total uses before they need to be replaced. There are some reports of up to 80–100

uses before replacement is needed [49, 50]. Most of the damage that necessitates replacement incurs to the plastic sheath near the tip of the probe. This can represent a significant expense as most miniprobes cost between $ 3000 and 7000 each. Miniprobes also lack Doppler and FNA capabilities.

The development of miniprobes has allowed for their extension into numerous clinical applications. Miniprobes accurately stage several types of cancer, including colorectal, cholangiocarcinoma, esophageal, gastric, and pancreatic. The accuracy rates for diagnosing superficial lesions are relatively high and reported between 60 and 90% [51, 52]. Higher resolution of the gastrointestinal tract layers can potentially provide a new way to study motility disorders, since the muscularis mucosa and propria are more visible with miniprobes. This improved resolution also allows a more specific template for endoscopic mucosal resection (EMR). Intraductal ultrasound (IDUS), which previously was more difficult with larger diameter EUS probes, is possible with the smaller diameter miniprobes. They also pass through malignant strictures more easily, especially in the esophagus and biliary ducts. Future areas of expansion for miniprobes include the continued development of 3D products and further extension into more specialized therapeutic applications such as EMR and IDUS.

EUS Accessories

Since first being developed as a basic diagnostic tool in the 1980s, the role of EUS in technically advanced diagnostics and therapeutics within gastroenterology has exponentially expanded. Numerous accessories are available to aid gastroenterologists in the art of EUS. These are traditionally designed for linear echoendoscopes because the ultrasound image provided is in the same plane as the accessory about to be utilized. It is always important to verify the brand and diameter of the working channel of the specific echoendoscope being used because many of the EUS accessories have specific specifications needed in order to function properly.

What Different Types of EUS Needles Are Available for Fine-Needle Aspiration?

EUS Needles

FNA has become one of the most commonly used modalities of EUS in the last decade. Most FNA needles are disposable, however some models are reusable. Working channels on the echoendoscope should be at least 2.8 mm to accommodate most FNA needles with larger channel diameters (3.7–4.2 mm) required for additional devices such as stents and brushes [53]. FNA needles are available in three basic sizes: 19, 22, and 25G. In general, all FNA needles come with central stylets, which can be either ball or bevel-tipped [54, 55]. These stylets help provide rigidity to the needle, which assists in passing the needle through the targeted tissue. Similar to much of the data regarding FNA needles, there is no clear advantage with the type of stylet tip used.

When deciding on the needle to use during an EUS-guided biopsy, the question of cytology versus histology should be addressed. In general, cytology refers to obtaining only cells from tissue and can be performed with a smaller needle. In contrast, histology requires an intact piece of tissue that preserves the architecture. This usually takes longer and requires a larger bore needle. Typically, an FNA provides cytology with a minimum of the tissue microarchitecture intact. It is usually performed with a smaller, finer needle (22 or 25G). These smaller gauge needles can help prevent injury and bleeding, which potentially makes the cytology difficult to interpret [56]. Larger bore needles, such as 19G, may collect more cells if the aspirate is not complicated by bleeding. These larger bore needles are typically reserved for diagnosing malignancies that potentially require more cytology such as suspected lymphomas [57]. The accuracy of FNA in diagnosing cancer is relatively high with rates as high as 85–95% in pancreatic cancer [58–60].

To deliver more definitive tissue sample during an EUS, core biopsy needles were developed. A core biopsy provides more intact tissue architecture and aids in examining histology. The older core biopsy needles (QuickCore needle, Cook

Medical, Bloomington, IN) were more rigid than standard FNA needles, could rotate (which assists in the radial positioning of the tissue sampling), and were associated with greater complications [61]. In general, core biopsy needles are more expensive, and their use is usually reserved for cases when histology is absolutely necessary for diagnosis or FNA sampling and cytology are indeterminate. Core biopsy needles have been used to sample tissue from lymph nodes, pancreatic tissue including both solid and cystic lesions, hepatic lesions, and the celiac ganglia [62–64].

When comparing the different types of EUS needles, there are both limited and variable data on which of the 19, 22, or 25G needles provides the best diagnostic yield and least complications [65–68]. Future studies including cost analyses are needed to further discern which needles, if any, would consistently provide both a diagnostic and safety advantage. Several different types of EUS needles and other devices are listed in Table 22.4.

In addition to tissue sampling during EUS, specific needles are also used to deliver medications during celiac plexus block and neurolysis [69]. Medications such as steroids (e.g., triamcinolone), ethanol, and anesthetics (e.g., bupivicaine) can be injected during EUS to relieve pain in patients with chronic pancreatitis or pancreatic cancer. These medications can be administered through standard FNA needles, with the 22-G needle commonly used. A specialized 20-G needle, the EchoTip Celiac Plexus Neurolysis Needle (Cook Medical, Bloomington, IN), was specifically developed for this application. It does not contain a stylet and has numerous side holes at the end of the needle to deliver medications into the celiac plexus. There is a paucity of data comparing celiac plexus block and neurolysis via EUS and other modalities such as CT-guided blockades [70].

EUS-FNA needles can also deliver different types of medications, such as chemotherapy and botulinum toxin to various intraabdominal regions besides the celiac plexus. While further research is necessary, EUS may provide a very specialized modality to deliver more localized

Table 22.4 EUS needles and additional devices. (Adapted from Adler et al. [54] and Tharian et al. [53])

EUS device	Manufacturer	Max working length (cm)	Sheath diameter	Needle gauge	Max insertion depth (cm)
FNA/core biopsy					
Powershot[a]	Olympus	145	2.35 mm	22G	9
EZ shot	Olympus	140	1.8 mm	22G	8
Vizeon	Conmed	142.5	2.1 mm (19G) 1.8 mm (22G)	19G 22G	8.5
EchoTip	Cook Endoscopy	140	5.2F	22G	8
EchoTip Ultra	Cook Endoscopy	140	4.2-5.2F 5.2F	19G, 22G, 25G	8
EchoTip Procore	Cook Endoscopy	140	4.8F 5.2F	19G, 22G, 25G	8
Expect	Boston Scientific	141.5	5.5F 4.9F 4.6F	19G 22G 25G	8
BNX	Covidien	143	7.5F	19G, 22G, 25G	8
QuickCore EUS needle	Cook Endoscopy	140	5.2F	19G	8
EchoTip echobrush	Cook Endoscopy			Compatible w/19G needle	
EchoTip celiac plexus neurolysis needle	Cook Endoscopy			20G	

FNA fine-needle aspiration, *EUS* endoscopic ultrasound

chemotherapy to organs like the pancreas while potentially limiting the systemic side effects.

EUS Brushes

EUS brushes provide an alternate way of obtaining cytology that can be used in combination with FNA especially when biliary strictures are encountered during ERCP [71]. The EchoBrush (Cook Medical) passes through a 19-G needle and provides a 1×5 mm brush at its end. This brush can improve diagnostic yield, however, increased complications such as bleeding have been reported [72]. Despite attempts to improve the brush, successful products have not been developed, and future research in this area is needed.

Conclusion

EUS continues to prove valuable in both diagnostic and therapeutic applications within gastroenterology. Advancements in 3D imaging and needles will make EUS one of the more rewarding procedures for gastroenterologists in the future. With these new advances in technology, EUS will undoubtedly represent an important skill to both develop and master as a gastroenterologist.

Key Points

- There are currently two types of echoendoscopes: radial array and curved linear array.
- The linear array echoendoscope is used to perform FNA of lesions.
- EUS miniprobes can be passed down a channel of a conventional endoscope and provide high resolution radial ultrasound images with lower depth of penetration.
- Both 3D endosonography and elastography require specialized software to examine tissue during EUS. 3D EUS is a new tool that involves reconstructing a sequence of 2D images into multiplanar structures, potentially allowing for more accurate staging of gastrointestinal malignancies, while elastography relies on detecting variations in stiffness of tissue to differentiate benign from malignant lesions.
- CE-EUS requires intravenous injection of specialized contrast to potentially improve detection of malignant lesions and staging of tumors.
- A variety of EUS needles are available that either provide an aspirate for cytology or a core biopsy sample for histology.

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References

1. Hong HS, Han JK, Kim TK, Kim YH, Kim JS, Cha JH, Choi BI. Ultrasonographic evaluation of the gallbladder: comparison of fundamental, tissue harmonic, and pulse inversion harmonic imaging. J Ultrasound Med. 2001;20:35–41.
2. Ishikawa H, Hirooka Y, Itoh A, Hashimoto S, Okada N, Itoh T, Kawashima H, Goto H. A comparison of image quality between tissue harmonic imaging and fundamental imaging with an electronic radial scanning echoendoscope in the diagnosis of pancreatic diseases. Gastrointest Endosc. 2003;57:931–6.
3. Hikichi T, Irisawa A, Takagi T, Shibukawa G, Wakatsuki T, Imamura H, Takahashi Y, Sato A, Sato M, Ikeda T, Suzuki R, Watanabe K, Nakamura J, Ohira H, Obara K. An electronic radial scanning echoendoscope is superior to a mechanical radial scanning echoendoscope in ultrasound image quality for gastrointestinal tract and pancreaticobiliary lesions. Fukushima J Med Sci. 2010;56:99–106.
4. Niwa K, Hirooka Y, Niwa Y, Itoh A, Ohmiya N, Hashimoto S, Ishikawa H, Okada N, Itoh T, Goto H. Comparison of image quality between electronic and mechanical radial scanning echoendoscopes in pancreatic diseases. J Gastroenterol Hepatol. 2004;19:454–9.
5. Papanikolaou IS, Delicha EM, Adler A, Wegener K, Pohl H, Wiedenmann B, Rosch T. Prospective, randomized comparison of mechanical and electronic radial endoscopic ultrasound systems: assessment of performance parameters and image quality. Scand J Gastroenterol. 2009;44:93–9.
6. Gress F, Savides T, Cummings O, Sherman S, Lehman G, Zaidi S, Hawes R. Radial scanning and linear array endosonography for staging pancreatic cancer: a prospective randomized comparison. Gastrointest Endosc. 1997;45:138–42.
7. Matthes K, Bounds BC, Collier K, Gutierrez A, Brugge WR. EUS staging of upper GI malignancies: results of a prospective randomized trial. Gastrointest Endosc. 2006;64:496–502.

8. Nesje LB, Svanes K, Viste A, Laerum OD, Odegaard S. Comparison of a linear miniature ultrasound probe and a radial-scanning echoendoscope in TN staging of esophageal cancer. Scand J Gastroenterol. 2000;35:997–1002.
9. Niwa K, Hirooka Y, Niwa Y, Itoh A, Ohmiya N, Hashimoto S, Ishikawa H, Okada N, Itoh T, Goto H. Comparison of image quality between electronic and mechanical radial scanning echoendoscopes in pancreatic diseases. J Gastroenterol Hepatol. 2004;19:454–9.
10. Siemsen M, Svendsen LB, Knigge U, Vilmann P, Jensen F, Rasch L, Stentoft P. A prospective randomized comparison of curved array and radial echoendoscopy in patients with esophageal cancer. Gastrointest Endosc. 2003;58:671–6.
11. Eloubeidi MA. Initial evaluation of the forward-viewing echoendoscope prototype for performing fine-needle aspiration, Tru-cut biopsy, and celiac plexus neurolysis. J Gastroenterol Hepatol. 2011;26:63–7.
12. Iwashita T, Nakai Y, Lee JG, Park dH, Muthusamy VR, Chang KJ. Newly-developed, forward-viewing echoendoscope: a comparative pilot study to the standard echoendoscope in the imaging of abdominal organs and feasibility of endoscopic ultrasound-guided interventions. J Gastroenterol Hepatol. 2012;27:362–7.
13. Kida M, Araki M, Miyazawa S, Ikeda H, Kikuchi H, Watanabe M, Imaizumi H, Koizumi W. Fine needle aspiration using forward-viewing endoscopic ultrasonography. Endoscopy. 2011;43:796–801.
14. Lee YT. Basic functions of linear EUS processor and when to use them. Gastrointest Endosc. 2009;69:S64–7.
15. Hirooka Y, Itoh A, Kawashima H, Ohno E, Itoh Y, Nakamura Y, Hiramatsu T, Sugimoto H, Sumi H, Hayashi D, Ohmiya N, Miyahara R, Nakamura M, Funasaka K, Ishigami M, Katano Y, Goto H. Contrast-enhanced endoscopic ultrasonography in digestive diseases. J Gastroenterol. 2012;47:1063–72.
16. Hirooka Y, Itoh A, Kawashima H, Ohno E, Itoh Y, Nakamura Y, Hiramatsu T, Sugimoto H, Sumi H, Hayashi D, Ohmiya N, Miyahara R, Nakamura M, Funasaka K, Ishigami M, Katano Y, Goto H. Contrast-enhanced endoscopic ultrasonography in digestive diseases. J Gastroenterol. 2012;47:1063–72.
17. Kitano M, Sakamoto H, Matsui U, Ito Y, Maekawa K, von ST, Kudo M. A novel perfusion imaging technique of the pancreas: contrast-enhanced harmonic EUS (with video). Gastrointest Endosc. 2008;67:141–50.
18. Choi JH, Seo DW, Choi JH, Park DH, Lee SS, Lee SK, Kim MH. Utility of contrast-enhanced harmonic EUS in the diagnosis of malignant gallbladder polyps (with videos). Gastrointest Endosc. 2013;78:484–93.
19. Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: a meta-analysis. Gastrointest Endosc. 2012;76:301–9.
20. Imazu H, Uchiyama Y, Matsunaga K, Ikeda K, Kakutani H, Sasaki Y, Sumiyama K, Ang TL, Omar S, Tajiri H. Contrast-enhanced harmonic EUS with novel ultrasonographic contrast (Sonazoid) in the preoperative T-staging for pancreaticobiliary malignancies. Scand J Gastroenterol. 2010;45:732–8.
21. Hirooka Y, Itoh A, Kawashima H, Ohno E, Itoh Y, Nakamura Y, Hiramatsu T, Sugimoto H, Sumi H, Hayashi D, Ohmiya N, Miyahara R, Nakamura M, Funasaka K, Ishigami M, Katano Y, Goto H. Contrast-enhanced endoscopic ultrasonography in digestive diseases. J Gastroenterol. 2012;47:1063–72.
22. Kitano M, Kudo M, Yamao K, Takagi T, Sakamoto H, Komaki T, Kamata K, Imai H, Chiba Y, Okada M, Murakami T, Takeyama Y. Characterization of small solid tumors in the pancreas: the value of contrast-enhanced harmonic endoscopic ultrasonography. Am J Gastroenterol. 2012;107:303–10.
23. Napoleon B, varez-Sanchez MV, Gincoul R, Pujol B, Lefort C, Lepilliez V, Labadie M, Souquet JC, Queneau PE, Scoazec JY, Chayvialle JA, Ponchon T. Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: results of a pilot study. Endoscopy. 2010;42:564–70.
24. Giovannini M. Contrast-enhanced and 3-dimensional endoscopic ultrasonography. Gastroenterol Clin North Am. 2010;39:845–58.
25. Saftoiu A, Gheonea DI. Tridimensional (3D) endoscopic ultrasound—a pictorial review. J Gastrointestin Liver Dis. 2009;18:501–5.
26. Kim JC, Kim HC, Yu CS, Han KR, Kim JR, Lee KH, Jang SJ, Lee SS, Ha HK. Efficacy of 3-dimensional endorectal ultrasonography compared with conventional ultrasonography and computed tomography in preoperative rectal cancer staging. Am J Surg. 2006;192:89–97.
27. Santoro GA, Gizzi G, Pellegrini L, Battistella G, Di FG. The value of high-resolution three-dimensional endorectal ultrasonography in the management of submucosal invasive rectal tumors. Dis Colon Rectum. 2009;52:1837–43.
28. Santoro GA. Preoperative staging of rectal cancer: role of 3D endorectal ultrasonography. Acta Chir Iugosl. 2012;59:57–61.
29. Giovannini M. Endoscopic ultrasound elastography. Pancreatology. 2011;11(Suppl 2):34–9.
30. Janssen J, Schlorer E, Greiner L. EUS elastography of the pancreas: feasibility and pattern description of the normal pancreas, chronic pancreatitis, and focal pancreatic lesions. Gastrointest Endosc. 2007;65:971–8.
31. Giovannini M, Hookey LC, Bories E, Pesenti C, Monges G, Delpero JR. Endoscopic ultrasound elastography: the first step towards virtual biopsy? Preliminary results in 49 patients. Endoscopy. 2006;38:344–8.
32. Ying L, Lin X, Xie ZL, Hu YP, Tang KF, Shi KQ. Clinical Utility of Endoscopic Ultrasound Elastography for Identification of Malignant Pancreatic Masses: a Meta-Analysis. J Gastroenterol Hepatol. 2013;28:1434–43.

33. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology. 2010;139:1172–80.
34. Menzel J, Domschke W, Brambs HJ, Frank N, Hatfield A, Nattermann C, Odegaard S, Seifert H, Tamada K, Tio TL, Foerster EC. Miniprobe ultrasonography in the upper gastrointestinal tract: state of the art 1995, and prospects. Endoscopy. 1996;28:508–13.
35. Silverstein FE, Martin RW, Kimmey MB, Jiranek GC, Franklin DW, Proctor A. Experimental evaluation of an endoscopic ultrasound probe: in vitro and in vivo canine studies. Gastroenterology. 1989;96:1058–62.
36. Yanai H, Yoshida T, Harada T, Matsumoto Y, Nishiaki M, Shigemitsu T, Tada M, Okita K, Kawano T, Nagasaki S. Endoscopic ultrasonography of superficial esophageal cancers using a thin ultrasound probe system equipped with switchable radial and linear scanning modes. Gastrointest Endosc. 1996;44:578–82.
37. Liu J, Carpenter S, Chuttani R, Croffie J, Disario J, Mergener K, Mishkin DS, Shah R, Somogyi L, Tierney W, Petersen BT. Endoscopic ultrasound probes. Gastrointest Endosc. 2006;63:751–4.
38. Hurlstone DP, Cross SS, Sanders DS. 20-MHz high-frequency endoscopic ultrasound-assisted endoscopic mucosal resection for colorectal submucosal lesions: a prospective analysis. J Clin Gastroenterol. 2005;39:596–9.
39. Hurlstone DP, Cross SS, Sanders DS. 20-MHz high-frequency endoscopic ultrasound-assisted endoscopic mucosal resection for colorectal submucosal lesions: a prospective analysis. J Clin Gastroenterol 2005;39:596–599.
40. Kimmey MB, Martin RW, Silverstein FE. Endoscopic ultrasound probes. Gastrointest Endosc. 1990;36:S40–6.
41. Schembre D, Ayub K, Jiranek G. High-frequency mini-probe ultrasound: the Rodney Dangerfield of endoscopy? J Clin Gastroenterol. 2005;39:555–6.
42. Watanabe H, Miwa H, Terai T, Imai Y, Ogihara T, Sato N. Endoscopic ultrasonography for colorectal cancer using submucosal saline solution injection. Gastrointest Endosc. 1997;45:508–11.
43. Waxman I, Raju GS, Critchlow J, Antonioli DA, Spechler SJ. High-frequency probe ultrasonography has limited accuracy for detecting invasive adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia or intramucosal carcinoma: a case series. Am J Gastroentero.l 2006;101:1773–9.
44. Bhutani MS. Interventional endoscopic ultrasonography: state of the art at the new millenium. Endoscopy. 2000;32:62–71.
45. Chak A, Canto M, Stevens PD, Lightdale CJ, Van de MF, Cooper G, Pollack BJ, Sivak MV Jr. Clinical applications of a new through-the-scope ultrasound probe: prospective comparison with an ultrasound endoscope. Gastrointest Endosc. 1997;45:291–5.
46. Kimmey MB, Martin RW, Silverstein FE. Endoscopic ultrasound probes. Gastrointest Endosc. 1990;36:S40–6.
47. Inoue H, Kawano T, Takeshita K, Iwai T. Modified soft-balloon methods during ultrasonic probe examination for superficial esophageal cancer. Endoscopy. 1998;30(Suppl 1):A41–3.
48. Wallace MB, Hoffman BJ, Sahai AS, Inoue H, Van VA, Hawes RH. Imaging of esophageal tumors with a water-filled condom and a catheter US probe. Gastrointest Endosc. 2000;51:597–600.
49. Liu J, Carpenter S, Chuttani R, Croffie J, Disario J, Mergener K, Mishkin DS, Shah R, Somogyi L, Tierney W, Petersen BT. Endoscopic ultrasound probes. Gastrointest Endosc. 2006;63:751–4.
50. Martin RW, Silverstein FE, Kimmey MB. A 20-MHz ultrasound system for imaging the intestinal wall. Ultrasound Med Biol. 1989;15:273–80.
51. Chak A, Canto M, Stevens PD, Lightdale CJ, Van de MF, Cooper G, Pollack BJ, Sivak MV Jr. Clinical applications of a new through-the-scope ultrasound probe: prospective comparison with an ultrasound endoscope. Gastrointest Endosc. 1997;45:291–5.
52. Liu J, Carpenter S, Chuttani R, Croffie J, Disario J, Mergener K, Mishkin DS, Shah R, Somogyi L, Tierney W, Petersen BT. Endoscopic ultrasound probes. Gastrointest Endosc. 2006;63:751–4.
53. Tharian B, Tsiopoulos F, George N, Pietro SD, Attili F, Larghi A. Endoscopic ultrasound fine needle aspiration: technique and applications in clinical practice. World J Gastrointest Endosc. 2012;4:532–44.
54. Adler DG, Conway JD, Coffie JM, Disario JA, Mishkin DS, Shah RJ, Somogyi L, Tierney WM, Wong Kee Song LM, Petersen BT. EUS accessories. Gastrointest Endosc. 2007;66:1076–81.
55. Tharian B, Tsiopoulos F, George N, Pietro SD, Attili F, Larghi A. Endoscopic ultrasound fine needle aspiration: technique and applications in clinical practice. World J Gastrointest Endosc. 2012;4:532–44.
56. vanSonnenberg E, Goodacre BW, Wittich GR, Logrono R, Kennedy PT, Zwischenberger JB. Image-guided 25-gauge needle biopsy for thoracic lesions: diagnostic feasibility and safety. Radiology. 2003;227:414–8.
57. Adler DG, Conway JD, Coffie JM, Disario JA, Mishkin DS, Shah RJ, Somogyi L, Tierney WM, Wong Kee Song LM, Petersen BT. EUS accessories. Gastrointest Endosc. 2007;66:1076–81.
58. Gress F, Gottlieb K, Sherman S, Lehman G. Endoscopic ultrasonography-guided fine-needle aspiration biopsy of suspected pancreatic cancer. Ann Intern Med. 2001;134:459–64.
59. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Lehman GA. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. Gastrointest Endosc. 1997;45:243–50.
60. 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.
61. Adler DG, Conway JD, Coffie JM, Disario JA, Mishkin DS, Shah RJ, Somogyi L, Tierney WM, Wong Kee Song LM, Petersen BT. EUS accessories. Gastrointest Endosc. 2007;66:1076–81.
62. Varadarajulu S, Fraig M, Schmulewitz N, Roberts S, Wildi S, Hawes RH, Hoffman BJ, Wallace MB. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. Endoscopy. 2004;36:397–401.
63. Levy MJ, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided Trucut biopsy needle compared with EUS-guided FNA. Gastrointest Endosc 2003;57:101–106.
64. Wiersema MJ, Levy MJ, Harewood GC, Vazquez-Sequeiros E, Jondal ML, Wiersema LM. Initial experience with EUS-guided Trucut needle biopsies of perigastric organs. Gastrointest Endosc. 2002;56:275–8.
65. Imazu H, Uchiyama Y, Kakutani H, Ikeda K, Sumiyama K, Kaise M, Omar S, Ang TL, Tajiri H. A prospective comparison of EUS-guided FNA using 25-gauge and 22-gauge needles. Gastroenterol Res Pract. 2009;2009:546390.
66. Levy MJ, Jondal ML, Clain J, Wiersema MJ. Preliminary experience with an EUS-guided Trucut biopsy needle compared with EUS-guided FNA. Gastrointest Endosc. 2003;57:101–6.
67. Sakamoto H, Kitano M, Komaki T, Noda K, Chikugo T, Dote K, Takeyama Y, Das K, Yamao K, Kudo M. 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.
68. Varadarajulu S, Fraig M, Schmulewitz N, Roberts S, Wildi S, Hawes RH, Hoffman BJ, Wallace MB. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. Endoscopy. 2004;36:397–401.
69. Adler DG, Conway JD, Coffie JM, Disario JA, Mishkin DS, Shah RJ, Somogyi L, Tierney WM, Wong Kee Song LM, Petersen BT. EUS accessories. Gastrointest Endosc. 2007;66:1076–81.
70. Gress F, Schmitt C, Sherman S, Ikenberry S, Lehman G. 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.
71. Fogel EL, deBellis M, McHenry L, Watkins JL, Chappo J, Cramer H, Schmidt S, Lazzell-Pannell L, Sherman S, Lehman GA. Effectiveness of a new long cytology brush in the evaluation of malignant biliary obstruction: a prospective study. Gastrointest Endosc. 2006;63:71–7.
72. Al-Haddad M, Raimondo M, Woodward T, Krishna M, Pungpapong S, Noh K, Wallace MB. Safety and efficacy of cytology brushings versus standard FNA in evaluating cystic lesions of the pancreas: a pilot study. Gastrointest Endosc. 2007;65:894–8.

Techniques of Endoscopic Ultrasound-Guided Fine Needle Aspiration

23

Abdurrahman Kadayifci and William R. Brugge

Introduction

Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is an essential diagnostic tool and currently the most accurate technique for tissue diagnosis of tumors and lesions of the gastrointestinal (GI) wall and adjacent organs. It can safely provide, both, cytological and histological samples from mural and extra-mural lesions within reach of the linear echoendoscope. In daily GI practice, it is most commonly used for pancreatic masses and cysts as it is the best method for sampling pancreatic lesions. Implementation of EUS-FNA in GI practice has significantly improved the diagnostic sensitivity and specificity for pancreatic cancer [1]. The overall current sensitivity, specificity, and diagnostic accuracy of EUS-FNA for the diagnosis of malignant pancreatic neoplasms are 77–95%, 96–100%, and 79–97%, respectively [2]. A recent study using medicare data to investigate changing trends in tissue acquisition in pancreatic disease found out that over the span of 5 years (2006–2010), use of EUS-FNA increased approximately to 70% in the USA [3].

Depending on the target lesion, EUS-FNA provides adequate cytological or histological material in 70–100% of cases [2, 4–7]. However, the reported high success and diagnostic accuracy rates of EUS-FNA is mostly operator-dependent, and endoscopist experience is the most critical factor for obtaining these results [8, 9]. Proper training of endosonographers increased the accuracy of EUS-FNA from 33 to 91% in one study; and EUS-FNA errors during the initial learning phase were primarily due to inadequate specimens [10]. Therefore, similar to many other complicated interventions, proficiency in EUS-FNA also requires learning the useful technical details and tips from all available sources. This chapter mainly reviews the current literature for EUS-FNA and provides up-to-date information on patient selection, technical details, equipment, and diagnostic accuracy.

Case Study

Initial Presentation

A 72-year-old woman presented with a history of periumbilical pain, abdominal bloating, and discomfort over the past 4 weeks. Physical examination and basic laboratory tests, including blood count, biochemistry, urine analysis, and plain abdominal X-ray, were unremarkable. She was given symptomatic treatment at a nearby hospital but admitted again 4 weeks later with increased symp-

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toms. A transabdominal ultrasonography (US) and then CT scan demonstrated significant retroperitoneal adenopathy from the aortic bifurcation up to the celiac axis. A right inguinal lymph node biopsy was performed, which was unremarkable. A bone marrow aspirate, biopsy, and a bone scan were also unremarkable. An MRI of the abdomen again confirmed retroperitoneal adenopathy. Ultimately, patient was referred to a tertiary center for an EUS-FNA of abdominal lymph nodes given the high suspicion of non-Hodgkin lymphoma.

Is This An Appropriate Indication for EUS-FNA, and What Impact Does EUS-FNA Have on Management of This Patient?

EUS-FNA is generally safe and reliable with a low complication rate. However, the cost effectiveness and possible risks and benefits should always be weighed carefully before the procedure. The procedure is indicated if the results will potentially impact patient management. If there is an alternative method for diagnosis, which is safer and reliable, it should be the first priority. The indications and contraindications of EUS-FNA are summarized in Table 23.1.

In our case, the patient had unexplained diffuse abdominal lymphadenopathy. Evaluation of unexplained periluminal lymphadenopathy is among the important indications of EUS and EUS-FNA. Before an FNA procedure, the patient first needs a diagnostic EUS to assess for a possible mediastinal or abdominal lesion, which may be related to lymphadenopathy.

EUS and EUS-FNA may have an important impact in the management of this patient. The procedures will likely provide a tissue diagnosis. Furthermore, the risk of EUS-FNA of enlarged lymph nodes is relatively low.

Case Continued

The patient underwent a diagnostic EUS with a linear array echoendoscope. Many malignant-appearing, round, hypoechoic lymph nodes with well-defined margins were visualized in the aortopulmonary window, the paraesophageal mediastinum, and the mediastinal periaortic region. The largest measured 10 by 10 mm in maximal cross-sectional diameter (Fig. 23.1). A round, well-defined, hypoechoic and homogenous, 20 mm by 20 mm in maximal cross-sectional diameter mass was identified in the pancreatic

Table 23.1 Indications and contraindications of EUS-FNA

Indications
Primary diagnosis of pancreatic masses
Differentiation of cystic pancreatic lesions
Evaluation of unexplained periluminal lymphadenopathy
Diagnosis of gastrointestinal intramural lesions
Staging of digestive and pulmonary malignancies
Sampling of peritoneal and pleural fluid
Contraindications
Risks outweigh the expected benefits
Results would not affect patient management
Lesions that cannot be visualized clearly
Lack of informed consent or cooperation of the patient
Uncorrectable coagulopathy (INR >1.5) or thrombocytopenia ($<50{,}000/\mu l$)
Under thienopyridines therapy
Relative contraindications
Failure of control of needle position
Biliary obstruction without prior decompression
Luminal stenosis
Venous collaterals in the path of the needle tract

EUS endoscopic ultrasound, *FNA* fine needle aspiration

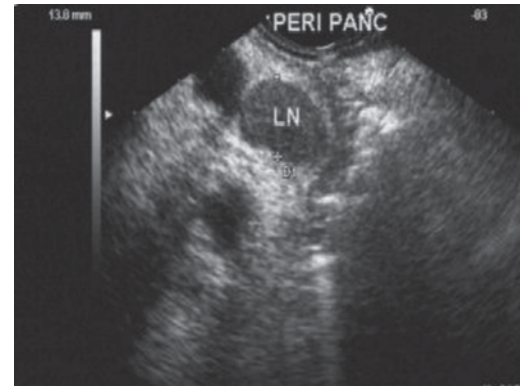

Fig. 23.1 Round, hypoechoic, and well-defined lymph node in peripancreatic area

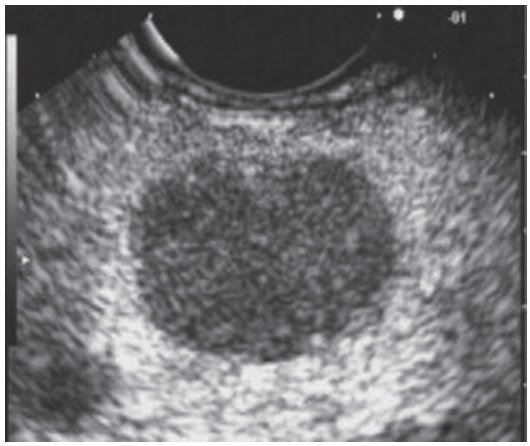

Fig. 23.2 A round, well-defined, hypoechoic and homogenous, 2 cm in maximal diameter mass in the pancreatic body

body (Fig. 23.2). The mass appeared atypical for pancreatic adenocarcinoma. There was no sign of significant endosonographic abnormality in the left lobe of the liver.

Does the Patient Still Need EUS-FNA and Which Lesion Should Be Sampled?

This patient had a pancreatic mass and diffuse lymphadenopathy. The EUS findings were not typical for a pancreatic adenocarcinoma. However, a pancreatic cancer with diffuse metastasis still remained in the differential diagnosis. The atypical imaging findings of diffuse lymphadenopathy also raised suspicion of pancreatic lymphoma. As management of these two conditions differ, a definite cytological or histological diagnosis was necessary to guide treatment of the patient at this stage, and EUS-FNA of both the lymph nodes and pancreatic mass was required. The first EUS-FNA should always target the lesion, which likely represents the most advanced stage of malignancy. This approach will help prevent subsequent seeding.

When sampling a suspected pancreatic cancer is indicated, EUS-FNA should be the first-line procedure. It has significant advantages over percutaneous US or CT-guided biopsies [11, 12]. EUS and EUS-FNA are superior for detecting early malignancies, obtaining cytologic material, and minimizing the risk of tissue seeding. EUS-FNA may diagnose a potentially resectable mass or pancreatic metastasis, and exclude other pancreatic tumors such as lymphoma or neuroendocrine tumor, in addition to benign disease such as chronic or autoimmune pancreatitis.

A preoperative diagnostic EUS-FNA is controversial in patients who are good surgical candidates with a high suspicion of pancreatic adenocarcinoma. The negative predictive value of EUS-FNA for pancreatic cancer is approximately 70%; thus, a negative result cannot rule out malignancy with adequate reliability [13–15]. Therefore, routine preoperative EUS-FNA of potentially resectable pancreatic adenocarcinomas is not generally advised. However, in cases where other types of pancreatic malignancies (e.g., neuroendocrine tumors, lymphomas, metastatic disease) are suspected, EUS-FNA is indicated to assist in planning appropriate management.

What Is the Preparation for EUS-FNA?

Initial planning and preparation for EUS-FNA is similar to other endoscopic interventions. Prior to starting the procedure, the medical history and records of the patient should be reviewed with all necessary laboratory and radiological tests, and then informed consent should be obtained after discussing the indication, benefits, and risks of the procedure with the patient and the family. The diagnostic success of EUS-FNA is highly related to the preparation of the patient and instruments as well as the expertise of the whole endoscopy team. Therefore, each step of the procedure needs to be carefully planned and executed with the entire team. The risk of bacteremia is rare and similar to other endoscopic procedures. As such, prophylactic antibiotics are not routinely recommended [16]. Serious infectious complications have only been reported after EUS-FNA of cysts (e.g., pancreatic and mediastinal) and the American Society for Gastrointestinal Endoscopy (ASGE) guideline recommends periprocedural antibiotics only in these patients [17, 18].

EUS alone, without FNA, is a low-risk procedure for bleeding, but EUS with FNA is classified as a high-risk procedure. There is no need to stop aspirin, thienopyridines including clopidogrel or warfarin for patients undergoing a low-risk procedure for bleeding [19]. Aspirin may be continued even in patients undergoing EUS-FNA of solid lesions, but clopidogrel should be discontinued 7–10 days prior to the procedure. Warfarin should be stopped 2–5 days before the procedure in all patients who are scheduled for EUS-FNA and restarted within 24 h after the procedure. A bridge therapy with low molecular weight heparin should be considered in patients with higher risk conditions for thromboembolic event [19]. These decisions regarding antiplatelet agents and anticoagulants should be discussed with the patient's cardiologist and/or neurologist prescribing those medications.

Sudden movements during FNA may lead to injury of adjacent structures and effective sedation of patients is important for a complication-free procedure. Sedation may be provided with intravenous conscious sedation (IVCS) or with monitored total anesthesia during EUS-FNA. A recent study compared the impact of IVCS and general anesthesia (GA) on diagnostic yield of EUS-FNA in patients with pancreatic mass [20]. Anesthesiologist-delivered GA was associated with a significantly higher diagnostic yield of EUS-FNA compared to IVCS. The authors commented that GA may improve EUS-FNA yield by improving patient cooperation and stillness during the procedure. There was no difference in the complication rates between the groups.

Before proceeding with EUS-FNA, a complete diagnostic EUS should be performed to evaluate the lesion and adjacent structures to allow adequate staging and in order to choose the optimal needle tract. A radial EUS examination is usually suggested for areas other than the pancreas, but selecting the radial or linear scope for diagnostic EUS depends on the endoscopist's experience. The linear echoendoscope provides complete visualization of the pancreas. After the target lesion is identified, the scope should be placed in a stable position adjacent to the lesion, and if possible, within the projected plane of the needle path. Doppler function should be utilized to exclude an interposed vessel between the transducer and the target lesion.

Once the target lesion is localized and an appropriate position is achieved, the needle catheter device is advanced through the biopsy channel to begin the puncture. The location of the target lesion affects the difficulty of the procedure. In general, transduodenal FNA is difficult, while transgastric is easier and transesophageal easiest.

What Factors Impact the Choice of Needle Type and Size?

EUS-FNA is classically performed with 19-, 22-, and 25-gauge (G) aspiration needles from several manufacturers (Table 23.2 and Fig. 23.3). There is no optimal needle size for EUS-FNA, and each size may have advantages and disadvantages depending on the location and type of lesion. Larger diameter needles do not increase the risk of the procedure, and no significant difference in com-

Table 23.2 Commercially available fine-needle aspiration and biopsy needles

Type of needle	Available sizes (G)	Device	Manufacturer
Aspiration	19, 22, 25	Expect	Boston Scientific
		EchoTip Ultra	Cook Medical
		EzShot2	Olympus
		SonoTipII	Medi-Globe
		BNX system	Covidien
		Clearview	Conmed
Trucut biopsy	19	Quick-Core	Cook Medical
Core biopsy	19, 22, 25	Echotip Procore	Cook Medical
Aspiration flex	19	Expect flex	Boston Scientific

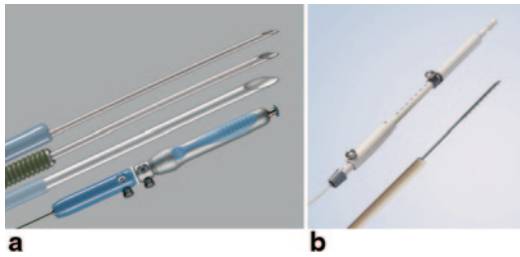

Fig. 23.3 Fine-needle aspiration needles in different type and sizes. (Cook Medical Inc. and Olympus Inc)

plication rates has been shown among the different sized FNA needles [6]. The 19G needle is the stiffest and may be difficult to manipulate in the duodenum where the scope is sharply angulated. For this reason, technical failure rate is higher with 19G needles used for pancreatic head lesions [21, 22]. Although the 19G needle may obtain tissue fragments from suspected tumors and potentially increase diagnostic accuracy, it may cause more trauma and bloodier samples. Conversely, a 25G needle offers ease of use and less risk of a bloody aspirate [23]. The 25G needle may be particularly useful for difficult pancreatic head lesions [24]. Several prospective studies have compared the 22G and 25G needles for their performance, diagnostic accuracy, and safety [7, 25, 26]. In general, diagnostic yield and complications appear comparable between the 22G and 25G needles [27, 28]. Endoscopists should be familiar with all needle sizes and choose the size based on the flexibility needed, the size which may provide optimal tissue yield, and the safest size for a particular location and type of lesion.

A new 19G aspiration needle made of nitinol with enhanced flexibility (Expect flex, Boston Scientific, Marlborough, MA, Fig. 23.4) was designed to overcome the limitations of current 19G needles. A recent study demonstrated successful tissue acquisition adequate for cytological assessment in all 38 patients (100%), which included transduodenal passes, and therapeutic interventions were also effective in 12 patients [29]. In another pilot study with this needle, EUS-FNA was successful in all eight cases with six involving the pancreatic head, and adequate specimen was obtained with a mean of 1.2 passes [30].

Fig. 23.4 A new 19G aspiration needle made of nitinol with enhanced flexibility (Boston Scientific)

To obtain adequate histologic samples and overcome some limitations of EUS-FNA, EUS-fine needle biopsy (EUS-FNB) has been performed with a 19G Tru-cut biopsy needle (TBN) (Fig. 23.5). The needle consists of a 5 mm stylet tip, an 18-mm specimen tray, a 19G internal cutting sheath, the outer catheter sheath, and the handle portion. It permits procurement of tissue specimen automatically with a spring-loaded handle mechanism. The needle is advanced to the target lesion with the handle in the retracted firing position. The specimen tray is inserted into the target lesion and the handle is pressed forward until resistance is felt. The specimen tray and cutting sheath are visualized within the target tissue with distinct echo features. Increased pressure on the handle fires the device, moving the cutting sheath quickly over the tray to acquire a tissue sample. Straightening the echoendoscope and needle, proper device orientation, and targeting the lesion are important technical details when using this needle. By preserving the tissue architecture, this needle may be more helpful for the diagnosis of specific conditions such as gastrointestinal stromal tumors, lymphomas, well-differentiated neoplasia, neuroendocrine

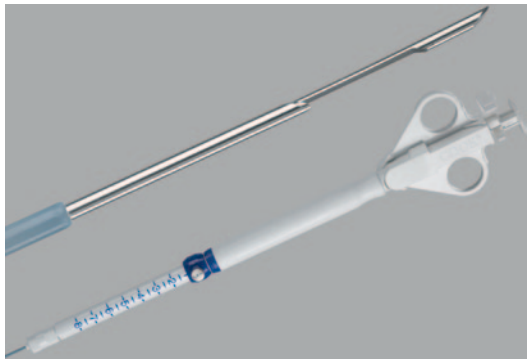

Fig. 23.5 19G Tru-cut EUS biopsy needle (Cook Medical Inc.). *EUS* endoscopic ultrasound

tumors, and autoimmune pancreatitis. However, the rigidity of the needle limits its usage especially in difficult locations such as duodenal bulb, fundus, and antrum [22].

Recently, 19G, 22G, and 25G biopsy needles were designed with a cutting knife (Procore, Cook Medical, Fig. 23.6, Table 23.2). The flexibility of the 22G and 25G core needles may offer advantages in difficult locations. Several recent studies compared the diagnostic yield of 22G aspiration needles with 22G core needles for solid lesions of the pancreas and gastrointestinal tract with inconclusive findings. Depending on the study, the diagnostic yield of the 22G aspiration needle was equal, superior, or inferior to the 22G core biopsy needle [6, 7, 28]. Procore needles may require fewer passes compared to aspiration needles. The diagnostic yield on the first pass of the 22G Procore needle was approximately twice compared to the 22G aspiration needle [31]. Downsides of the core needles include their greater expense and need for additional training and technical assistance. A new core needle (SharkCore fine needle biopsy, Covidien) is now available in 19G, 22G, and 25G with a unique design of 6 cutting surfaces, and needs study to determine its utility and place within the current armamentarium of aspiration and biopsy needles. Both types of needles may offer advantages and may prove more useful in different lesions and individuals. Table 23.3 summarizes suggested needle type and size according to specific characteristics of the case.

In our case, the mediastinal and peripancreatic lymph nodes were suitable for EUS-FNA. For better staging and to prevent subsequent seeding, the first EUS-FNA should target the lesion, which likely represents the most advanced stage of malignancy. Thus, the mediastinal lymph nodes were targeted first by a transesophageal approach. For lymph node aspiration, 22G and 25G needles may be easiest to use. The mass in the pancreatic

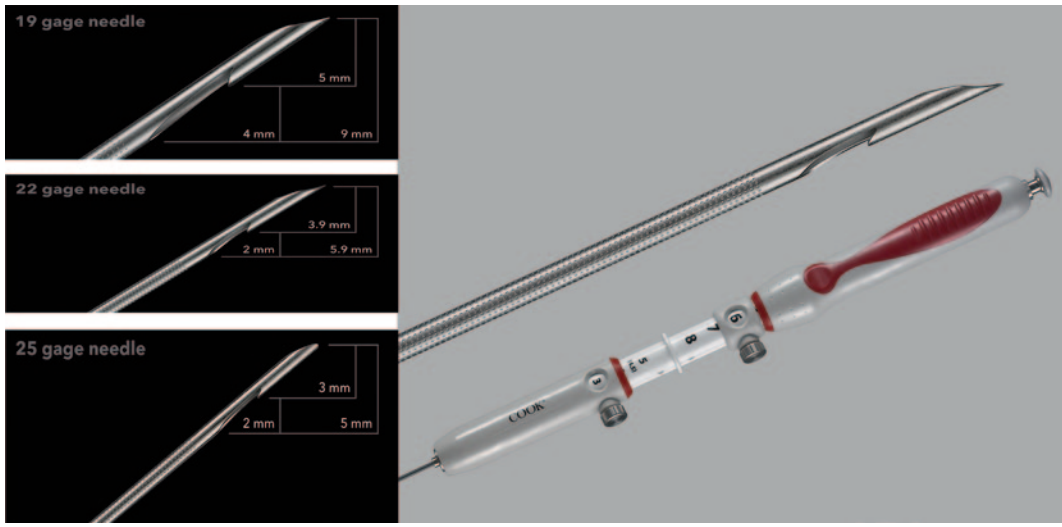

Fig. 23.6 Procore EUS biopsy needle in different sizes. (Cook Medical Inc.). *EUS* endoscopic ultrasound

Table 23.3 Suggested EUS-guided aspiration or biopsy needle according to lesion and patient characteristics

Characteristics	Suggested needles
Access	22 and 25G for transduodenal approach 19 and 22G for transgastric and transesophageal puncture
Location	22 and 25G for pancreatic head, neck, and uncinate 19 and 22G for other locations
Cellularity and diagnostic yield	22 and 25G for pancreatic head and uncinate 19G for other locations (possible more cells obtained)
Nature of the lesion	For lesions with a high suspicion of GIST, lymphoma, and metastatic tumor, Trucut and core biopsy needles. Alternative: 19G aspiration flex
On-site cytopathology	Aspiration needles. If on-site evaluation is not available, core needles and 19 G aspiration flex may be better
Ancillary studies and histological samples	Core biopsy needles. Alternative: 19G aspiration needle and 19G aspiration flex
Contamination and bleeding	Smaller gauge needles (possible decreased contamination and risk of bleeding)
Cost effectiveness	Aspiration needles
Safety	No definite data, but 19G aspiration and Trucut possibly more traumatic

body was accessed transgastrically. For atypical lesions, a larger needle to obtain tissue fragments for histology may be more helpful for diagnosis. Considering all these factors, starting with a 22G for the lymph nodes and then a 19G for the pancreatic mass or using a 22G aspiration needle for both lesions are reasonable choices in this case. EUS-FNB with a 22G Procore needle for both the lymph nodes and pancreatic mass may be an alternative, especially for atypical lesions, and if Rapid Onsite Evaluation (ROSE) is not available.

How Is EUS-FNA Performed?

Most single-use EUS-FNA needles are very similar in design and operation [32]. They consist of a hollow metallic needle inside a semirigid protective sheath with a plastic rigid cylinder handle containing a port (Figs. 23.3, 23.4, 23.6). From the port, there is a solid removable stylet inside the needle to enhance its rigidity during puncture and to prevent clogging the needle tip with intestinal mucosa. The port is also used to attach a vacuum syringe. The handle is attached to the accessory channel of the echoendoscope via a Luer Lock to stabilize the system during use. Markings at 1 cm intervals on the handle enable to set and monitor the depth of the needle. The maximum needle length from the tip of the echoendoscope is usually 8–9 cm. The handle has a stopping device to set the maximum needle excursion. This safety mechanism helps to keep the needle within the limits of the target lesion. To facilitate the passage of multiple needles through a single delivery catheter, a new system called BNX (Beacon Needle Exchange) has been developed (Beacon Endoscopic, Covidien) (Fig. 23.7). The system has the ability to remove the needle from the sheath and place different sized needles through the same sheath to perform multiple passes. The aim of the system is to increase the diagnostic yield of EUS-FNA with low cost and

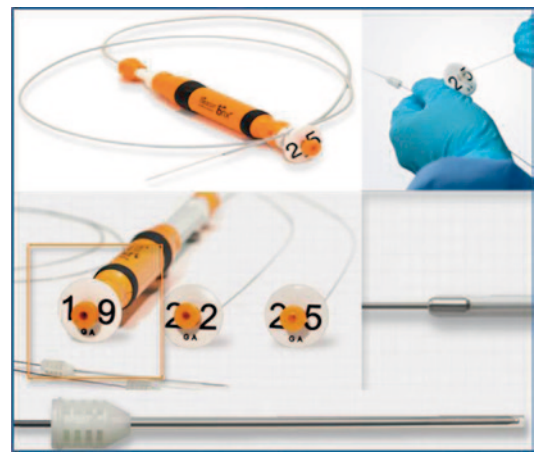

Fig. 23.7 Beacon needle exchange FNA system with multiple size needles and delivery device (Beacon Endoscopic, Covidien). *FNA* fine needle aspiration

increased efficiency, but no clinical study has been published yet about the effectiveness of this system.

After the target lesion is identified and the scope placed into a stable and proper position for the lesion, the needle system is inserted through the working channel of the echoendoscope and advanced to the tip of the scope with the lesion in close proximity. To achieve the proper position, the transducer of echoendoscope should contact the luminal wall firmly near the target lesion, and the lesion should be within the potential direction of the needle in order to perform FNA without difficulty, which is usually at the 6 o'clock position on the EUS screen. Slow movements of the echoendoscope and using the up and down knob and the elevator may help to achieve the proper position and to set the needle angle. Straightening the tip of the echoendoscope is especially important when puncturing lesions located in the pancreatic head. It may be difficult to pass the needle system if the echoendoscope is angulated. In this situation, instead of pushing the system by force, the endoscopist should reduce the scope to a straight position, insert the needle system completely, and then reposition the scope at the target lesion. The use of small gauge needles reduces the difficulty of passing the needle through an angulated scope.

After the needle system is completely inserted into the channel, it is firmly screwed onto the biopsy channel and the needle stop is set to limit the maximum distance that the needle can be advanced. The stylet inside the needle may prevent contamination of the needle tip during puncturing the intestinal wall; although, recent studies have questioned the benefit of using a stylet [33, 34]. If the stylet is used, it is withdrawn slightly before advancing the needle into the target tissue to facilitate entry and then may be readvanced to remove any potential tissue clogging the tip of the needle. Transgastric puncture sometimes may be difficult due to the thicker and redundant gastric wall. Suctioning the gastric wall and advancing the needle with a brisk but controlled, forceful maneuver may overcome this problem.

The needle is always advanced into the target lesion under direct EUS guidance. To avoid excessive needle excursion, the palm of the right hand grasps the handle with the last three fingers and the movable part is controlled by the thumb and index finger. The elevator of the scope can help deflect the needle with small adjustments. After the lesion is punctured properly, the stylet may be removed completely or left inside the needle. If a vacuum syringe is used, the stylet is removed completely after puncturing the lesion and a 10 ml vacuum syringe is affixed to the handle port for permanent suction. Then, the needle is moved back and forth about 5–10 times through the lesion to shear-off cells under sonographic control. If a vacuum suction syringe is not used, the stylet is retracted slightly inside the needle and the needle passed through the lesion. Before withdrawing the needle from the lesion, 5–10 ml of suction may be applied for a few seconds. The endoscopist should be careful to keep the needle inside the lesion and to turn the suction off before withdrawing the needle from the lesion. After the procedure has been completed, the needle is removed from the scope and the aspirant is expressed onto a slide or container. An air-filled 10 ml syringe or stylet through the needle can be used to express the aspirate from the needle tip. After all the material is evacuated from the needle, it is cleansed and rinsed in sterile saline or alcohol by aspiration and flushing. Then it is reassembled for the next pass.

The overall experience with EUS-FNB is limited compared to EUS-FNA. Suction or stylet use is not suggested when using a 19G needle or core biopsy needle since it might increase the bloodiness of specimens. Repeated insertion of the needle into the same area should be avoided. Multiple biopsies may increase bleeding, and more than three passes is usually not suggested. The needle may be moved back and forth within the lesion 2 or 3 times.

How Can We Increase Diagnostic Yield of EUS-FNA?

Small technical tricks and details during EUS-FNA may increase diagnostic yield and success of the whole procedure. A "fanning" technique

involves advancing the needle into different areas within the lesion to secure cells from, both, the center and periphery of the mass (Fig. 23.8). A recent study has shown that this FNA technique was superior to the standard approach because fewer passes were required for diagnosis, and there was a trend towards increased diagnostic accuracy (96 vs. 77 %, $p = 0.05$) [35].

The use of 5–10 ml of suction for a few seconds before withdrawing the needle from the target lesion may increase cellular yield. A prospective randomized controlled trial showed that EUS-FNA of solid masses using suction yielded significantly higher sensitivity and negative predictive value for diagnosis without increasing bloodiness [36]. However, another study found that applying suction during FNA of lymph nodes did not improve diagnostic accuracy and increased specimen bloodiness compared to without suction [37]. It may be suggested to start EUS-FNA of solid lesions without suction but add further passes with suction if the cellular yield is inadequate. The European Society of Gastrointestinal Endoscopy (ESGE) technical guideline recommends using suction for EUS-FNA of solid masses/cystic lesions and not using suction for lymph nodes [38].

The number of needle passes to obtain cytologically adequate samples is unclear. ROSE may decrease the number of passes [39]. If on-site cytopathology is not available, 4–6 passes for a mass lesion, 3–4 passes for a lymph node, 5 for subepithelial lesions, and 2–3 for liver lesions is generally suggested to optimize diagnostic yield [37, 40]. Directing the needle to different parts of the lesion with each pass may increase the quality of sample. Advancing the needle repeatedly through the same tract may result in bloodier samples with decreased quality. Moreover, targeting the periphery of large lesions may also increase the diagnostic yield since the central areas are usually associated with necrosis.

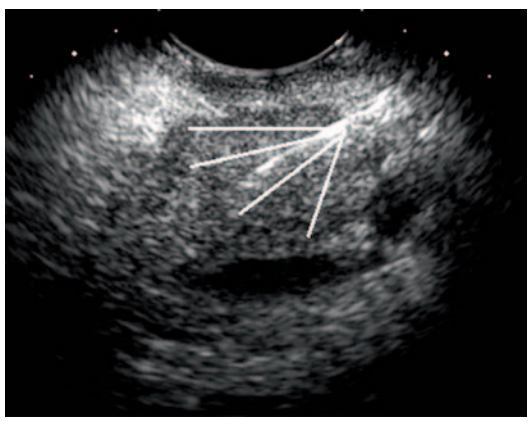

Fig. 23.8 Fine needle aspiration of a pancreatic mass and schematization of "fanning" technique

What If Enough Material Cannot Be Aspirated or Cytology Shows Inconclusive Results?

When confronted with nondiagnostic or indeterminate cytology, the patient should be reevaluated carefully. If there is a high clinical and/or imaging suspicion of cancer, the next step may be surgery.

If a cytological diagnosis is essential for management, patients can undergo repeat EUS-FNA. The diagnostic yield for repeat EUS-FNA of suspected pancreatic cancer ranged between 27 and 82 % in different studies [41–43]. The rate of repeat FNA varied among the centers from 5 to 10 % [41–43].

One of the important factors to increase diagnostic yield of FNA is ROSE of the cytological material. Nearly all published studies have demonstrated advantages of on-site cytopathology during EUS-FNA [44]. The use of ROSE for EUS-FNA decreases the number of patients who require a repeat procedure [41]. ROSE increases the diagnostic yield of EUS-FNA approximately 10–15 to 92 % sensitivity and 100 % specificity [45]. However, despite data supporting ROSE, widespread use remains limited due to restricted availability beyond academic and specialized centers, and low reimbursement rates.

Using a core needle to obtain a histological sample may be another option. Adequate histological samples may overcome the problem with limited use of ROSE. Core histology specimens may enable tissue profiling and cell culture as molecular-targeted agents and biological

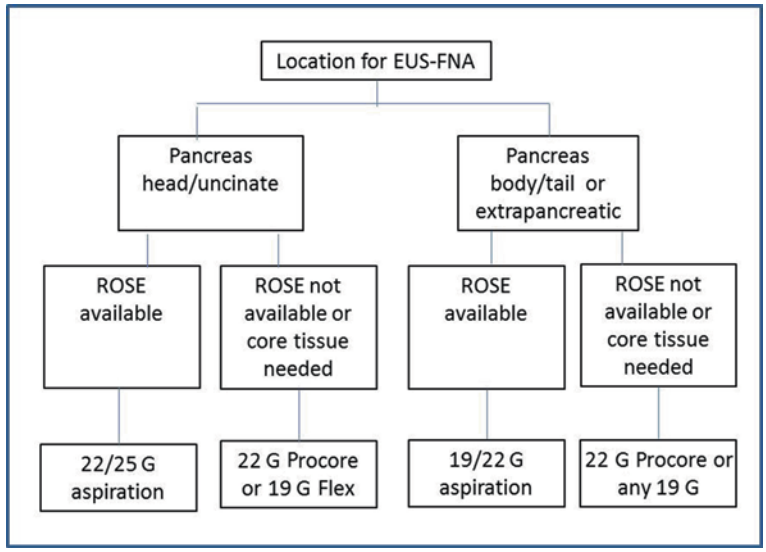

Fig. 23.9 An algorithm for needle type and size choices based on location of lesion, availability of ROSE, and need for core tissue

therapies are assuming more importance in the treatment of GI cancers. EUS-FNB can be performed during the same EUS session if FNA failed or ROSE showed inconclusive results after three or four passes. If ROSE is not available, using a core needle to procure a histological sample may increase diagnostic yield. A recent, multicenter prospective study showed that EUS-FNB with a 22G Procore needle produced a sample suitable for histological evaluation in 88.5 % of the cases after only one needle pass [46]. No study has evaluated the value of using a Procore needle during the same session following failed EUS-FNA or inconclusive ROSE results. However, this seems a more efficient option than repeating EUS-FNA. We suggest an algorithm for choosing needle type and size based on location of the lesion, ROSE availability, and desire for core tissue (Fig. 23.9).

Case Continued

Two passes into a mediastinal lymph node were performed using a 22G aspiration needle (Fig. 23.10). ROSE was available, and the smear was positive for malignant cells. The lymph node was diagnosed as a metastatic large cell carcinoma. Then, the pancreatic mass was targeted with the 22G aspiration needle and after two passes, ROSE showed positive malignant cells consistent with high grade adenocarcinoma. Subsequent cytological diagnosis confirmed the ROSE results. The patient was diagnosed with an advanced stage pancreatic adenocarcinoma and referred to oncology for chemotherapy.

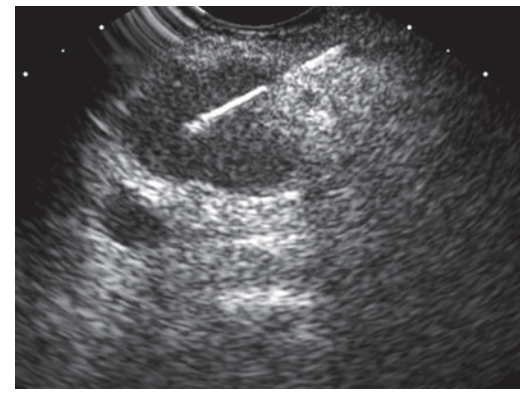

Fig. 23.10 EUS-FNA of lymph node in the patient. *EUS* endoscopic ultrasound; *FNA* fine needle aspiration

EUS-FNA for Cystic Lesions

Cystic lesions of the pancreas show a wide spectrum of demographic, morphological, and histological characteristics. The accurate diagnosis and discrimination of these lesions are very important because of the presence of malignancy or tendency to develop malignancy over time in some pancreatic cysts. Clinically, mucinous (intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN)), and nonmucinous cysts (pseudocysts and serous cystadenoma) must be distinguished. Cross-sectional imaging tests and EUS alone are often inadequate to accurately differentiate between benign or malignant and mucinous or nonmucinous cysts. EUS-FNA is currently the most helpful procedure for the differentiation and clinical management of these patients [47–49].

EUS-FNA of pancreatic cystic (Video 23.1) lesions needs extra care compared to solid lesions. Complications including infection, bleeding, and pancreatitis have been reported more frequently following EUS-FNA of cystic lesions compared to solid masses [38, 50, 51]. Prophylactic antibiotics are usually recommended for patients undergoing FNA of pancreatic cysts. The aspiration of all cyst contents may minimize the risk of infection and maximize diagnostic yield. The tip of the needle should be carefully maintained within the cyst lumen since wall abrasion may lead to bleeding during complete evacuation of the cyst. The largest and most accessible locule should be targeted in multilocular cysts. A solid component associated with the cyst should increase the suspicion of malignancy and be targeted for FNA. Due to the high viscosity of mucinous fluid, a 22G or 19G aspiration needle is more appropriate for cyst aspiration; however, a 25G needle may also be used for small (<2 cm) nonmucinous cysts or a transduodenal approach. The 19G needle may aspirate viscous fluid more efficiently and allows the use of novel instruments such as cytobrushing and confocal probes. The new 19G Flex needle may offer the large diameter of a 19G needle while providing a more flexible device for accessing head lesions.

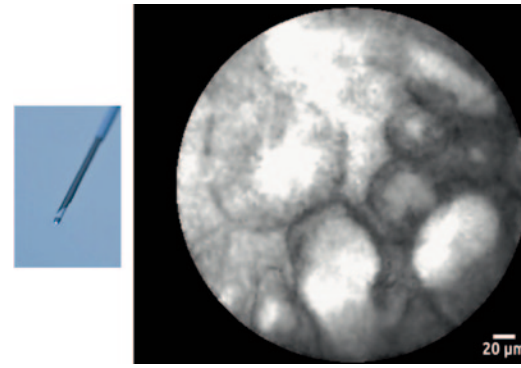

Fig. 23.11 Confocal laser endomicroscopy miniprobe on *left*, and papillary structures in a patient with IPMN on *right. IPMN* intraductal papillary mucinous neoplasm

Occasionally, debris or clot may block the needle tip and interfere with cyst aspiration. Clot, mucin globules, and septations should be avoided during FNA. The stylet may be used to dislodge adherent or obstructing material from the needle tip and/or channel by advancing the stylet through the needle.

After EUS-FNA, cyst fluid is routinely evaluated for gross appearance, amylase levels, CEA, and cytology. Genetic mutations (*KRAS* and *GNAS*) may aid in the diagnosis in select cases [52]. Recently, a confocal laser endomicroscopy miniprobe (nCLE) has been developed for use during EUS-FNA to visualize cyst wall and epithelium directly (Fig. 23.11). Preliminary studies of pancreatic cystic lesions showed promising cyst wall imaging findings to differentiate mucinous and nonmucinous cysts [53]. A pilot study reported 100% specificity to diagnose mucinous pancreatic cysts by nCLE with 3% rate of pancreatitis [54]. Further studies are needed to ascertain the contribution of nCLE for diagnosing cystic pancreatic lesions.

What Are Complications of EUS-FNA and How Can they Be Avoided?

EUS-FNA is generally a safe procedure with low incidence of complications. The most frequent complications are infection, bleeding, and acute

pancreatitis. The frequency and severity of complications vary according to the type of lesion and endosonographer experience. Most studies reported a procedure-related complication rate between 0.5 and 3.5%. A systematic review pooling 10,941 patients from 51 articles reported an approximately 1% overall morbidity rate for EUS-FNA [50]. The mortality rate attributable to EUS-FNA was 0.02%. The morbidity rate was significantly higher in prospective studies compared to retrospective studies (2.44 vs. 0.35% for pancreatic mass and 5.07 vs. 2.33% for pancreatic cysts). Therefore, complication rates may be underestimated in retrospective studies.

The most important risk factors for complications include endosonographer inexperience and FNA of cystic lesions [38, 50, 51]. Cysts are more prone to infection and bleeding. Antibiotic prophylaxis typically with a fluoroquinolone is administered routinely before and for 3–5 days after aspiration of any cystic lesion [38]. In large prospective series using antibiotic prophylaxis, 0–1.4% rate of infectious complications have been reported [17, 55]. Multiple passes into a cyst may increase risk of infection. Therefore, the goal of cyst aspiration is to completely drain the cyst contents to minimize risk of infection and maximize diagnostic yield. Aspiration of simple mediastinal cysts is contraindicated and indicated only when the cyst appears atypical or complex to rule out malignancy. There is no clear evidence that EUS-FNA of solid lesions may cause bacteremia and infectious complications.

A single-center study including 327 procedures of solid pancreatic lesions reported 3.4% post-procedural adverse event [56]. Multivariate analysis showed that pancreatic lesions less than 2 cm in diameter and neuroendocrine tumors were associated with more frequent complications. These results have not been confirmed by other studies.

Rates of acute pancreatitis after EUS-FNA range from 0.26 to 2% in different studies [17, 57, 58]. No significant risk factors were identified for post-EUS-FNA pancreatitis. A history of recent pancreatitis appeared to be a potential risk factor in one study [58]. If there is not a clear indication that may change clinical management, it is best to avoid EUS-FNA in the setting of recent pancreatitis.

Self-limited minor bleeding without clinical findings may occur following EUS-FNA of solid lesions, but clinically significant extra-luminal bleeding is very rare [59, 60]. Bleeding is more frequent and may cause significant consequences in FNA of cystic lesions. The rate was reported as 6% in a prospective study [61]. A gradually expanding hyperechoic area within the cyst after needle puncture is an important finding indicative of bleeding. In these cases, the procedure should be stopped and a short course of antibiotic is suggested. EUS-FNA should not be performed in patients with uncorrectable coagulopathy or on antiplatelet agents [62].

Less frequent complications have been reported after EUS-FNA in case reports and most were not directly related to FNA. Tumor cell seeding following EUS-FNA has been reported in a few cases. The actual risk of this is unknown, but significantly lower compared to percutaneous CT or US-guided FNA [63].

Key Points

- EUS-FNA should be performed if the results will impact patient management.
- Endosonographer experience, availability of adequate equipment, expertise of endoscopy staff, effective sedation, and quality of cytological examination are key factors for success.
- The location, route of access, nature of the lesion, need for histologic sample, and availability of rapid onsite evaluation (ROSE) should be considered when deciding the type and size of needle to use.
- Procore biopsy needles can obtain histologic samples, which may decrease the number of passes necessary for diagnosis and may be a better choice when ROSE is not available.
- The use of a stylet does not seem to impact diagnostic yield. Suction may help increase cellular yield. The “fanning” technique likely improves diagnostic accuracy.

- Complication rates may be higher in EUS-FNA of cystic lesions; and thus, require extra care compared to solid lesions.

Conflict of Interest The authors declare no conflict of interest.

Financial Disclosures None

Video Caption

Video 23.1 EUS-FNA of pancreatic cyst

References

1. Eltoum IA, Alston EA, Roberson J. Trends in pancreatic pathology practice before and after implementation of endoscopic ultrasound-guided fine-needle aspiration: an example of disruptive innovation effect? Arch Pathol Lab Med. 2012;136:447–53.
2. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75:319–31.
3. Roy AK, Kim M, Hawes R, Varadarajulu S. 196 changing trends in tissue acquisition in pancreatic diseases. Gastrointest Endosc. 2013;77:AB134.
4. Kim TH, Choi KH, Song HS, Kim JW, Jeon BJ. Histology combined with cytology by endoscopic ultrasound-guided fine needle aspiration for the diagnosis of solid pancreatic mass and intra-abdominal lymphadenopathy. Gut Liver. 2013;7:605–10.
5. Larghi A, Verna EC, Ricci R, et al. EUS-guided fine-needle tissue acquisition by using a 19-gauge needle in a selected patient population: a prospective study. Gastrointest Endosc. 2011;74:504–10.
6. Varadarajulu S, Fockens P, Hawes RH. Best practices in endoscopic ultrasound-guided fine-needle aspiration. Clin Gastroenterol Hepatol. 2012;10:697–703.
7. Bang JY, Varadarajulu S. Procore and flexible 19 gauge needle can replace trucut biopsy needle? Clin Endosc. 2013;46:503–5.
8. Mertz H, Gautam S. The learning curve for EUS-guided FNA of pancreatic cancer. Gastrointest endosc. 2004;59:33–7.
9. Eloubeidi MA, Tamhane A. EUS-guided FNA of solid pancreatic masses: a learning curve with 300 consecutive procedures. Gastrointest endosc. 2005;61:700–8.
10. Harewood GC, Wiersema LM, Halling AC, Keeney GL, Salamao DR, Wiersema MJ. Influence of EUS training and pathology interpretation on accuracy of EUS-guided fine needle aspiration of pancreatic masses. Gastrointest endosc. 2002;55:669–73.
11. Jhala D, Eloubeidi M, Chhieng DC, et al. Fine needle aspiration biopsy of the islet cell tumor of pancreas: a comparison between computerized axial tomography and endoscopic ultrasound-guided fine needle aspiration biopsy. Ann Diagn Pathol 2002;6:106–12.
12. Mizuno N, Hara K, Hijioka S, et al. Current concept of endoscopic ultrasound-guided fine needle aspiration for pancreatic cancer. Pancreatology: official journal of the International Association of Pancreatology. 2011;11 (Suppl 2):40–6.
13. Hartwig W, Schneider L, Diener MK, Bergmann F, Buchler MW, Werner J. Preoperative tissue diagnosis for tumours of the pancreas. Br J Surg. 2009;96:5–20.
14. Karoumpalis I, Sigalas P, Salla C, et al. Endoscopic ultrasound staging and guided fine needle aspiration biopsy in patients with resectable pancreatic malignancies: a single-center prospective experience. Onkologie. 2011;34:533–7.
15. Baghbanian M, Shabazkhani B, Ghofrani H, et al. Efficacy of endoscopic ultrasound guided fine needle aspiration in patients with solid pancreatic neoplasms. Saudi J Gastroenterol. 2012;18:358–63.
16. Levy MJ, Norton ID, Wiersema MJ, et al. Prospective risk assessment of bacteremia and other infectious complications in patients undergoing EUS-guided FNA. Gastrointest Endosc. 2003;57:672–8.
17. Lee LS, Saltzman JR, Bounds BC, Poneros JM, Brugge WR, Thompson CC. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. Clin Gastroenterol Hepatol. 2005;3:231–6.
18. Banerjee S, Shen B, Baron TH, et al. Antibiotic prophylaxis for GI endoscopy. Gastrointest Endosc. 2008;67:791–8.
19. Anderson MA, Ben-Menachem T, Gan SI, et al. Management of antithrombotic agents for endoscopic procedures. Gastrointest Endosc. 2009;70:1060–70.
20. Ootaki C, Stevens T, Vargo J, et al. Does general anesthesia increase the diagnostic yield of endoscopic ultrasound-guided fine needle aspiration of pancreatic masses? Anesthesiology. 2012;117:1044–50.
21. Itoi T, Itokawa F, Sofuni A, et al. Puncture of solid pancreatic tumors guided by endoscopic ultrasonography: a pilot study series comparing Trucut and 19-gauge and 22-gauge aspiration needles. Endoscopy. 2005;37:362–6.
22. 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.
23. Hasan MK, Hawes RH. EUS-guided FNA of solid pancreas tumors. Gastrointest Endosc Clin N Am. 2012;22:155–67, vii.
24. Yusuf TE, Ho S, Pavey DA, Michael H, Gress FG. Retrospective analysis of the utility of endoscopic ultrasound-guided fine-needle aspiration (EUS-

FNA) in pancreatic masses, using a 22-gauge or 25-gauge needle system: a multicenter experience. Endoscopy. 2009;41:445–8.
25. Lee JH, Stewart J, Ross WA, Anandasabapathy S, Xiao L, Staerkel G. Blinded prospective comparison of the performance of 22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of the pancreas and peri-pancreatic lesions. Dig Dis Sci. 2009;54:2274–81.
26. Siddiqui UD, Rossi F, Rosenthal LS, Padda MS, Murali-Dharan V, Aslanian HR. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. Gastrointest Endosc. 2009;70:1093–7.
27. Affolter KE, Schmidt RL, Matynia AP, Adler DG, Factor RE. 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.
28. Brugge WR. EUS. Gastrointest Endosc. 2013; 78:414–20.
29. Varadarajulu S, Bang JY, Hebert-Magee S. Assessment of the technical performance of the flexible 19-gauge EUS-FNA needle. Gastrointest Endosc. 2012;76:336–43.
30. Chavalitdhamrong D, Draganov PV. Performance characteristics of a new flexible nitinol 19-gauge endoscopic ultrasound-guided fine needle aspiration needle. Gut Liver. 2013;7:756.
.31. Korenblit J, Singh H, Butt M, et al. 1018 prospective randomized trial of the 22G EchoTip Procore™ Needle Versus the 22G Cook EchoTip Ultra 3® needle in patients with solid mass lesions undergoing EUS-guided fine needle aspiration (FNA). Gastrointest Endosc. 2013;77:AB178.
32. Adler DG, Conway JD, Coffie JM, et al. EUS accessories. Gastrointest Endosc. 2007;66:1076–81.
33. 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.
34. 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.
35. Bang JY, Magee SH, Ramesh J, Trevino JM, Varadarajulu S. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. Endoscopy. 2013;45:445–50.
.36. Puri R, Vilmann P, Saftoiu 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.
37. 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.
38. Polkowski M, Larghi A, Weynand B, et al. Learning, techniques, and complications of endoscopic ultrasound (EUS)-guided sampling in gastroenterology: European Society of Gastrointestinal Endoscopy (ESGE) technical guideline. Endoscopy. 2012;44:190–206.
39. Schmidt RL, Walker BS, Howard K, Layfield LJ, Adler DG. Rapid on-site evaluation reduces needle passes in endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesions: a risk-benefit analysis. Dig Dis Sci. 2013;58:3280–6.
40. LeBlanc JK, Ciaccia D, Al-Assi MT, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. Gastrointest Endosc. 2004;59:475–81.
41. Collins BT, Murad FM, Wang JF, Bernadt CT. Rapid on-site evaluation for endoscopic ultrasound-guided fine-needle biopsy of the pancreas decreases the incidence of repeat biopsy procedures. Cancer Cytopathol. 2013;121:518–24.
42. Suzuki R, Lee JH, Krishna SG, et al. Repeat endoscopic ultrasound-guided fine needle aspiration for solid pancreatic lesions at a tertiary referral center will alter the initial inconclusive result. J Gastrointest Liver Dis. 2013;22:183–7.
43. Nicaud M, Hou W, Collins D, Wagh MS, Chauhan S, Draganov PV. The utility of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. Gastroenterol Res Pract. 2010;2010:268290.
.44. 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.
45. Jhala NC, Eltoum IA, Eloubeidi MA, et al. Providing on-site diagnosis of malignancy on endoscopic-ultrasound-guided fine-needle aspirates: should it be done? Ann Diagn Pathol. 2007;11:176–81.
46. Larghi A, Iglesias-Garcia J, Poley JW, et al. Feasibility and yield of a novel 22-gauge histology EUS needle in patients with pancreatic masses: a multicenter prospective cohort study. Surg Endosc. 2013;27:3733–8.
47. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126:1330–6.
48. Farrell JJ, Fernandez-del Castillo C. Pancreatic cystic neoplasms: management and unanswered questions. Gastroenterology. 2013;144:1303–15.
49. Pitman MB, Lewandrowski K, Shen J, Sahani D, Brugge W, Fernandez-del Castillo C. Pancreatic cysts: preoperative diagnosis and clinical management. Cancer Cytopathol. 2010;118:1–13.
50. Wang KX, Ben QW, Jin ZD, et al. Assessment of morbidity and mortality associated with EUS-guided FNA: a systematic review. Gastrointestinal Endosc. 2011;73:283–90.

51. Tarantino I, Fabbri C, Di Mitri R, et al. Complications of endoscopic ultrasound fine needle aspiration on pancreatic cystic lesions: Final results from a large prospective multicenter study. Dig Liver Dis. 2013.
52. Yoon WJ, Brugge WR. Pancreatic cystic neoplasms: diagnosis and management. Gastroenterol Clin N Am. 2012;41:103–18.
53. Konda VJ, Aslanian HR, Wallace MB, Siddiqui UD, Hart J, Waxman I. First assessment of needle-based confocal laser endomicroscopy during EUS-FNA procedures of the pancreas (with videos). Gastrointestinal Endosc. 2011;74:1049–60.
54. 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.
55. Al-Haddad M, Wallace MB, Woodward TA, et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. Endoscopy. 2008;40:204–8.
56. Katanuma A, Maguchi H, Yane K, et al. Factors predictive of adverse events associated with endoscopic ultrasound-guided fine needle aspiration of pancreatic solid lesions. Dig Dis Sci. 2013;58:2093–9.
57. Eloubeidi MA, Gress FG, Savides TJ, et al. Acute pancreatitis after EUS-guided FNA of solid pancreatic masses: a pooled analysis from EUS centers in the United States. Gastrointestinal Endosc. 2004;60:385–9.
58. Gress F, Michael H, Gelrud D, et al. EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. Gastrointestinal Endosc. 2002;56:864–7.
59. Eloubeidi MA, Tamhane A, Varadarajulu S, Wilcox CM. Frequency of major complications after EUS-guided FNA of solid pancreatic masses: a prospective evaluation. Gastrointestinal Endosc. 2006;63:622–9.
60. Bournet B, Migueres I, Delacroix M, et al. Early morbidity of endoscopic ultrasound: 13 years' experience at a referral center. Endoscopy. 2006;38:349–54.
61. Varadarajulu S, Eloubeidi MA. Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. Gastrointestinal Endosc. 2004;60:631–5.
62. Boustiere C, Veitch A, Vanbiervliet G, et al. Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy. 2011;43:445–61.
63. Chaya C, Nealon WH, Bhutani MS. EUS or percutaneous CT/US-guided FNA for suspected pancreatic cancer: when tissue is the issue. Gastrointestinal Endosc. 2006;63:976–8.

Essential Cytopathology Concepts for the Endosonographer

24

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Abbreviations

ROSE	Rapid on-site evaluation
EUS-FNA	Endoscopic ultrasound-guided fine-needle aspiration
FNA	Fine-needle aspirate
Pap stain	Papanicolaou stain
RPMI	Roswell Park Memorial Institute
GIST	Gastrointestinal stromal tumor
IPMN	Intraductal papillary mucinous neoplasm
MCN	Mucinous cystic neoplasm
HCC	Hepatocellular carcinoma

General Principles of Rapid On-site Evaluation (ROSE)

Rapid on-site evaluation (ROSE) entails having either a cytopathologist or cytotechnologist attend the EUS-FNA in order to provide immediate assessment and feedback about cellular material obtained during the procedure. In some institutions, however, physical distance may preclude the attendance by the pathologist, and in this setting, telepathology may be a formidable substitute. The reported sensitivity and specificity of EUS-FNA at most sites are between 80–90 % and 85–100 %, respectively, and ROSE has been demonstrated to improve the sensitivity and accuracy of EUS-FNA procedures [1–4]. It maximizes diagnostic yield, results in fewer fine-needle aspiration (FNA) passes, allows for proper triaging of the obtained material, and leads to an overall decrease in repeat procedures minimizing healthcare expenditure.

What is needed for the establishment of a successful ROSE service? Foremost, it requires the time of both the endoscopist and pathologist. ROSE may delay the turnaround time for endoscopic procedures with the hope of improved patient outcomes. A schedule of planned procedures should be made available to the pathologist in order to guarantee his/her presence at the time of the procedure. A stationary setup including glass slides, stains, and microscope should be located in or near the endoscopy suite; alternatively, the pathology service may have mobile carts with the necessary equipment (Fig. 24.1).

At a minimum, the endoscopist can expect the cytopathologist or cytotechnologist to provide an assessment of specimen adequacy, i.e., determining whether or not sufficient cellular material has been aspirated in order to obtain a diagnosis. However, oftentimes the pathologist will be able

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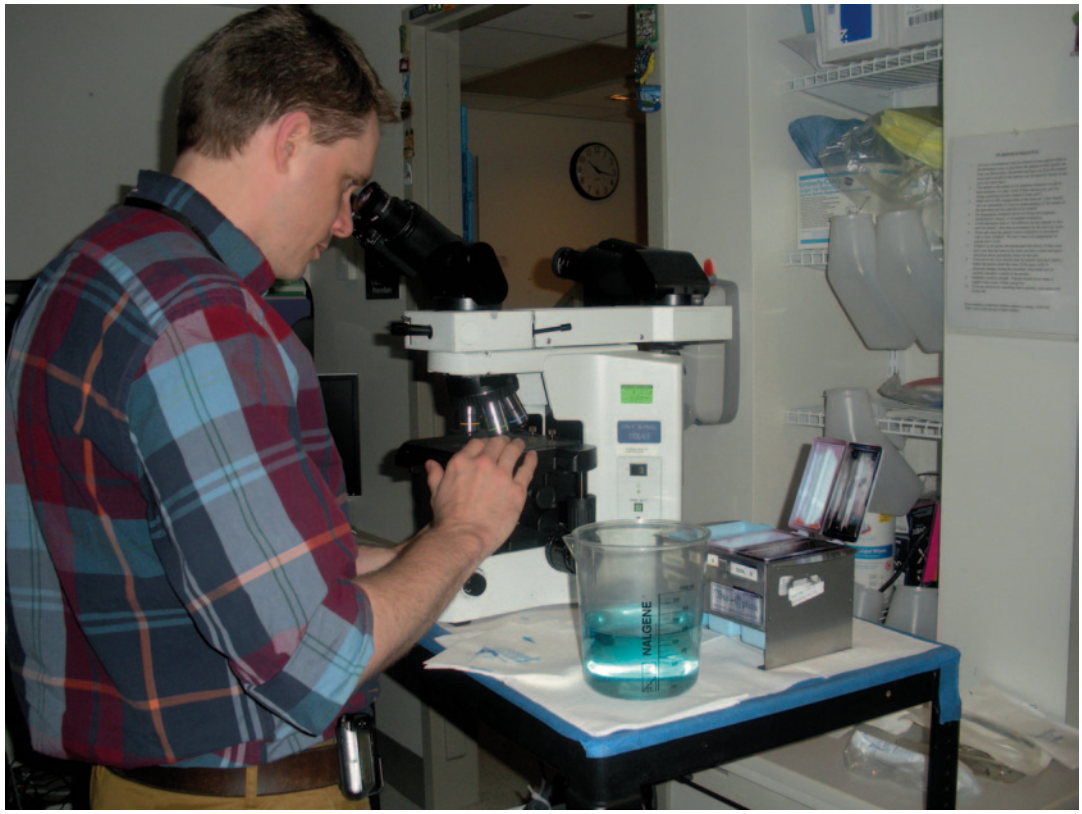

Fig. 24.1 The FNA mobile cart is equipped with a double-headed microscope as well as a Diff–Quik setup to stain slides for on-site assessment

to accurately render a preliminary interpretation. Of note, preliminary interpretations can sometimes differ from the final diagnosis, and thus, it is crucial that clinical decisions and treatment are based on finalized reports whenever possible. Clear communication between the endoscopist and the pathologist is essential during EUS-FNA. The clinical history and imaging features of the targeted lesion represent invaluable information and this should be communicated to the pathologist, particularly at the time of preliminary assessment.

Preparation and Triaging of Cellular Material

Preparation and triaging cellular material are key elements in diagnostic EUS-FNA procedures. Various techniques can be utilized with the most common ones concisely summarized and illustrated below.

In our institutions, once the lesion has been aspirated, the FNA needle is passed to the cytopathologist or cytotechnologist, and using the stylet, the material is extruded onto a single, properly labeled glass slide (Fig. 24.2a and 24.2b). Attaching a syringe to the FNA needle can further help expel residual cellular material. Depending on the cellularity of the obtained sample, direct smears can then be prepared. The preparation of direct smears is somewhat of an art, and it takes experience to recognize how much material should and should not be placed on the slide as well as the degree of pressure that is needed to produce an evenly distributed smear. In our practice, we use two glass slides placed parallel to each other with enough contact pressure to break up and distribute the material evenly (Fig. 24.2c). With a quick gliding motion, pulling the slides

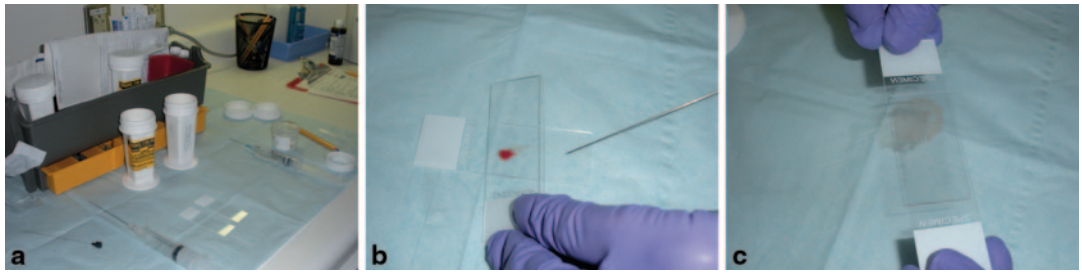

Fig. 24.2 Slide preparation during FNA. **a**. A typical setup during FNA. At our institution, the cytotechnologist carries a container that holds all the material needed to make smears including slides, ethanol fixative, and media for ancillary studies such as RPMI into the procedure room. **b**. The needle is placed onto a slide, and a second slide is used to capture the spray of any splashed material. The material is then extruded onto the slide. **c**. The two slides are then placed parallel to each other, and enough contact pressure is used to disperse the material evenly between the two slides. The slides are then pulled in opposite directions to produce two slides. One slide is left to air-dry (for on-site assessment), while the other is placed in an ethanol fixative (for later processing)

in opposite directions, two slides are produced; one is left to air-dry (for the on-site rapid Romanowsky stain), while the other is immediately placed in an ethanol fixative (for later laboratory staining via the Papanicolaou method). Alternatively, the top slide can be quickly pulled apart from the bottom slide in an upward motion. In either technique, if performed correctly, the two resulting slides are mirror images of each other and should provide identical cellular material for the two complementary stains in the evaluation of the obtained lesional material.

As previously mentioned, the air-dried slide is then stained using a Romanowsky technique. Many utilize Diff–Quik, a commercially prepared Romanowsky stain. This particular staining method consists of only three solutions, allows for rapid staining on-site, and highlights cytoplasmic detail well; however, detailed nuclear morphology is not readily evaluable with this stain. In contrast, the strength of the Papanicolaou stain (Pap stain), which is more time-consuming and performed later in the laboratory with the ethanol-fixed slide, lies in its revelation of nuclear detail. While particular pathologists tend to prefer one or the other stain, both stains complement each other.

After rapid Diff–Quik staining of the air-dried slides, the pathologist examines the slides under the microscope. The major goal at this point is to ensure that adequate material has been obtained and, if necessary, to triage the material for ancillary studies such as flow cytometry or microbiology. Acquisition of sample for ancillary tests may require several additional FNA passes. Of note, Roswell Park Memorial Institute (RPMI) medium is a cell preservative devoid of formalin and the preferred medium for flow cytometry and cytogenetics, especially if the suspicion for a hematolymphoid malignancy is high.

Oftentimes, abundant cellular material and blood are expelled onto a glass slide. Immediate preparation of direct smears will yield thick smears that greatly hinder the preliminary microscopic examination and may even result in interpretative errors. Hence, in this scenario, using the "pick and smear" technique, a portion of the cellular material is separated and transferred onto additional glass slides to produce direct smears [5]. The remaining material is allowed to congeal, thus forming a clot/pseudotissue biopsy, which can easily be picked up with the tip of a small needle or end of another slide and subsequently transferred directly into formalin for later use as a cell block.

Alternatively, needle rinses or additional FNA passes can be expelled directly into formalin or other media such as RPMI or CytoLyt in order to create a cell block. Many cell block preparation techniques are in use, and they often involve mixing the cellular material with a gelling agent to create a mold that can be processed like a routine

surgical biopsy specimen. The cell block has the advantage of providing material for subsequent immunohistochemistry which may be necessary to best classify a lesion.

In some practices, the pathologist may prefer to use a thin-layer cytologic technique such as ThinPrep. This technique does not allow for rapid on-site interpretation but does produce a concentrated preparation, which reduces the number of slides to be examined [6]. Many pathologists reserve this technique for cyst fluid interpretation in the setting of EUS-FNA.

Pathology Terminology

Pathology reports aim to state a diagnosis in concise and direct terms. For example, in the category of "positive for malignancy," the pathologist will try to render the most specific subcategorization possible (such as "adenocarcinoma"). However, sometimes the pathologist may resort to terms such as "atypical" and "suspicious." Unfortunately, the meaning that is conveyed by these terms is subject to interobserver variability. In our practice, the term "suspicious" is used when the specimen is quantitatively insufficient for a specific diagnosis. For example, an aspirate may consist of only one or two groups of cells with the features of malignancy. "Atypical" suggests that the cytologic features deviate from normal, but there are insufficient features to make a specific diagnosis. Therefore, "atypical" may refer to cellular changes seen in non-neoplastic or neoplastic lesions. Often, these indeterminate diagnoses are accompanied by an explanatory note. These comments convey essential information regarding the pathologist's overall interpretation and should be read in their entirety; they should figure heavily when the clinician is considering the pathology results.

Cytologic Features of Normal Structures Sampled in EUS-FNA

As EUS-FNA traverses the luminal gut, the presence of contaminating (normal) structures such as esophageal, duodenal, and gastric epithelium is frequently seen in aspirate smears (Fig. 24.3). The approach of the aspirate, for example transgastric versus transduodenal, should thus be conveyed to the pathologist.

Cytopathologic Features of Commonly Sampled Entities

This section will give the endoscopist a brief overview of the most commonly sampled pathologic entities by EUS-FNA. A detailed description of rare non-neoplastic and neoplastic lesions and an expansion on ancillary studies are beyond the scope of this chapter.

Luminal Gut

The vast majority of cancers affecting the luminal gut are epithelial. Most of these epithelial tumors are sampled by forceps biopsy; however, some tumors may predominate beneath the mucosa and are better accessed by EUS-FNA.

Epithelial Malignancies

Adenocarcinomas are gland forming malignancies and account for the majority of tumors in the distal esophagus, stomach, and small and large intestines. Although there are some site-specific cytologic features, in general, these tumors look remarkably similar. In metastatic adenocarcinoma, immunohistochemistry can be helpful for localization of the primary [7]. Colorectal adenocarcinomas typically express CK20 and lack expression of CK7 [15]. Esophageal, gastric, and small intestinal adenocarcinomas often show expression of both CK20 and CK7 [8]. CDX2, a gene involved in intestinal differentiation, is expressed in the vast majority of luminal gut adenocarcinomas as well as a subset of pancreaticobiliary adenocarcinomas [9].

Cytologically, adenocarcinomas are characterized by three-dimensional aggregates and sheets of cohesive cells. The neoplastic cells demonstrate high nuclear-to-cytoplasmic ratios, nuclear hyperchromasia and irregularities, coarse chromatin pattern, and prominent nucleoli (Fig. 24.4).

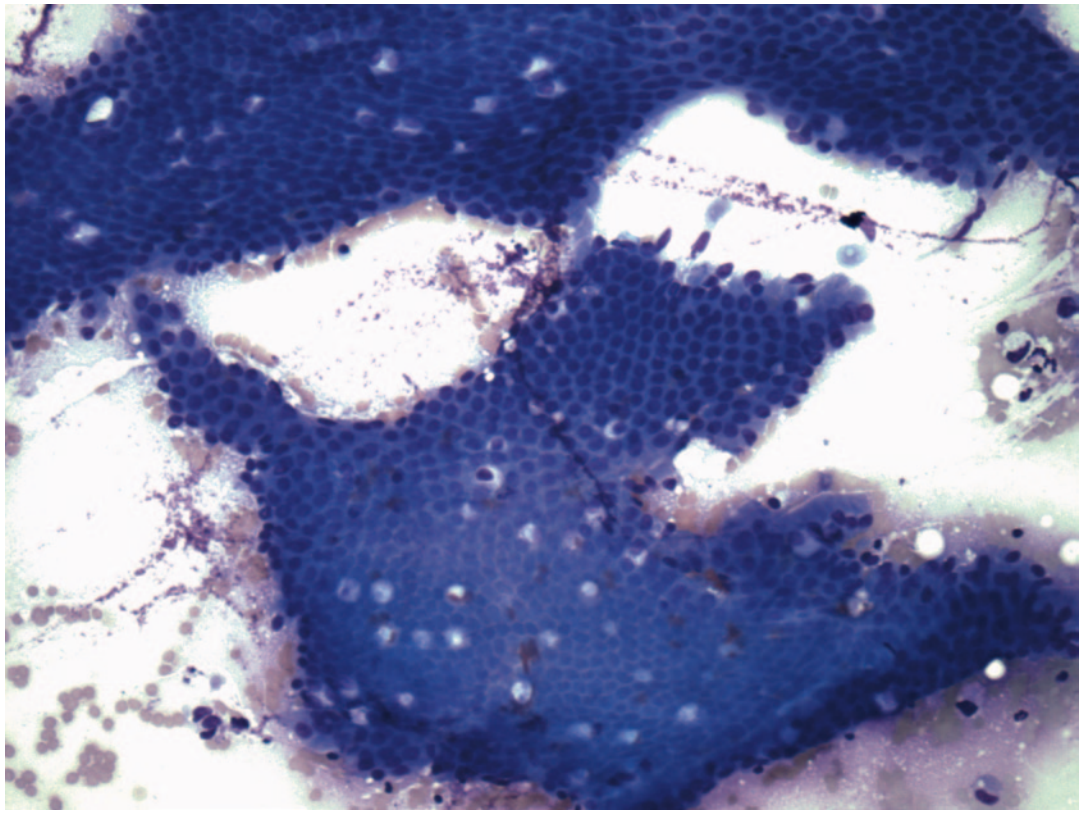

Fig. 24.3 Contaminating duodenal epithelium from EUS-FNA of pancreatic mass. Duodenal epithelium can appear as large sheets containing small, round nuclei. The pale staining cells interspersed throughout the sheet represent goblet cells, which are helpful in recognizing this epithelium as duodenal (Pap stain, 10x)

These nuclear features, while etiologically non-specific, indicate malignancy. Evidence of glandular differentiation such as cytoplasmic vacuolization, lumen formation, or mucin, when present, is very helpful in supporting a diagnosis of adenocarcinoma. Of note, colorectal carcinoma tends to have characteristic tall columnar cells and contains a "dirty" necrotic background (Fig. 24.5). These cytologic features may help in the setting of malignancy of unknown primary.

Squamous cell carcinomas tend to arise in areas lined by squamous epithelium (esophagus and anus), but they can occur anywhere along the luminal gut. Aspirates demonstrate flat sheets of cohesive cells with polygonal shapes and dense cytoplasm (Fig. 24.6). The nuclear features are similar to those described for adenocarcinoma. Keratinization, which is best appreciated on the Papanicolaou stain as orangeophilic staining, is a defining feature of squamous cell carcinoma (Fig. 24.6). Immunohistochemistry (p63, p40, cytokeratin 5/6) can be used to confirm that a tumor has squamous differentiation; however, it does not provide information regarding site of origin [10].

Neuroendocrine carcinomas including carcinoid tumors can occur anywhere along the luminal gut [11, 12]. Aspirates are in general very cellular, composed of a loosely cohesive, monomorphic cell population [13]. Nuclei are round to oval, eccentrically placed, and exhibit regular nuclear contours and finely stippled, "salt-and-pepper" chromatin (best seen on a Pap-stained slide). As the cytologic features of neuroendocrine tumors can overlap with other entities, immunohistochemistry may be needed for confirmation. Neuroendocrine carcinomas express cytokeratins as well as specific neuroendocrine antigens such as synaptophysin and chromogranin [11, 12]

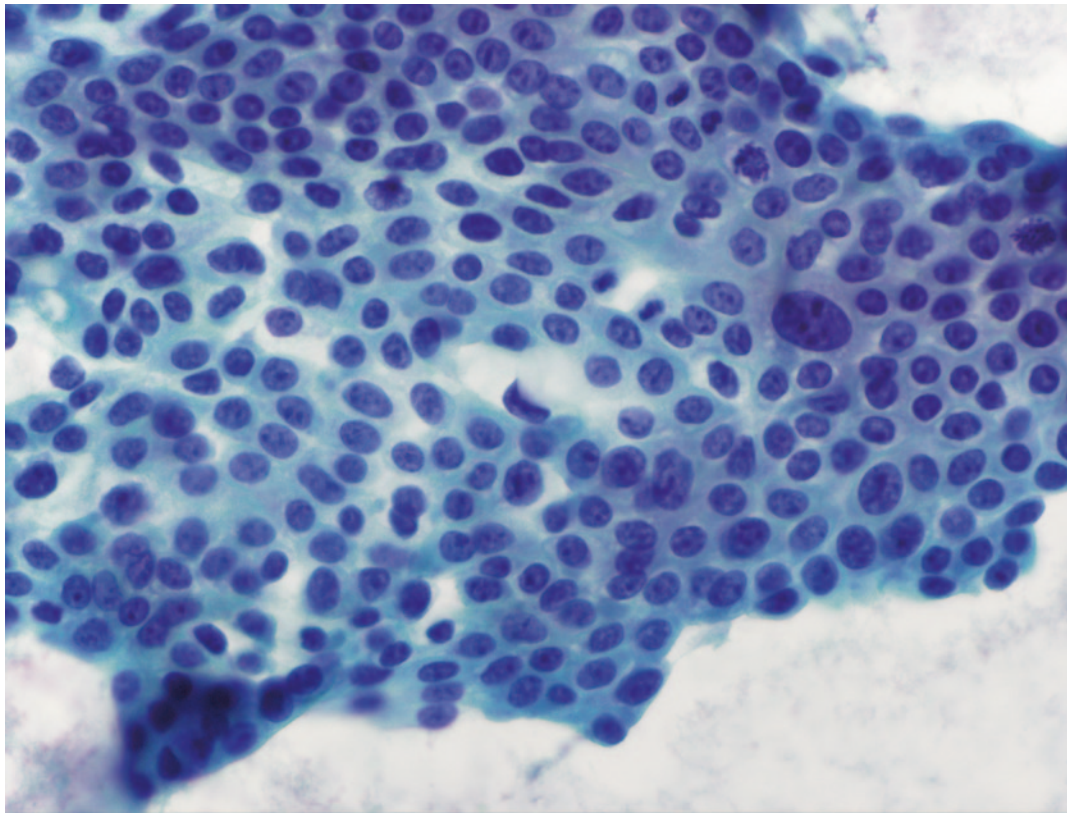

Fig. 24.4 Pancreatic adenocarcinoma. The general features of malignancy can be appreciated in this image. The cells demonstrate variability in cell size, nuclear hyperchromasia, and occasional nuclear membrane irregularities. Many of the cells demonstrate prominent nucleoli. Some of the tumor cells also demonstrate nuclear overlapping and loss of polarity which creates a "drunken honeycomb" appearance (Pap stain, 20x)

Mesenchymal Neoplasms

Most gastrointestinal mesenchymal tumors are subepithelial and best sampled by EUS-FNA. There are a host of mesenchymal tumors that can occur in the gastrointestinal tract. Location matters as leiomyomas are most commonly seen in the esophagus, whereas gastrointestinal stromal tumors (GISTs) are more common in the stomach and small intestine [14, 15]. A preliminary interpretation of "spindle cell neoplasm" is reserved for the majority of these cases. Procurement of additional material for cell block preparation is crucial as immunohistochemistry is essentially required for a more definitive diagnosis. In this section, we will limit our discussion to the most common mesenchymal tumor of the luminal gut, the gastrointestinal stromal tumor (GIST).

A GIST on aspirate is usually characterized by cellular fragments of spindle-shaped tumors cells (Fig. 24.7) [15, 16]. Some cases may feature round-to-oval tumor cells and these are designated as epithelioid GISTs. Perinuclear vacuoles are sometimes seen. Neoplastic nuclei typically have delicate chromatin and inconspicuous nucleoli. The cytoplasm may appear metachromatic on a rapid Romanowsky stain. Necrosis and mitoses are uncommon and suggest a more aggressive behavior.

GISTs are often responsive to treatment with tyrosine kinase inhibitors such as imatinib and sunitinib [15]. Molecular testing is sometimes performed prior to treatment, and sufficient material to form a cell block should be obtained. Additionally, immunohistochemistry is essential

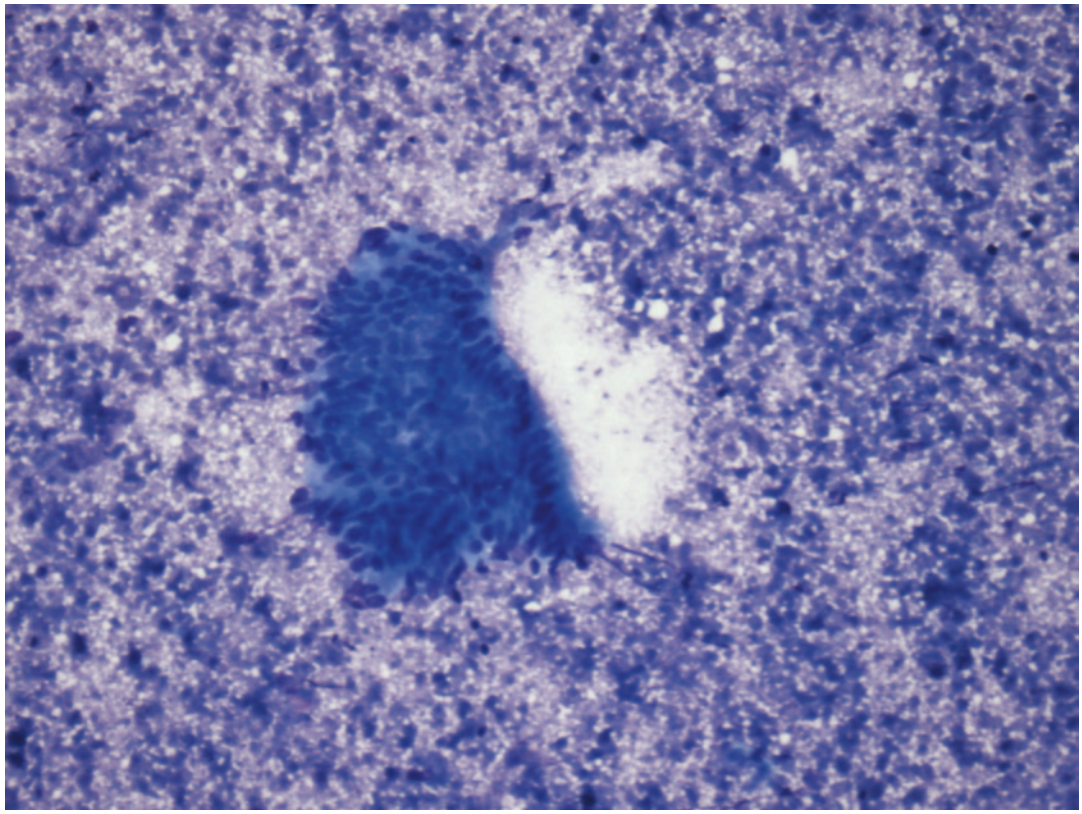

Fig. 24.5 Colonic adenocarcinoma. Aspirates contain tall, columnar, hyperchromatic cells. The nuclei often retain a basal orientation which imparts a "picket fence" appearance. Note the extensive, grungy, amorphous debris in the background (Diff–Quik, 10x)

to confirm and distinguish a GIST from other spindle cell lesions. Most GISTs demonstrate expression of CD117, DOG1, and CD34 by immunohistochemistry [14, 15]. In fact, the aspirate appearance of both leiomyoma and schwannoma can look almost identical to GISTs, and we always perform a small panel of immunohistochemistry (CD117, CD34, SMA, S100) to distinguish these tumors [14–16].

Lung and Mediastinum

EUS-FNA can be used to sample the lung, mediastinum, and even pleura. Epithelial malignancies are the most common lesions evaluated in the lung. General categories of primary malignant pulmonary epithelial neoplasms include adenocarcinoma, squamous cell carcinoma, large cell undifferentiated carcinoma, and tumors with neuroendocrine differentiation (typical and atypical carcinoid tumors, small cell carcinoma, and large cell neuroendocrine carcinoma). The cytologic features of pulmonary adenocarcinomas and squamous cell carcinomas do not substantially differ from their counterparts arising in other sites. However, pulmonary adenocarcinomas can be extremely well differentiated with very little atypia, making diagnosis potentially very difficult. A helpful feature in distinguishing a well-differentiated adenocarcinoma from reactive bronchial epithelial cells is the lack of cilia in the former and the presence of intranuclear pseudoinclusions in the latter [17]. At the time of a preliminary

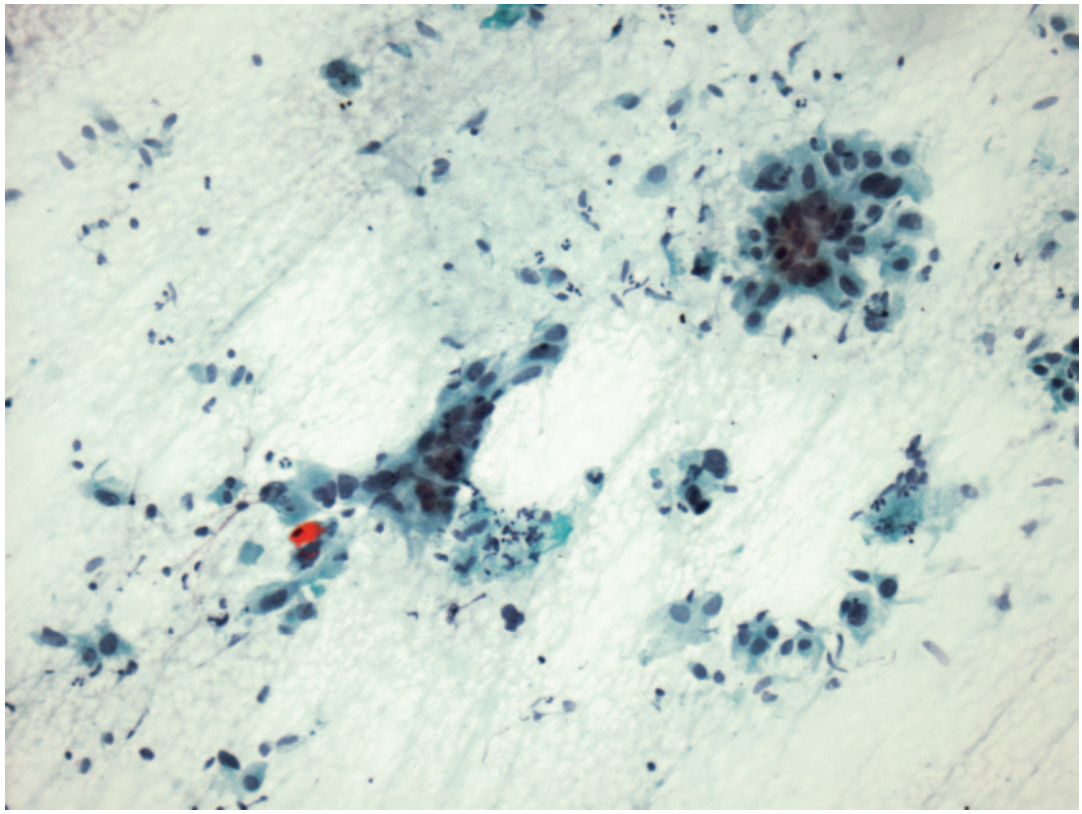

Fig. 24.6 Squamous cell carcinoma. Aspirates of squamous cell carcinomas have flat sheets with polygonal cells. Nuclear pleomorphism is also demonstrated in this image. A hallmark finding is the single-cell component with prominent dense, orangeophilic cytoplasm (Pap stain, 10x)

assessment, the term "non-small cell carcinoma" may be used; this term encompasses epithelial malignancies other than small cell carcinoma and other low-grade neuroendocrine carcinomas. A more specific final diagnosis is highly encouraged as targeted molecular therapies are now available. With the advent of molecular-based targeted therapies, testing for *EGFR, KRAS*, and *ALK* mutations is often requested by oncologists and obtaining adequate material for a cell block in order to perform these tests should be considered.

In the setting of a poorly differentiated malignancy, immunohistochemistry may be helpful to confirm the epithelial differentiation of the tumor and to further define the specific epithelial subtype. For example, TTF-1 and Napsin are markers for primary lung adenocarcinomas [18, 19]. These markers are typically negative in squamous cell carcinoma, although TTF-1 expression can be seen in small cell carcinoma [20].

It is important to recognize small cell carcinoma as treatment modalities differ compared to non-small cell carcinoma. The tumor cells of small cell carcinoma are approximately three times larger than a standard lymphocyte and feature fine chromatin with inconspicuous nucleoli (Fig. 24.8) [21, 22]. Nuclear molding, apoptotic bodies, frequent mitoses, and crush artifact are all typical cytologic features (Fig. 24.8) [21, 22]. Unlike other pulmonary epithelial tumors, small cell carcinoma demonstrates a dotlike immunohistochemical staining pattern with antibodies to cytokeratins [22]. These tumors also demonstrate expression of CD56, synaptophysin, and chromogranin and

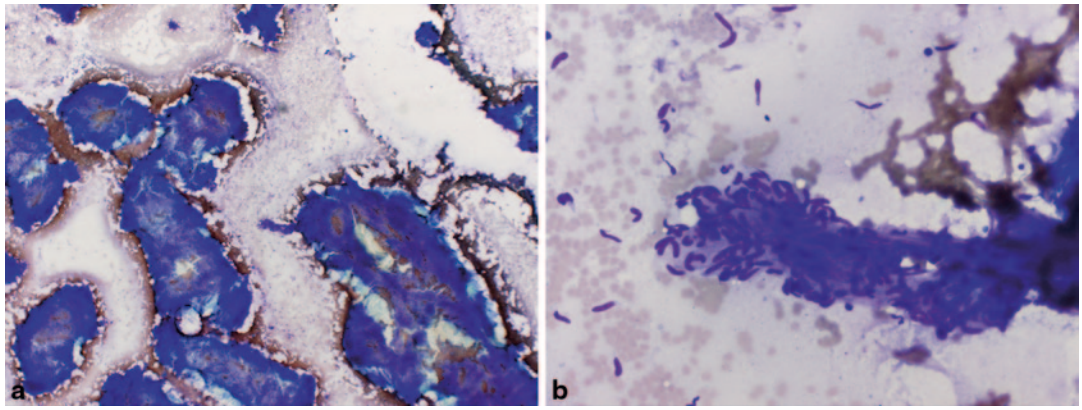

Fig. 24.7 **a** Gastrointestinal stromal tumor. Large cellular sheets of tumor cells can be appreciated on low power (Diff–Quik, 2x). **b** Gastrointestinal stromal tumor. At higher power, the tumor is composed of spindled cells with poorly demarcated cell borders (Diff–Quik, 20x)

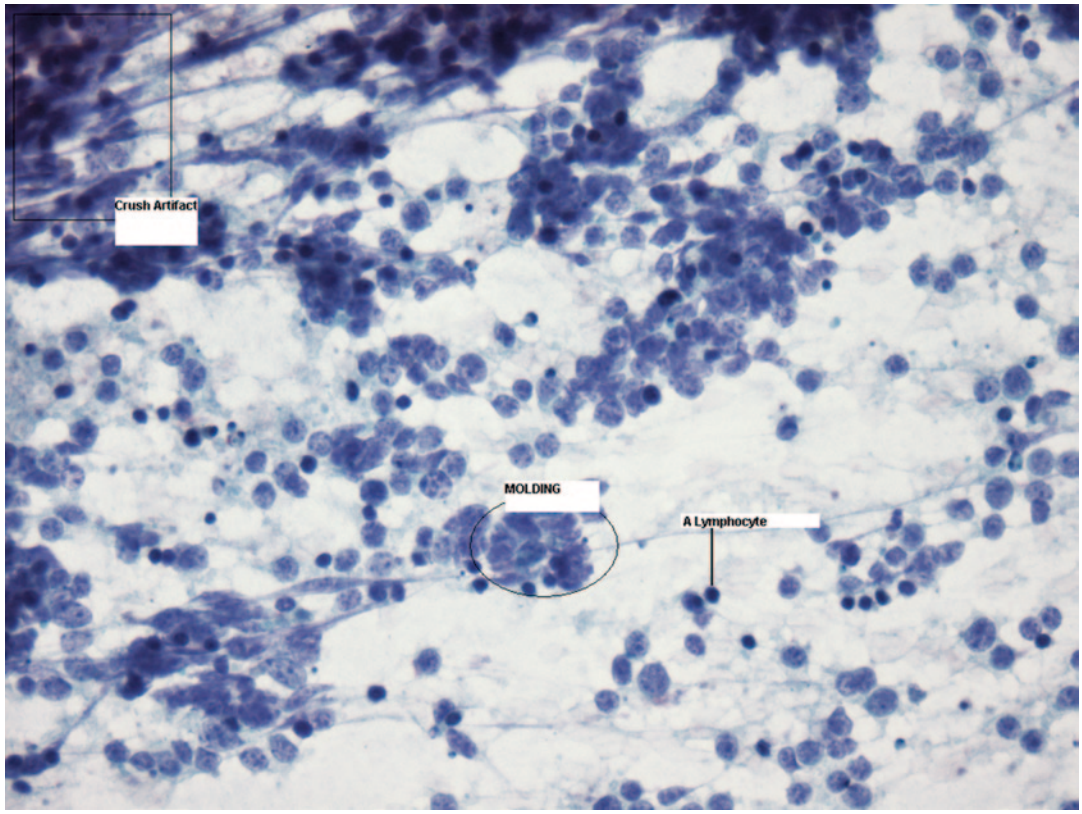

Fig. 24.8 Small cell carcinoma. The tumor cells of small cell carcinoma are two to three times larger than a resting lymphocyte. The tumor cells have scant cytoplasm and fine nuclear chromatin with inconspicuous nucleoli. Crush artifact and nuclear molding are characteristic features of small cell carcinoma (Pap stain, 20x)

lack expression of p63 [22, 23]. p63 is a marker that is expressed by the majority of squamous cell carcinomas and can be helpful in distinguishing a basaloid squamous cell carcinoma from other high-grade epithelial malignancies such as small cell carcinoma [23].

The mediastinum can be sampled to stage lymph nodes most commonly in the setting of lung cancer or to investigate adenopathy of unknown etiology. Primary neoplasms and other pathologic processes in the mediastinum can also be aspirated. It is important that the pathologist knows the patient's history, mediastinal location (anterior, middle, or posterior), and imaging characteristics of the lesion as the differential diagnosis varies depending on these variables.

Lymph Nodes

EUS-FNA can be used to evaluate adenopathy of unknown etiology as well as to stage epithelial malignancies. Commonly sampled nodes that are accessible by EUS-FNA include paraesophageal, mediastinal, perigastric, peripancreatic, retroperitoneal, and perirectal lymph nodes. The differential diagnosis for adenopathy is extensive; however, common etiologies include metastases, lymphoma, infection, or non-neoplastic conditions such as sarcoidosis. On-site assessment of lymph nodes can be extremely helpful in appropriately triaging material obtained for ancillary studies.

With respect to metastatic tumors, the cytomorphology is in most cases identical or similar to the primary tumor. However, sometimes the metastatic tumor cells will be few in number and admixed with the background nodal lymphocytes that can make identification of rare tumor cells difficult. Occasionally, immunohistochemistry may be needed to further define the site of origin and a cell block will be necessary. Following treatment of adenocarcinomas, often all that remains is thick mucinous pools admixed with inflammatory cells. In this post-treatment setting, mucin signifies prior disease and does not constitute residual tumor.

EUS-FNA is useful for diagnosing lymphoproliferative disorders. Most lymphoma aspirates are characterized by a monotonous population of discohesive, often enlarged cells with a very high nuclear-to-cytoplasmic ratio, i.e., very scant cytoplasm (Fig. 24.9). The cytologic appearance of lymphomas is heterogeneous and beyond the scope of this chapter. However, a preliminary interpretation of "lymphoma" or "suspicious for lymphoma" and even "polymorphous lymph node favor reactive lymphadenopathy" often requires an additional important step: triaging material for flow cytometry. Flow cytometry is helpful in identifying B-cell clonality but less useful in detecting T-cell lymphomas. While cytomorphology with flow cytometry may provide a diagnosis, subclassification sometimes requires additional tests. Other ancillary studies such as cytogenetics, fluorescent in situ hybridization, and molecular testing may aid in diagnosis. Multiple separate FNA passes are often required to yield an adequate sample for these ancillary studies, and a generous lesional sample for cell block is often desired. A recent study demonstrated that sufficient material can be recovered from EUS-FNA to perform immunohistochemistry [24]. A specific lymphoma was diagnosed in 88.8% cases (135 of 152 cases), and enough material was obtained for flow cytometry and cytogenetics in this study [24]. In our experience, the diagnosis of some lymphoproliferative disorders, such as T-cell lymphomas and Hodgkin's lymphomas, can be challenging with EUS-FNA, and repeat procedures are sometimes needed to obtain diagnostic material.

For infectious etiologies (e.g., preliminary interpretations of "acute inflammation," "granulomatous inflammation," or "reactive lymphadenopathy"), some of the obtained material or additional passes should be submitted for culture. Clues to a possible fungal or mycobacterial infection include granulomatous inflammation and necrotic debris. Unstained direct smear slides or adequate cell block samples can also be prepared for special histochemical studies such as a silver stain to identify fungal organisms and a FITE/AFB stain to identify mycobacteria. In general, both microbiology and histochemical stains should be performed as a dual approach to identify an infectious etiology.

Sarcoidosis is considered a diagnosis of exclusion and requires clinical correlation. As such, cytology can only suggest the diagnosis. The typical cytologic finding in sarcoidosis is non-necrotizing, granulomatous inflammation.

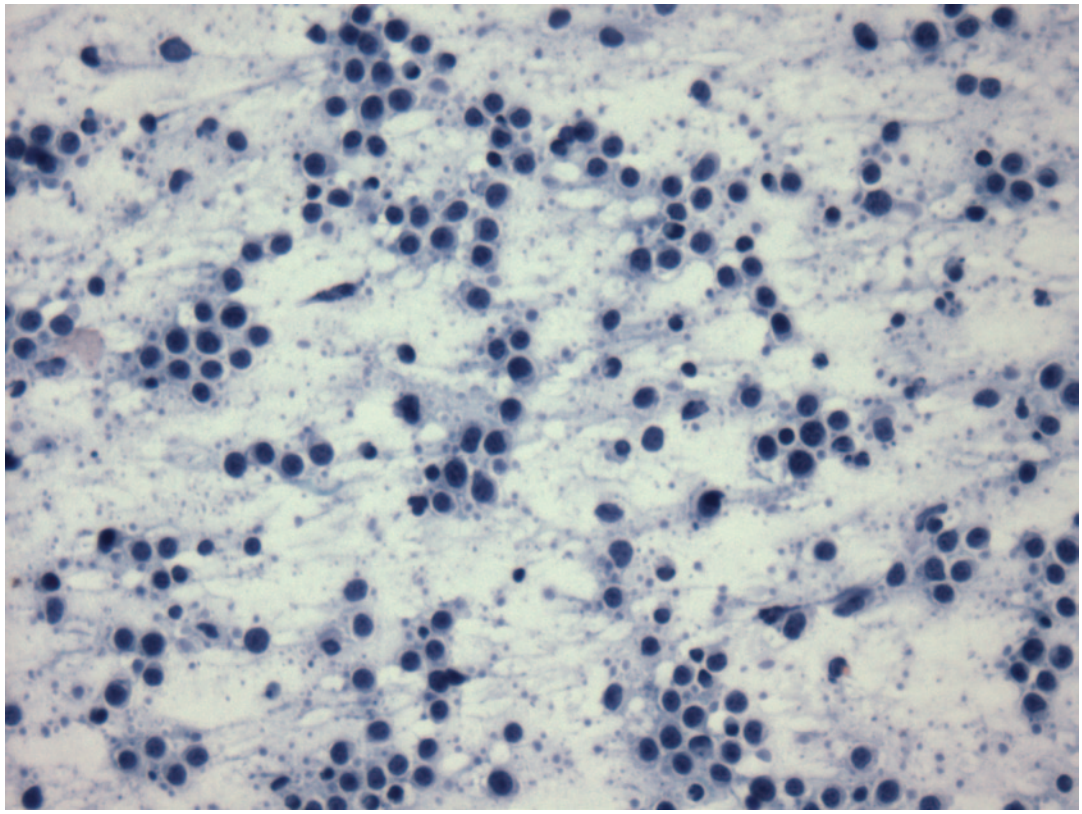

Fig. 24.9 Diffuse large B-cell lymphoma. The tumor cells are discohesive and relatively monotonous with very scant cytoplasm (Pap stain, 10x)

The granulomas of sarcoid are tightly clustered and contain epithelioid macrophages that impart a fairly distinct appearance. Necrosis is notably absent. In addition, cultures and histochemical stains for fungal elements and mycobacteria are negative.

Pancreas

A diagnostic algorithmic approach can be utilized with aspirates of pancreatic lesions (Fig. 24.10). The differential diagnosis varies depending on whether the lesion is predominantly solid or cystic. The first step for the cytopathologist always starts with determining whether lesional material has been obtained. Second, the pathologist must establish whether the tissue represents a neoplastic or non-neoplastic condition. The final initial step is to ensure that adequate material has been obtained to render a specific diagnosis. With regard to pancreatic adenocarcinoma, the most common pancreatic neoplasm, the diagnosis is usually straightforward and requires no immunohistochemical stains [25]. However, other lesions such as pancreatic neuroendocrine tumors, acinar cell carcinomas, and solid pseudopapillary neoplasms can look very similar on cytology and often require immunohistochemistry [26]. For the latter three, a preliminary interpretation of "epithelioid neoplasm, defer to cell block and immunohistochemistry" is prudent. A brief discussion regarding the more commonly encountered primary pancreatic tumors follows; however, as with other sites, the pancreas can be involved by metastases and lymphoproliferative disorders.

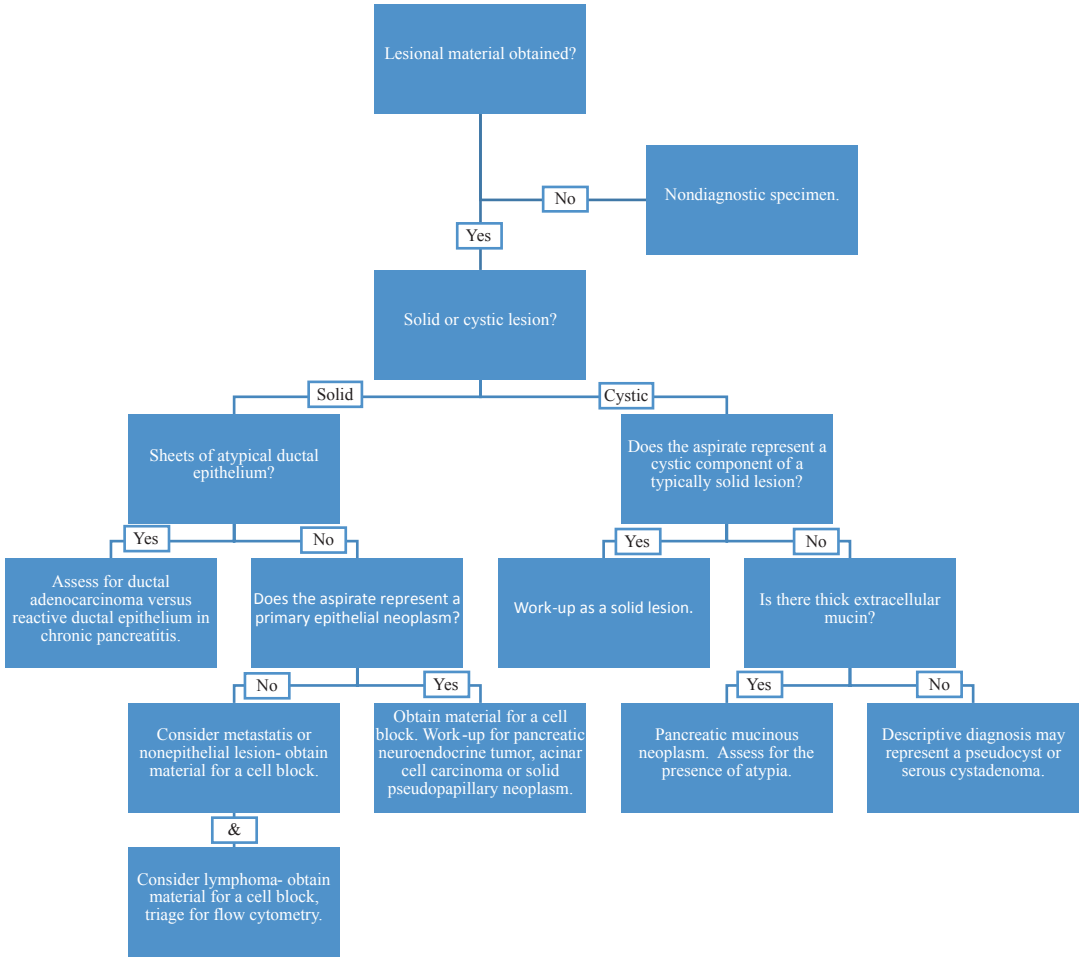

Fig. 24.10 An algorithmic approach to the cytopathologic classification of pancreatic masses

Solid Lesions

Pancreatic Ductal Adenocarcinoma

Variability in nuclear size (anisonucleosis) is one of the key cytologic features that distinguishes pancreatic ductal adenocarcinoma from benign ductal or reactive epithelial cells (Fig. 24.4). The cells of pancreatic ductal adenocarcinoma are often enlarged and have enlarged nuclei with irregular nuclear membranes, granular chromatin, and prominent nucleoli (Fig. 24.4). The architecture or arrangement of cells can also be a helpful feature especially in well-differentiated tumors. Normal ductal epithelium displays an orderly "honeycomb" arrangement; however, the cells of ductal adenocarcinoma are often overlapping and demonstrate a loss of polarity, thus rendering the so-called drunken honeycomb appearance (Fig. 24.4). Single atypical cells in the background are also helpful. Necrosis and mucinous and inflammatory debris are often observed in the background.

Pancreatitis, A Mimicker of Pancreatic Ductal Adenocarcinoma

Chronic pancreatitis can mimic ductal adenocarcinoma in its both clinical presentation and radiologic appearance [27]. Not infrequently, the two processes can coexist. Aspirates of chronic pancreatitis are composed of fragments of pancreatic tissue with some degree of fibrosis (Fig. 24.11). When present, acini are separated

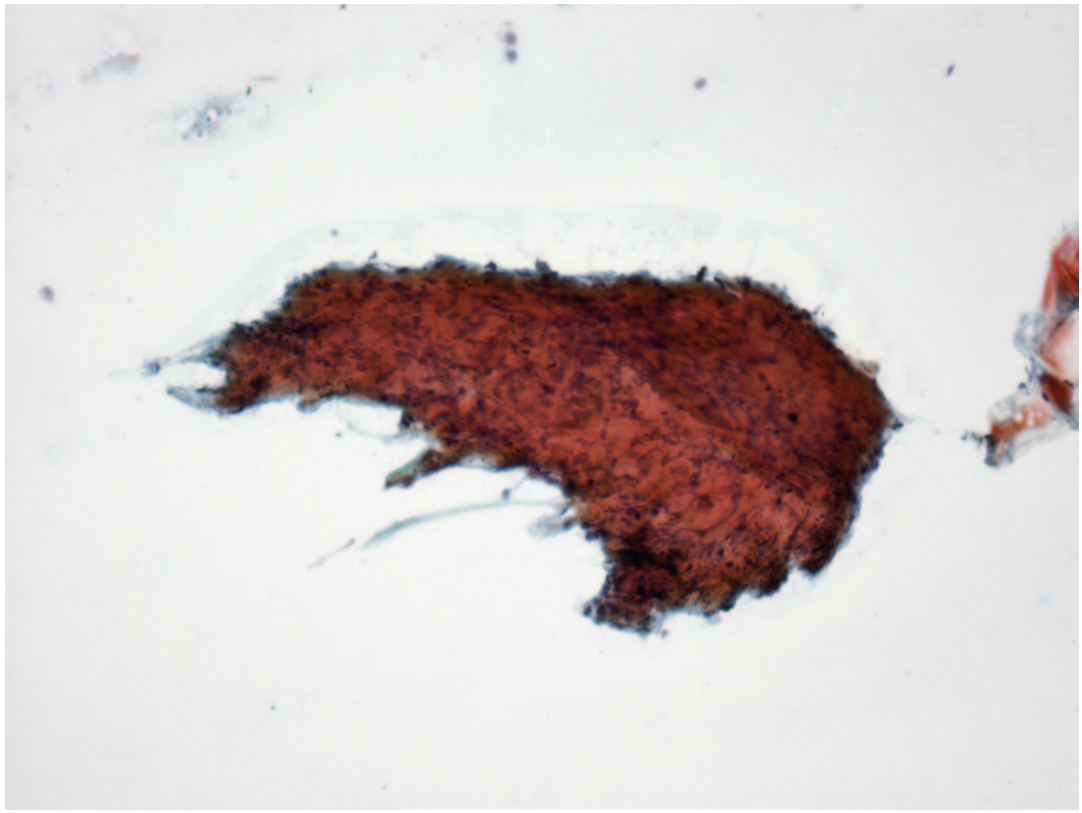

Fig. 24.11 Chronic pancreatitis. Stromal fragments composed of spindled cells are often seen in aspirates of chronic pancreatitis (Pap stain, 10x)

by fibrotic stroma and a mixed inflammatory infiltrate together with calcific debris and foamy histiocytes in the background. The ductal epithelium may demonstrate reactive changes such as a mild increase in cell size and more conspicuous nucleoli. The honeycomb architecture is often preserved, but some nuclear overlapping may be seen. Anisonucleocytosis, however, is usually minimal. Distinguishing a well-differentiated ductal adenocarcinoma from reactive ductal epithelial cells can be exceptionally challenging and may require several passes before convincing evidence to support either diagnosis is obtained. Moreover, as the Pap stain helps evaluate the nuclear features of neoplasia, a definite diagnosis may not be possible during ROSE.

Acute pancreatitis is not often sampled by FNA. However, the cytologic findings of acute pancreatitis include cellular degeneration, acute inflammation, and granular debris [1]. Fat necrosis and foam cells (histiocytes filled with lipid) may also be present. The ductal epithelium can appear markedly atypical mimicking ductal adenocarcinoma. Thus, the pathologist should exercise caution before making a diagnosis of cancer in the setting of acute pancreatitis.

Autoimmune pancreatitis can present as a mass-forming lesion or bile duct stricture [28]. Aspirates sometimes demonstrate cellular stromal fragments with lymphocytes and plasma cells [28]. The venulitis often seen on histology is not visualized in cytologic samples [28]. Autoimmune pancreatitis can be a difficult, if not impossible, diagnosis to render on cytology and requires clinical correlation. Evaluation of adequate cell block material for the presence of IgG4-positive plasma cells aids in the diagnosis of type 1 autoimmune pancreatitis (IgG4-related disease). Patients may have elevated levels of serum IgG4, but up to 30% of patients will have a normal level [29].

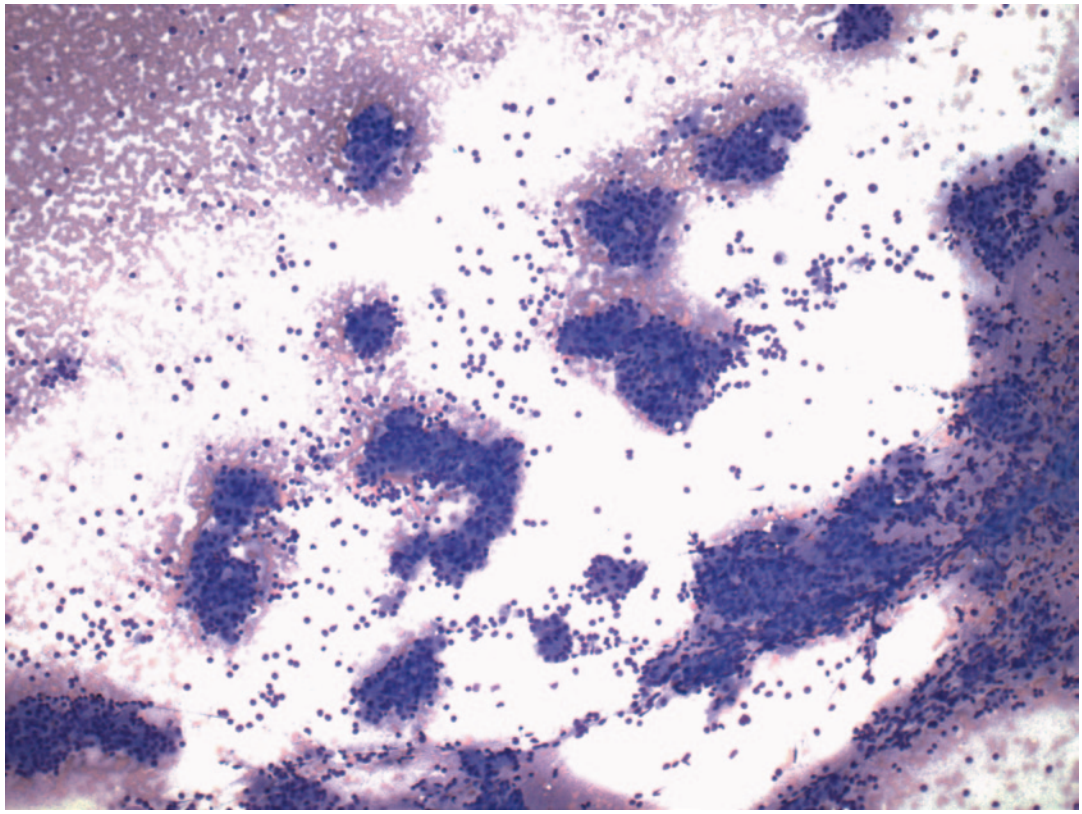

Fig. 24.12 Acinar cell carcinoma. This aspirate of acinar cell carcinoma demonstrates sheets, single cells, and small acinar structures (Diff–Quik, 4x). The tumor cells as well as the architectural pattern can look remarkably similar to those seen with pancreatic neuroendocrine tumors. Immunohistochemistry is often needed to distinguish these neoplasms

Acinar Cell Carcinoma

Acinar cell carcinoma is a relatively uncommon malignancy [30]. In contrast to the cohesive grapelike clusters seen in aspirates of normal pancreas, the neoplastic cells of acinar cell carcinoma tend to be less cohesive with sheets, single cells, and occasional acinar structures (Fig. 24.12) [30]. Aspirates are typically very cellular [30]. Tumor nuclei are enlarged with prominent nucleoli, and cells contain moderate amounts of granular cytoplasm. The degree of atypia and pleomorphism are not as striking as seen with ductal adenocarcinoma. Caution should be exercised with sparsely cellular samples to avoid the overdiagnosis of normal acinar parenchyma as acinar cell carcinoma.

Pancreatic Neuroendocrine Tumor

Aspirates of the more common pancreatic neuroendocrine tumors can look very similar to those of acinar cell carcinomas. These are also very cellular aspirates, composed of loose clusters and single cells with frequent "naked" nuclei in the background (Fig. 24.13). The tumor cells contain round, often eccentrically placed nuclei and a moderate amount of cytoplasm which may be vacuolated or contain granules. Binucleation is a common feature. Distinguishing a pancreatic neuroendocrine neoplasm from an acinar cell carcinoma and solid pseudopapillary neoplasm often requires the use of cell block and immunohistochemistry [26, 30].

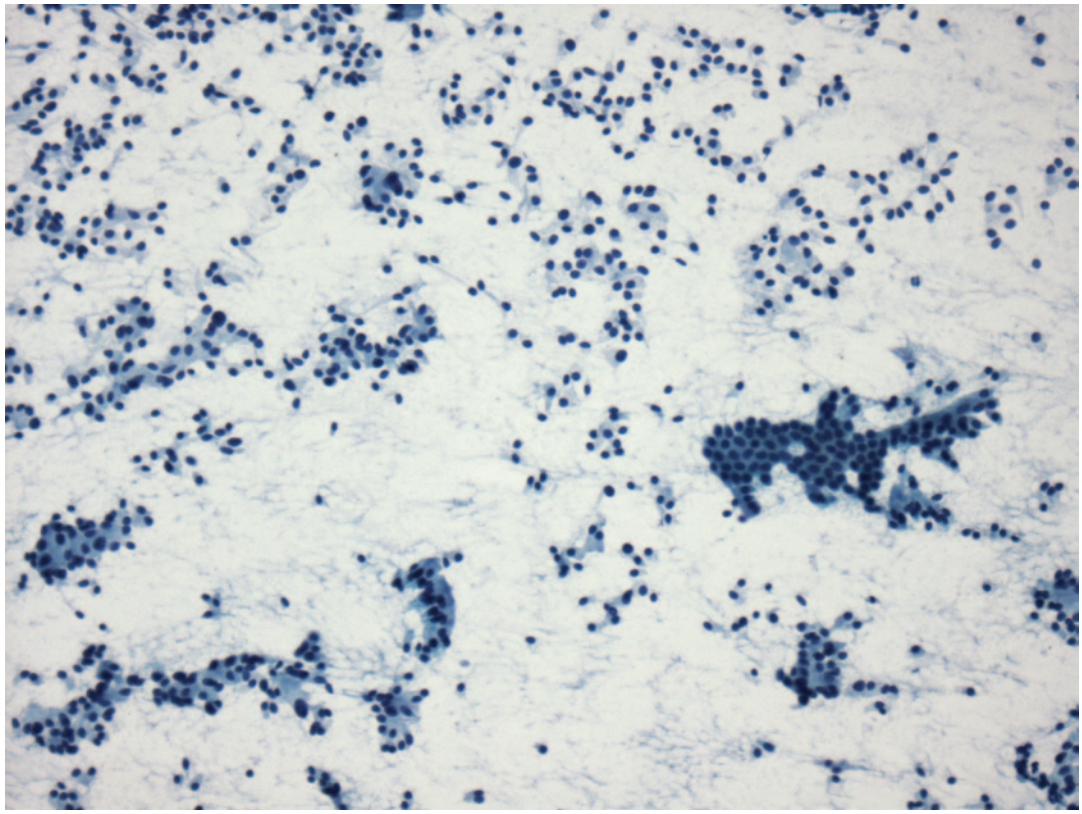

Fig. 24.13 Pancreatic neuroendocrine tumor. The tumor cells in this aspirate have round nuclei, and many are eccentrically placed. Tumor cells have a moderate amount of cytoplasm

Solid Pseudopapillary Neoplasm

Solid pseudopapillary neoplasm tends to occur in young- to middle-aged women; however, they have been rarely reported in men, children, and older patients [31]. Aspirates display certain characteristic features such as papillary fronds with central capillaries and a myxoid to metachromatic stroma (Fig. 24.14) [31]. The low power appearance has been likened to that of a "Chinese character" arrangement. However, single cells and loose clusters are also observed and may predominate. The tumor cells are round to oval and occasionally have grooved nuclei. Hyaline globules and cercariform cells (tumor cells with a cytoplasmic tail-like extension) have been described in aspirates of these tumors [31]. The background contains granular debris, cholesterol clefts, metachromatic globular material, and foam cells. Nuclear expression of beta-catenin is very helpful in distinguishing this tumor from pancreatic neuroendocrine tumors and acinar cell carcinomas [31, 32].

Cystic Lesions

There are several neoplastic and non-neoplastic cystic lesions that can affect the pancreas. It is important to remember that any solid tumor can undergo cystic change and these should be considered in the differential diagnosis. The pathologist should be made aware of the patient's clinical history, the radiologic and sonographic impression as well as the results from cyst fluid analysis prior to rendering a cytologic diagnosis.

Pancreatic Pseudocyst

Pancreatic pseudocyst is the most common cystic lesion of the pancreas. These arise in patients with a prior history of pancreatitis. Aspirates have a "dirty," granular background with calcification, proteinaceous material, and variable

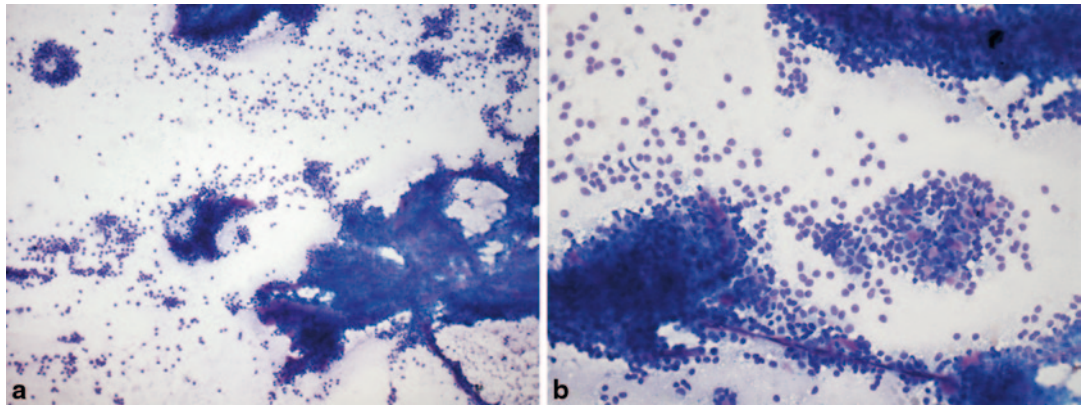

Fig. 24.14 **a** Solid pseudopapillary neoplasm. At low power, the aspirate demonstrates papillary fronds with central capillaries that have a surrounding metachromatic stroma (Diff–Quik, 4x). **b** Solid pseudopapillary neoplasm. At higher power, single cells and naked nuclei are appreciated. This image also demonstrates characteristic round, metachromatic intracytoplasmic, and extracellular hyaline globules (Diff–Quik, 10x)

numbers of inflammatory cells. The term pseudocyst implies that there is no true epithelial lining of the cyst, and as such, the only epithelium present in the aspirate should be contaminating gastrointestinal epithelium.

Mucinous Neoplasms

Mucinous neoplasms include both intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). Aspirates of these often yield thick mucin that is typically thicker than contaminating gastrointestinal mucin. These aspirates are variably cellular and often paucicellular. When epithelium is present, it is often contaminating gastrointestinal epithelium. The procedural approach, transgastric versus transduodenal, should be conveyed to the pathologists to help them decipher contaminating epithelium from lesional epithelium (Fig. 24.3). Mucinous neoplasms can demonstrate a spectrum of atypical change, and the degree of atypia should be mentioned in the cytology report. In general, the more the atypia that is present, the more cellular the aspirate (in IPMNs, even papillary fragments may be seen). When features of malignancy are present, it must be mentioned that the presence or absence of invasion cannot be assessed on an aspirate. In addition, cytology alone cannot distinguish IPMN from MCN, as the ovarian-like stroma that characterizes a MCN is not present on aspirates.

Immunohistochemistry, cyst fluid analysis, and molecular testing have all been used to separate mucinous neoplasms from other pancreatic cysts and to risk stratify mucinous cysts [33, 34]. In our experience, cyst fluid analysis is the most commonly used modality. Typically, mucinous neoplasms have higher CEA concentrations compared to other cysts [34]. Amylase concentration is increased in pseudocysts as well as IPMNs [35, 36].

Serous Cystadenomas

Serous cystadenomas are almost impossible to diagnose on cytology [37, 38]. They can be microcystic or macrocystic and may demonstrate a central stellate scar on endoscopy [37]. Aspirates demonstrate clear or serosanguinous fluid and are often paucicellular. When epithelium is present, it often has a sheetlike architecture and the tumor cells are cuboidal to columnar. If sufficient epithelium is available for a cell block, a PAS stain will highlight the glycogen present in the cells of this neoplasm.

Extrahepatic and Biliary System

EUS-FNA is effective for sampling extrahepatic biliary and gallbladder lesions. Adenocarcinoma is the most common neoplasm affecting these sites, and the cytologic features are remarkably similar to those of pancreatic ductal adenocarcinoma. These lesions can be diagnostically challenging as reactive epithelium, due to prior stent or other obstructive processes, can look very similar to well-differentiated adenocarcinoma. Information regarding the presence or absence of a mass-forming lesion and history of prior stenting should be provided to the pathologist. Often these cases may be signed out as "atypical" or "suspicious" with a note discussing the limitations in rendering a specific diagnosis.

Liver

The liver is another commonly sampled organ by EUS-FNA. Both a variety of primary neoplasms and metastatic tumors can affect the liver. The cytologic findings of metastatic tumors will vary depending on the primary tumor site, and cytologic features alone may be insufficient for the pathologist to render an entirely specific diagnosis [39]. In this setting, immunohistochemistry will be helpful. The importance of providing the pathologist with a good clinical history cannot be overemphasized, especially when the patient has a history of a remote malignancy. Often the liver is sampled as part of tumor staging; this is especially true for pancreatic malignancy [40]. If the primary tumor has not already been assessed for malignancy, sampling both organs simultaneously may prove valuable by providing a morphologic comparison.

Hepatocellular carcinoma (HCC) accounts for the vast majority of primary liver malignancies [40]. HCC often presents as a single tumor mass in a background of cirrhosis. The cytologic features of a well-differentiated HCC include numerous background stripped atypical nuclei with tumor cells having macronucleoli, increased mitoses, and multinucleation [41, 42]. On aspirates, widened trabeculae with capillaries traversing tissue fragments can be seen [39]. Characteristic rimming of tumor fragments by endothelial cells, a feature known as "endothelial wrapping," is often present (Fig. 24.15) [39]. Poorly differentiated HCC can mimic metastatic tumors as well as intrahepatic cholangiocarcinomas, and immunohistochemistry may be required for a definitive diagnosis. Furthermore, there are cases of combined hepatocellular carcinomas and cholangiocarcinomas.

Intrahepatic and extrahepatic cholangiocarcinomas appear morphologically similar to pancreatic adenocarcinomas [43]. These tumors also share a similar immunophenotypic profile, and thus, it is not unreasonable to diagnose these tumors as adenocarcinomas of pancreaticobiliary origin. However, with adequate clinical and radiologic history, a definitive diagnosis can usually be achieved.

Of note, cytology alone cannot reliably distinguish most benign hepatocellular growths such as hepatocellular adenoma, dysplastic nodules, or focal nodular hyperplasia. Aspiration of these lesions yields hepatocytes only. Clinicoradiographic correlation and cell block preparation can help to secure the diagnosis in this setting.

Adrenal Gland

The adrenal gland can be involved by both metastases and primary tumors [44]. These can usually be distinguished by their radiographic features; however, occasionally FNA is performed to differentiate between them [44]. Because of its proximity to the gastrointestinal tract, the left adrenal gland is much more commonly sampled by EUS-FNA than the right. In the setting of metastatic tumors, obtaining a cell block to perform immunohistochemical studies is often needed. Lung adenocarcinoma is the most common tumor to metastasize to the adrenal gland [45].

With regard to primary adrenal tumors, benign adrenal cortical adenomas far exceed the rare adrenal cortical carcinomas. The cytologic features of an adrenal cortical adenoma resemble normal cortical elements. Therefore, a preliminary interpretation of "adrenal cortical cells" with the endosonographer's assurance that the lesion has

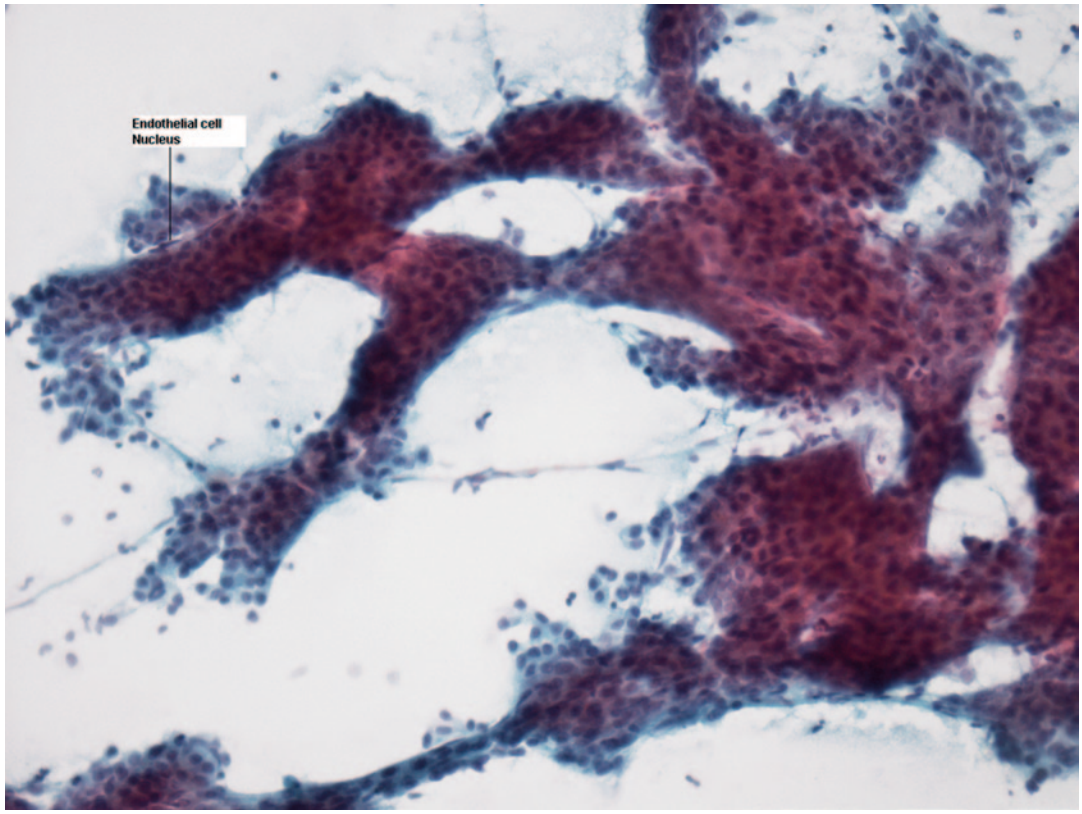

Fig. 24.15 Hepatocellular carcinoma. Characteristic endothelial cell wrapping of neoplastic hepatocytes is seen. The trabeculae are also widened, and capillaries are seen traversing the tissue fragments (Pap stain, 10x)

been sampled equates to a diagnosis of adrenal cortical adenoma. In most cases, the cytologic findings together with the clinical and radiographic features can separate an adrenal adenoma from a carcinoma. However, adrenal cortical carcinomas can exhibit a spectrum of morphologic features mimicking both benign adenomas and metastatic tumors [46]. Immunohistochemistry may be needed for the diagnosis of an adrenal cortical carcinoma [46].

Conclusion

EUS-FNA is a powerful diagnostic modality that is increasingly being used to sample the gastrointestinal tract and peri-intestinal organs, especially the pancreas. A thoughtful approach to triaging material obtained at the time of procedure is necessary and best achieved through on-site collaboration with a cytopathologist. If on-site assessment is not feasible, the endoscopist needs to have a thorough understanding of the variety of pathologic entities that can occur in the various sites and the ancillary studies (immunohistochemistry, flow cytometry, culture, molecular testing, etc.) that may be necessary to provide a specific diagnosis or guide treatment. With this knowledge, appropriate decisions regarding sample preparation and triaging of material can be made. It is our hope that the content in this chapter has provided a framework for these concepts.

Key Points

- A basic understanding of cytopathology is requisite for the successful endosonographer.
- Rapid on-site evaluation can improve the sensitivity and accuracy of EUS-FNA.

- A rapid Romanowsky stain is used during on-site evaluation. This stain highlights cytoplasmic detail well; however, nuclear morphology is best appreciated on Papanicolaou-stained slides.
- A thoughtful approach to triaging material obtained at the time of EUS-FNA is necessary. Sometimes ancillary testing such as flow cytometry, microbiology, or molecular analysis may be needed to guide further diagnosis and treatment.
- Occasionally, a specific cytopathologic diagnosis can only be achieved with the use of adjunct immunohistochemistry. In this setting, a cell block is highly desirable.

References

1. Bardales RH, Stelow EB, Mallery S, Lai R, Stanley MW. Review of endoscopic ultrasound-guided fine-needle aspiration cytology. Diagn Cytopathol. 2006;34(2):140–75.
2. LeBlanc JK, Emerson RE, Dewitt J, Symms M, Cramer HM, McHenry L, et al. A prospective study comparing rapid assessment of smears and ThinPrep for endoscopic ultrasound-guided fine-needle aspirates. Endoscopy. 2010;42(5):389–94.
3. Alsohaibani F, Girgis S, Sandha GS. Does onsite cytotechnology evaluation improve the accuracy of endoscopic ultrasound-guided fine-needle aspiration biopsy. Can J Gastroenterol. 2009;23(1):26–30.
4. Klapman JB, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. Am J Gastroenterol. 2003;98(6):1289–94.
5. Stanley MW, Lowhagen T. Fine needle aspiration of palpable masses. 1st ed. Stoneham: Butterworth-Heinemann; 1993.
6. de Luna R, Eloubeidi MA, Sheffield MV, Eltoum I, Jhala N, Jhala D, et al. Comparison of ThinPrep and conventional preparations in pancreatic fine-needle aspiration biopsy. Diagn Cytopathol. 2004;30(2):71–6.
7. Dabbs DJ. Immunohistology of metastatic carcinoma of unknown primary. In Dabbs DJ, editor. Diagnostic immunohistochemistry. 2nd ed. Philadelphia: Churchill Livingstone; 2006. pp. 180–226.
8. Chu P, Wu E, Weiss LM. Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol. 2000;13(9):962–72.
9. Barbareschi M, Murer B, Colby TV, Chilosi M, Macri E, Loda M, et al. CDX-2 homeobox gene expression is a reliable marker of colorectal adenocarcinoma metastases to the lungs. Am J Surg Pathol. 2003;27(2):141–9.
10. Collins BT, Wang JF, Bernadt CT. Utilization of p40 (DNp63) with p63 and Cytokeratin 5/6 Immunohistochemistry in Non-Small Cell Lung Carcinoma Fine-Needle Aspiration Biopsy. Acta Cytol. 2013;57(6):619–24.
11. Capella C, Solcia E, Sobin LH, Arnold R. Endocrine tumours of the stomach. In: Hamilton SR, Aaltonen LA, editors. Pathology and genetics of tumours of the digestive system. Lyon: IARC; 2000. pp. 53–7.
12. Capella C, Solcia E, Sobin LH, Arnold R. Endocrine tumuors of the small intestine. In: Hamilton SR, Aaltonen LA, editors. Pathology and genetics of tumours of the digestive system. Lyon: IARC; 2000. pp. 77–82.
13. Wang HH. Gastrointestinal tract. In: Cibas ES, Ducatman BS, editors. Cytology: diagnostic principles and clinical correlates. 2nd ed. Edinburgh: Saunders; 2003. pp. 189–214.
14. Stelow EB, Murad FM, Debol SM, Stanley MW, Bardales RH, Lai R, et al. A limited immunocytochemical panel for the distinction of subepithelial gastrointestinal mesenchymal neoplasms sampled by endoscopic ultrasound-guided fine-needle aspiration. Am J Clin Pathol. 2008;129(2):219–25.
15. Rubin BP, Hornick JL. Mesenchymal tumors of the gastrointestinal tract. In: Hornick JL, editor. Practical soft tissue pathology: a diagnostic approach. Philadelphia: Elsevier Saunders; 2013. pp. 437–46.
16. Stelow EB, Stanley MW, Mallery S, Lai R, Linzie BM, Bardales RH. Endoscopic ultrasound-guided fine-needle aspiration findings of gastrointestinal leiomyomas and gastrointestinal stromal tumors. Am J Clin Pathol. 2003;119(5):703–8.
17. Ohori NP, Santa Maria EL. Cytopathologic diagnosis of bronchioloalveolar carcinoma: does it correlate with the 1999 World Health Organization definition? Am J Clin Pathol. 2004;122(1):44–50.
18. Whithaus K, Fukuoka J, Prihoda TJ, Jagirdar J. Evaluation of napsin A, cytokeratin 5/6, p63, and thyroid transcription factor 1 in adenocarcinoma versus squamous cell carcinoma of the lung. Arch Pathol Lab Med. 2012;136(2):155–62.
19. Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. Am J Surg Pathol. 2011;35(1):15–25.
20. Turner BM, Cagle PT, Sainz IM, Fukuoka J, Shen SS, Jagirdar J. Napsin A, a new marker for lung adenocarcinoma, is complementary and more sensitive and specific than thyroid transcription factor 1 in the differential diagnosis of primary pulmonary carcinoma: evaluation of 1674 cases by tissue microarray. Arch Pathol Lab Med. 2012;136(2):163–71.
21. French CA. Respiratory tract. In: Cibas ES, Ducatman BS, editors. Cytology: diagnostic principles and clinical correlates. 2nd ed. Edinburgh: Saunders; 2003. pp. 61–95.

22. Travis WD. Update on small cell carcinoma and its differentiation from squamous cell carcinoma and other non-small cell carcinomas. Mod Pathol. 2012;25(Suppl 1):S18–30.
23. Wu M, Wang B, Gil J, Sabo E, Miller L, Gan L, Burstein DE. p63 and TTF-1 immunostaining. A useful marker panel for distinguishing small cell carcinoma of lung from poorly differentiated squamous cell carcinoma of lung. Am J Clin Pathol. 2003;119(5):696–702.
24. Yasuda I, Goto N, Tsurumi H, Nakashima M, Doi S, Iwashita T, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy for diagnosis of lymphoproliferative disorders: feasibility of immunohistological, flow cytometric, and cytogenetic assessments. Am J Gastroenterol. 2012;107(3):397–404.
25. Kloppel G, Hruban RH, Longnecker DS, Adler G, Kern SE, Partanen TJ. Ductal adenocarcinoma of the pancreas. In: Hamilton SR, Aaltonen LA, editors. World health organization classification of tumours. Pathology and genetics of tumours of the digestive system. Lyon: IARC; 2000. pp. 221–30.
26. Sigel CS, Klimstra DS. Cytomorphologic and immunophenotypical features of acinar cell neoplasms of the pancreas. Cancer Cytopathol. 2013;121(8):459–70.
27. Stelow EB, Bardales RH, Lai R, Mallery S, Linzie BM, Crary GS, et al. The cytological spectrum of chronic pancreatitis. Diagn Cytopathol. 2005;32(2):65–9.
28. Deshpande V, Mino-Kenudson M, Brugge WR, Pitman MB, Fernandez-del Castillo C, Warshaw AL, et al. Endoscopic ultrasound guided fine needle aspiration biopsy of autoimmune pancreatitis: diagnostic criteria and pitfalls. Am J Surg Pathol. 2005;29(11):1464–71.
29. Cheuk W, Chan JK. IgG4-related sclerosing disease: a critical appraisal of an evolving clinicopathologic entity. Adv Anat Pathol. 2010;17(5):303–32.
30. Stelow EB, Bardales RH, Shami VM, Woon C, Presley A, Mallery S, et al. Cytology of pancreatic acinar cell carcinoma. Diagn Cytopathol. 2006;34(5):367–72.
31. Samad A, Shah AA, Stelow EB, Alsharif M, Cameron SE, Pambuccian SE. Cercariform cells: another cytologic feature distinguishing solid pseudopapillary neoplasms from pancreatic endocrine neoplasms and acinar cell carcinomas in endoscopic ultrasound-guided fine-needle aspirates. Cancer Cytopathol. 2013;121(6):298–310.
32. Kim MJ, Jang SJ, Yu E. Loss of E-cadherin and cytoplasmic-nuclear expression of beta-catenin are the most useful immunoprofiles in the diagnosis of solid-pseudopapillary neoplasm of the pancreas. Hum Pathol. 2008;39(2):251–8.
33. Khalid A, McGrath KM, Zahid M, Wilson M, Brody D, Swalsky P, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clin Gastroenterol Hepatol. 2005;3(10):967–73.
34. van der Waaij LA van Dullemen HM Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005;62(3):383–9.
35. Linder JD, Geenen JE, Catalano MF. Cyst fluid analysis obtained by EUS-guided FNA in the evaluation of discrete cystic neoplasms of the pancreas: a prospective single-center experience. Gastrointest Endosc. 2006;64(5):697–702.
36. Cunningham SC, Hruban RH, Schulick RD. Differentiating intraductal papillary mucinous neoplasms from other pancreatic cystic lesions. World J Gastrointest Surg. 2010;2(10):331–6.
37. Belsley NA, Pitman MB, Lauwers GY, Brugge WR, Deshpande V. Serous cystadenoma of the pancreas: limitations and pitfalls of endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer. 2008;114(2):102–10.
38. Huang P, Staerkel G, Sneige N, Gong Y. Fine-needle aspiration of pancreatic serous cystadenoma: cytologic features and diagnostic pitfalls. Cancer. 2006;108(4):239–49.
39. Ducatman B. Liver. In: Cibas ES, Ducatman BS, editors. Cytology: diagnostic principles and clinical correlates. 2nd ed. Edinburgh: Saunders; 2003. pp. 345–66.
40. Cameron SEH, Evans RA, Debol SM, Mallery S, Stelow EB. Endoscopic ultrasound-guided fine needle aspiration of the liver. Mod Pathol. 2007;20:220A.
41. Das DK. Cytodiagnosis of hepatocellular carcinoma in fine-needle aspirates of the liver: its differentiation from reactive hepatocytes and metastatic adenocarcinoma. Diagn Cytopathol. 1999;21(6):370–7.
42. de Boer WB Segal A Frost FA Sterrett GF. Cytodiagnosis of well differentiated hepatocellular carcinoma: can indeterminate diagnoses be reduced? Cancer. 1999;87(5):270–7.
43. Chaudhary HB, Bhanot P, Logrono R. Phenotypic diversity of intrahepatic and extrahepatic cholangiocarcinoma on aspiration cytology and core needle biopsy: case series and review of the literature. Cancer. 2005;105(4):220–8
44. Stelow EB, Debol SM, Stanley MW, Mallery S, Lai R, Bardales RH. Sampling of the adrenal glands by endoscopic ultrasound-guided fine-needle aspiration. Diagn Cytopathol. 2005;33(1):26–30.
45. Lam KY, Lo Cy. Metastatic tumours of the adrenal glands: a 30-year experience in a teaching hospital. Clin Endocrinol (Oxf). 2002;56(1):95–101.
46. Ren R, Guo M, Sneige N, Moran CA, Gong Y. Fine-needle aspiration of adrenal cortical carcinoma: cytologic spectrum and diagnostic challenges. Am J Clin Pathol. 2006;126:389–98.

Part VI
Diagnostic EUS in Luminal Disorders

Esophageal Cancer

25

Lauren G. Khanna and Charles J. Lightdale

Introduction

Esophageal cancer is the eighth most common cancer and the sixth most common cause of cancer-related mortality worldwide, with over 450,000 new cases and over 400,000 deaths annually [1]. In the USA, it is estimated that there will be 17,990 new diagnoses of esophageal cancer and 15,210 related deaths in 2013 [2]. Together, squamous cell carcinoma (SCC) and adenocarcinoma account for over 90 % of esophageal cancers. Worldwide, SCC is the most common type of esophageal cancer, and over 80 % of cases occur in developing countries. In Western countries, the incidence of SCC has decreased, but esophageal adenocarcinoma has become increasingly common over the past few decades [3, 4].

Tobacco use is associated with increased risk of both SCC and adenocarcinoma, and risk increases with both quantity of cigarettes smoked and duration of smoking. Medical radiation to the mediastinum also predisposes patients to both SCC and adenocarcinoma. However, other risk factors differ by histological subtype. SCC is increased with chronic irritation and inflammation, as can be seen with heavy alcohol intake, history of caustic ingestion, achalasia, or esophageal diverticuli. Risk factors for adenocarcinoma include gastroesophageal reflux disease, obesity, and Barrett's esophagus, where the rate of neoplastic transformation is estimated to be approximately 0.5 % per year [5–8].

At the time of diagnosis of esophageal cancer, at least three-quarters of patients have dysphagia. SCC is distributed along the entire esophagus, especially in the mid-esophagus, whereas 75 % of adenocarcinomas are found in the distal esophagus [9]. Regardless of subtype, cancer may spread rapidly once it develops; almost half of the patients with esophageal cancer have locally advanced or metastatic disease at the time of presentation. Therefore, five-year survival is poor, 3.5 % for those with metastatic disease and 17.3 % overall [2]. In patients with localized, potentially resectable disease, disease stage correlates with survival, especially in patients with disease confined to the mucosa or submucosa (T1), who have a high cure rate from surgical or in some cases endoscopic therapy alone [10]. Patients with locally advanced disease are increasingly being offered neoadjuvant chemoradiotherapy in an attempt to improve outcomes [11, 12]. However, those with tumors which invade through the esophageal wall (T3) or with positive nodes have poor long-term survival even with multimodality therapy. In addition, surgery for esophageal cancer has high morbidity and mortality.

Therefore, for esophageal cancer, preoperative assessment of disease stage is crucial for the appropriate selection of patients for endoscopic

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or surgical resection, chemotherapy, radiation, and palliative treatment.

Case 1

A 76-year-old male had a 6-year history of reflux symptoms. Four years prior, he underwent upper endoscopy which revealed Barrett's esophagus involving 4 cm proximal to the gastroesophageal junction. Four quadrant biopsies were taken every centimeter and revealed intestinal metaplasia with no dysplasia. He took a proton pump inhibitor intermittently for reflux symptoms and returned for follow-up when the medication failed to control his discomfort. He underwent repeat upper endoscopy which revealed a mass in the distal third of the esophagus (Fig. 25.1). Biopsies showed poorly differentiated adenocarcinoma arising in Barrett's mucosa.

Diagnosis of Esophageal Cancer

Esophageal cancer is usually diagnosed after identification of a lesion by barium swallow or endoscopy, followed by endoscopic biopsy for pathologic diagnosis to determine histological type (squamous cell, adenocarcinoma, or other rarer types) and grade (well, moderately, or poorly differentiated, or undifferentiated).

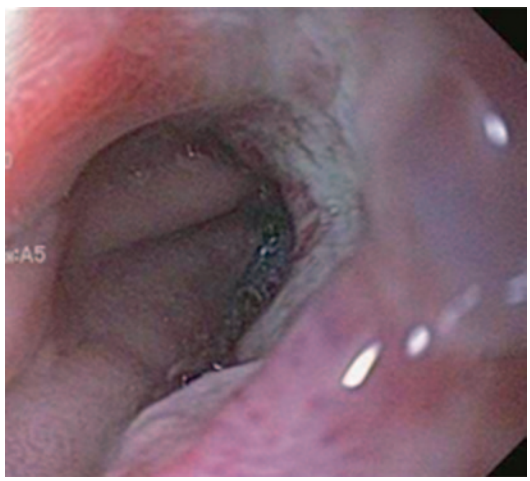

Fig. 25.1 White light endoscopy showing near circumferential mass in distal esophagus (Courtesy Dr. Tamas Gonda, Columbia University Medical Center, New York, NY)

Staging of Esophageal Cancer: How Do CT, PET, and EUS Compare in TNM Staging?

After the diagnosis of esophageal cancer is established, clinical staging is crucial to determine prognosis and choose appropriate therapy. Staging is performed according to the tumor, node, metastasis, histological grade (TNMG) classification of the 7th edition of the American Joint Committee on Cancer (AJCC) published in 2010 (Tables 25.1, 25.2 and 25.3). Since esophageal SCC and adenocarcinoma have different etiologies, natural histories, and outcomes, separate TNM staging has been developed for each subtype [13]. Assessment of T, N, M, and G status is usually based on a combination of endoscopy with biopsy, computed tomography (CT), positron emission tomography, and endoscopic ultrasound (EUS).

For tumor location, the esophageal regions are designated as follows: (1) the cervical esophagus (from the lower border of the cricoid cartilage to the thoracic inlet), (2) the upper thoracic esophagus (from the thoracic inlet to the tracheal bifurcation), (3) the mid-thoracic esophagus (from the tracheal bifurcation to 32 cm from the incisors), and (4) the lower thoracic and abdominal esophagus (from the mid-esophagus to the esophagogastric junction, at approximately 40 cm from the incisors).

Prior to the 2010 TNM staging system, if the primary tumor was located in the upper or middle thoracic esophagus or was SCC, the finding of a malignant celiac area lymph node was staged as M1a metastatic disease and considered unresectable. In the 2010 staging system, however, a regional lymph node was redefined to include any periesophageal lymph node from the cervical nodes to the celiac nodes. Therefore, instead of being staged as M1a, celiac node involvement is currently considered regional node disease [14].

Table 25.1 TNM staging (AJCC: Esophageal and esophagogastric junction. In: Edge SB, Byrd DR, Compton CC, et al., editors. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp. 103−15)

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosa, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosa
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures such as aorta, vertebral body, and trachea
Regional lymph nodes (N)	
NX	Regional lymph node(s) cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–2 regional lymph nodes
N2	Metastasis in 3–6 regional lymph nodes
N3	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Histological grade	
GX	Grade cannot be assessed—stage grouping as G1
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated—grouping as G3 squamous

Table 25.2 Anatomical stage/prognostic group: esophageal squamous cell cancer (AJCC: Esophageal and esophagogastric junction. In: Edge SB, Byrd DR, Compton CC, et al., editors. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 103−15)

Stage	T	N	M	Grade	Location
0	Tis (HGD)	N0	M0	1,X	Any
IA	T1	N0	M0	1,X	Any
IB	T1	N0	M0	2–3	Any
	T2–3	N0	M0	1,X	Lower, X
IIA	T2–3	N0	M0	1,X	Upper, middle
	T2–3	N0	M0	2–3	Lower, X
IIB	T2–3	N0	M0	2–3	Upper, middle
	T1–2	N1	M0	Any	Any
IIIA	T1–2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
IIIB	T3	N2	M0	Any	Any
IIIC	T4a	N1–2	M0	Any	Any
	T4b	Any	M0	Any	Any
	Any	N3	M0	Any	Any
IV	Any	Any	M1	Any	Any

Table 25.3 Anatomical stage/prognostic group: esophageal and esophagogastric junction adenocarcinoma (AJCC: Esophageal and esophagogastric junction. In: Edge SB, Byrd DR, Compton CC, et al., editors. AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 103−15)

Stage	T	N	M	Grade
0	Tis (HGD)	N0	M0	1, X
IA	T1	N0	M0	1–2, X
IB	T1	N0	M0	3
	T2	N0	M0	1–2, X
IIA	T2	N0	M0	3
IIB	T3	N0	M0	Any
	T1–2	N1	M0	Any
IIIA	T1–2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
IIIB	T3	N2	M0	Any
IIIC	T4a	N1–2	M0	Any
	T4b	Any	M0	Any
	Any	N3	M0	Any
IV	Any	Any	M1	Any

Computed Tomography

CT of the chest and upper abdomen can be utilized to evaluate the primary tumor and identify any enlarged regional lymph nodes or distant metastatic disease. For T staging, CT is not able to consistently determine the depth of primary tumor invasion [15, 16]. For regional lymph node involvement, the overall accuracy of CT is approximately 50 to 70% [17]. Because size is the criterion used to define malignant nodes on CT, CT is inherently unable to detect metastases in normal-sized nodes and may identify enlarged, reactive nodes as malignant, leading to false positives. It also has poor sensitivity for celiac axis node involvement [18]. For distant metastases, CT has a sensitivity of 40 to 80% and a specificity of 25 to 70% [19]. However, it has limited sensitivity for identifying small metastases, especially within the peritoneum [18, 19].

Positron Emission Tomography

PET scans may also be used to identify a metabolically active primary tumor and visualize metabolically active lymph nodes or metastatic foci. However, PET is not consistently sensitive in identifying the primary tumor [20–22]. Because of its reduced spatial resolution, PET has also limited ability to differentiate depth of tumor invasion. The sensitivity of PET for lymph node disease is only equivalent to CT, with a pooled sensitivity from 43 to 70% compared to 41–60% for CT. Because PET can detect disease in normal-sized lymph nodes, and may be able to differentiate between inflammatory and malignant activity, it has better specificity for N staging than CT, with a pooled specificity from 76 to 95% compared to 77–89% [18, 20, 21, 23–25]. PET is particularly limited when assessing nodal disease in the area of the primary tumor due to poor spatial resolution. The greatest utility of PET is in detecting M stage, as it is more sensitive for the detection of unsuspected metastatic disease than CT [21, 22, 24, 26–28]. Therefore, patients with no evident distant disease on CT are typically recommended to undergo PET to assess for metastatic foci. PET scans also offer the opportunity to identify synchronous neoplasms. Care must be taken to investigate areas of uptake that may be synchronous neoplasms, rather than metastases, to avoiding upstaging the primary tumor [29].

The combination of PET/CT is likely superior to CT alone in detecting nodal disease. A recent

study suggested significantly higher specificity and positive predictive value for detecting lymph nodes with PET/CT (97 % versus 94 % and 65 % versus 44 %, respectively) [30]. Similarly, PET/CT appears more sensitive than PET alone for nodal disease (46 % versus 33 %) [31].

Endoscopic Ultrasound

In patients without evident metastatic disease on CT or PET, EUS plays an important role in the staging of esophageal cancer because of its utility in determining the depth of tumor invasion (T status) and regional lymph node metastases (N status).

Utilizing a 7.5- or 12-MHz echoendoscope, EUS offers the ability to assess the relationship of an esophageal mass to the five different layers of the esophageal wall, as shown in Table 25.4 and Fig. 25.2. Regarding terminology, hyperechoic refers to structures appearing bright (light gray to white like fat and bone), hypoechoic is dark gray and darker than surrounding structures like muscle, and anechoic is black like fluid. It is easy to use a radial echoendoscope for luminal cancer staging, as it provides a 360 degree view and requires less torquing to assess the esophageal wall layers and mediastinal structures. However, utilizing a linear echoendoscope for staging permits the endoscopist to perform fine-needle aspiration without changing echoendoscopes during the procedure. A randomized study compared the radial and linear echoendoscopes for esophageal cancer staging and found 88 % agreement for T staging with more lymph nodes detected using the radial echoendoscope ($p = 0.009$) [32]. Therefore, this may favor the use of the radial echoendoscope, given that the 2010 TNM staging system now incorporates the number of malignant lymph nodes into N staging. Whichever echoendoscope is utilized, staging should be performed in a systematic manner beginning distally in the stomach and moving proximally to visualize the entire length of the mass, and the highest T stage present within the mass should be reported.

Table 25.4 Esophageal wall by EUS (echoendoscope)

EUS layer	Esophageal wall layer	Echogenicity
1	Lamina propria	Hyperechoic
2	Muscularis mucosa	Hypoechoic
3	Submucosa	Hyperechoic
4	Muscularis propria	Hypoechoic
5	Adventitia	Hyperechoic

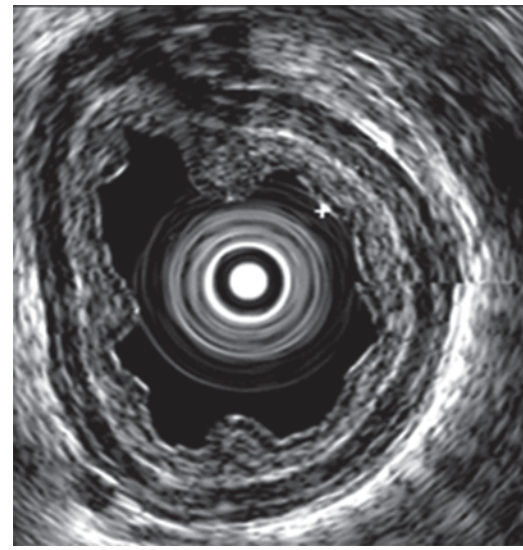

Fig. 25.2 Endoscopic ultrasound image of normal esophageal wall corresponding to wall layers described in Table 25.4 with outer muscularis propria (*layer 4*) visualized as inner circular (*hypoechoic*), connective tissue (*hyperechoic*), and outer longitudinal (*hypoechoic*) muscle layers (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

Esophageal cancer appears as a hypoechoic lesion disrupting the usual wall layers (Figs. 25.3, 25.4 and 25.5). There is no difference in the EUS appearance of squamous cell carcinoma and adenocarcinoma [33]. The endoscopic wall layer abnormality has been correlated with the tumor depth of invasion [34]. The accuracy of EUS for T staging, compared to surgical pathology, is clearly superior to CT and PET, and was found to be 80–90 % across various studies and meta-analyses [19, 35]. However, the accuracy of EUS varies by T stage. EUS is better for T3 and T4 tumors with 86 % accuracy for T4. Staging accuracy may be less for superficial tumors (T1) because the low frequency used with the echoendoscope impairs visualization of the muscularis mucosa [36].

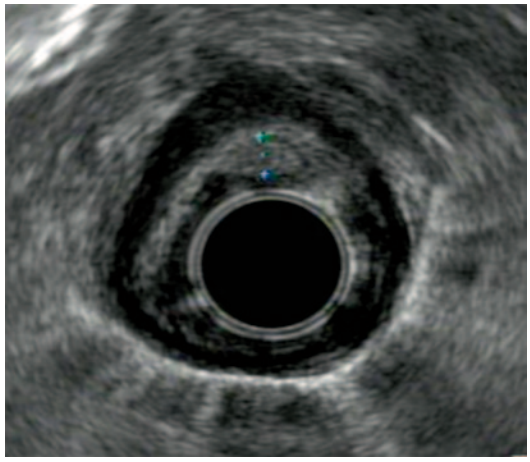

Fig. 25.3 Endoscopic ultrasound image showing small mass invading layer 3 tagged by blue marker (T1sm) (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

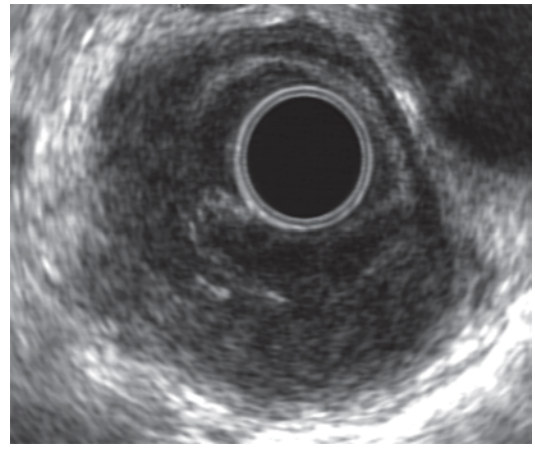

Fig. 25.5 Endoscopic ultrasound image showing hemicircumferential esophageal mass invading layer 5 (T3) (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

EUS also offers the ability to assess for regional lymph node disease. By endosonographic appearance, involved nodes may be enlarged, rounded, uniformly hypoechoic, or well-defined being distinctly differentiated from surrounding fat, as compared to benign nodes which are often hyperechoic, elongated, and with less demarcated borders [37–39]. The presence of all four features is 80–100% predictive of a malignant node; however, only a minority (20–30%) of all malignant lymph nodes harbor all four features [37–39]. The accuracy of EUS for N staging is 75% [35]. EUS is superior to CT and PET for N staging; in one study, the accuracy was 81% compared to 69 and 56%, respectively [40]. Because the visual characteristics are subjective, diagnostic error is possible with EUS imaging alone. Utilization of EUS-guided fine-needle aspiration (FNA) for lymph node cytology therefore improves sensitivity and specificity [41]. One study showed that, compared to EUS alone, EUS-FNA improved sensitivity from 63 to 93%, specificity from 81 to 100%, and accuracy from 70 to 93% [42]. When local lymph nodes are seen at the level of the primary tumor, FNA is usually not pursued due to the concern that traversing the tumor carries the risk of false-positive results as well as translocating tumor cells into an area without malignant disease [40]. If multiple periesophageal lymph nodes are visualized away from the primary tumor, it is reasonable and practical to perform FNA of one to two representative malignant-appearing nodes. Additional lymph nodes that appear malignant can be counted as such for staging purposes, based solely on their similar malignant appearance.

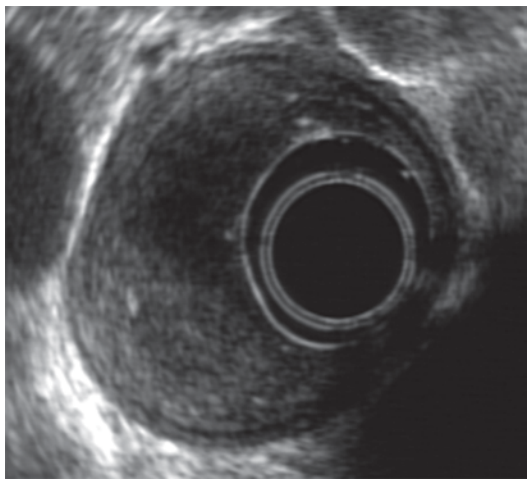

Fig. 25.4 Endoscopic ultrasound image showing hemicircumferential esophageal mass invading layer 4 (T2) (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

Many studies of EUS specifically evaluated its ability to detect celiac node involvement. EUS is highly sensitive and specific for the assessment of the celiac axis [43, 44]. Although in the 2010 TNM staging system, celiac node involvement contributes to regional node status and not distant metastatic disease, celiac node involvement, when identified, portends a poor prognosis [45–47].

EUS can contribute to M staging via assessment of the liver for lesions or identification of malignant ascites.

Obstructing Tumors: What Are the Options for EUS Staging?

In some cases, endoscopic ultrasound is limited by an obstructing esophageal tumor. The proportion of tumors which are non-traversable varies from study to study, but may be up to 45% [19, 48, 49]. Most non-traversable tumors are at least T3 tumors. Gentle dilation up to 14 to 16 mm may be pursued to facilitate passage of a gastroscope and echoendoscope. In a study of 132 patients with esophageal cancer, dilation was required to complete the EUS examination in 44 patients (32%), advanced disease was identified in 8 patients (19%), and no complications occurred. Dilation to 14 to 16 mm was sufficient for staging in 87% patients [50]. In another study of 267 patients, dilation was required to complete the EUS examination in 81 patients (30%) and was successfully performed to 14 mm in 69 patients (85%), with no complications. Staging was T3 in 57% and T4 in 21%, N1 in 75%, and M1 in 10% (49).

In cases of obstructing tumors, another alternative is to use ultrasound probes in place of standard echoendoscopes. These miniprobes operate at a higher ultrasound frequency and therefore have a decreased depth of penetration. One application is to assess tumors that cannot be traversed with upper echoendoscopes. However, the miniprobes' high frequency may limit their ability to evaluate the full depth of tumor penetration and regional lymph node involvement. Nonetheless, at least one study has shown better T staging and comparable N staging with miniprobe EUS compared to conventional EUS in patients with both traversable and non-traversable tumors [48].

Case 1 Continued

The patient underwent CT which showed thickening of the esophageal wall and subcentimeter periesophageal lymphadenopathy. No celiac lymphadenopathy was noted.

The patient then underwent EUS using a radial echoendoscope which showed a circumferential mass involving the middle and lower esophagus. The endosonographic borders were poorly defined. The mass was seen to invade into layer 5, the adventitia (Fig. 25.6). An abnormal periesophageal lymph node was visualized. It was 8 mm, oval, and hypoechoic and had well-defined margins. The celiac region also contained an abnormal node, which measured 17 mm by 16 mm. The node was round and hypoechoic and had well-defined margins (Fig. 25.7). EUS-FNA was performed of the celiac axis node as the periesophageal lymph node was lying deep to the mass, and the cytology from the celiac node revealed poorly differentiated carcinoma. No liver lesions were seen on EUS. EUS staging therefore showed T3N1 disease.

As the oncologists were formulating a treatment plan for the patient, the initial CT was rereviewed, and a small lesion in the right hepatic lobe was noted but was too small to be characterized, so the patient then underwent PET imaging. PET imaging showed FDG avidity of the thickened mid- and distal esophagus, FDG avid right periesophageal and gastroesophageal lymph

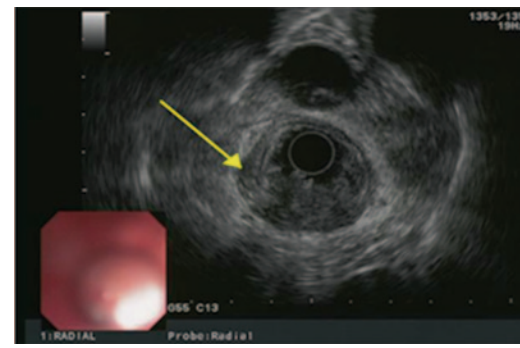

Fig. 25.6 Endoscopic ultrasound image showing poorly defined mass (*yellow arrow*) invading layer 5 (Courtesy Dr. Tamas Gonda, Columbia University Medical Center, New York, NY)

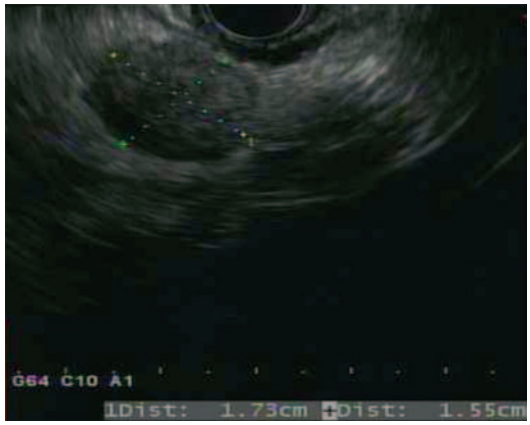

Fig. 25.7 Endoscopic ultrasound image showing 1.7 cm x 1.6 cm, round, hypoechoic, well-defined lymph node in celiac axis (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

nodes, and an FDG avid liver lesion, which was felt to be consistent with metastatic disease.

Thus, the patient was diagnosed with stage IV disease and initiated palliative chemotherapy.

After Chemoradiation: What is the Role of EUS in Staging

In patients with locally advanced but not metastatic disease, neoadjuvant therapy may be recommended to downstage the tumor, reduce recurrence, and enable more patients to have potentially curative surgery. Re-staging after therapy is crucial as it determines whether patients may be recommended for surgery or referred for palliative treatment. Although EUS plays an important role in the initial staging of esophageal cancer, after neoadjuvant chemotherapy and/or radiation, EUS is an unreliable tool for re-staging. In one recent study of patients who had EUS after neoadjuvant chemotherapy and had histological correlation from surgical specimens, the overall accuracy for T staging was only 29%, and the T stage was overstaged in 51% of patients [51]. This supports prior studies with similar results [52–54]. It is thought that the local responses to chemotherapy and radiation—particularly inflammation and fibrosis—lead to hypoechoic wall thickening which can result in overestimation of tumor invasion.

Case 2

A 72-year-old male developed symptoms of heartburn 12 years ago. He underwent endoscopy, was found to have reflux esophagitis, and started on daily PPI. A repeat endoscopy was done which showed Barrett's esophagus. Surveillance endoscopy revealed low-grade dysplasia on two occasions. His most recent endoscopy showed high-grade dysplasia with possible intramucosal carcinoma, so he was referred for further evaluation (Video 25.1).

Early Esophageal Cancer

As a consequence of surveillance endoscopies for Barrett's esophagus, high-grade dysplasia and early cancers are being increasingly detected. For many years, esophagectomy was the standard management for not only invasive esophageal cancer, but also malignancies limited to the mucosa. However, such superficial lesions may be amenable to endoscopic treatment, such as endoscopic mucosal resection (EMR), photodynamic therapy, or radiofrequency ablation. With the advent of these therapeutic options, pretreatment staging, particularly to determine the depth of invasion, is crucial to selecting appropriate therapy. It is thought that the disruption of the muscularis mucosa is directly linked to lymph node dissemination; for a lesion confined to the mucosa, the risk of lymph node involvement is 0–3%, and for a lesion invading the submucosa, the risk is 15–50% [55–57]. Therefore, surgical resection is indicated for any lesion involving the submucosa, while endoscopic options may be pursued for mucosal lesions.

EUS has been utilized to distinguish between these mucosal (T1m) and submucosal (T1sm) lesions. However, because of its lower frequency, conventional EUS does not allow accurate visualization of the muscularis mucosa [36]. Studies have shown that there may be thickening and duplication of the muscularis mucosa in patients with Barrett's esophagus. With EUS, these muscularis mucosa abnormalities may be mistaken

Table 25.5 Esophageal wall by EUS: (high-frequency miniprobe)

EUS layer	Esophageal wall layer	Echogenicity
1	Superficial mucosa	Hyperechoic
2	Superficial mucosa	Hypoechoic
3	Lamina propria	Hyperechoic
4	Muscularis mucosa	Hypoechoic
5	Submucosa	Hyperechoic
6	Muscularis propria: inner circular muscle	Hypoechoic
7	Muscularis propria: intermuscular connective tissue	Hyperechoic
8	Muscularis propria: Outer longitudinal muscle	Hypoechoic
9	Adventitia	Hyperechoic

for muscularis propria, perhaps contributing to inaccurate staging [58, 59].

Miniprobe ultrasound utilizes higher-frequency ultrasound for imaging, usually 20 to 30 MHz. This permits imaging of the esophageal wall in nine layers (Table 25.5). The muscularis mucosa in particular can be seen in greater detail. Therefore, for localized superficial carcinomas, the high frequency of the miniprobe may permit better differentiation of mucosal and submucosal lesions and may improve staging accuracy. Because the ultrasound miniprobe is passed through the working channel of a gastroscope, it also offers the advantage that the probe can be placed on the relevant lesion under direct endoscopic view. A 2010 randomized crossover study of patients with early cancer in Barrett's esophagus found that 93% versus 67% lesions were assessable, respectively, by high-frequency and conventional ultrasound [60]. Incorporating this improvement in accessibility into an "intention-to-diagnose" analysis, the study found that T staging was more accurate with miniprobe compared to conventional ultrasound (64% versus 49%, $p<0.0001$) compared to histology, although both were overall disappointing. A 2008 study of 106 early esophageal cancers including SCC and adenocarcinomas found a miniprobe accuracy of 74% in distinguishing T1m from T1sm tumors using pathology as the gold standard. There was a trend toward overstaging early lesions; 32 lesions were diagnosed as submucosal with 25 of these undergoing EMR due to surgical contraindications, and 68% were then found to be limited to the mucosa [61]. Using higher-frequency miniprobes (30 MHz) did not improve accuracy compared to the 20-MHz miniprobes, and inaccurate staging was significantly higher with distal compared to proximal esophageal lesions (48% versus 87%, $p=0.00039$). Interestingly, the technique of imaging with the miniprobe did seem to affect staging accuracy. Filling the lumen with water resulted in more accurate staging than using balloon-sheathed catheters (69% versus 43%, $p=0.015$).

For superficial esophageal malignancies, EMR may be used both as a diagnostic and staging method and as a potentially curative treatment. Given the limited accuracy of EUS in staging small, superficial lesions, EMR has largely replaced EUS as a staging modality. Evaluation of the resected specimen by a pathologist can determine the depth of invasion and possibly provide information regarding invasion of lymphatics and blood vessels. This information can assist in determining a final therapeutic strategy. EMR may be considered curative for lesions with a low risk of dissemination to lymph nodes. For larger lesions (>10 mm), prior to EMR or endoscopic submucosal dissection (ESD), EUS can play the important role of ruling out that the lesion has invaded the muscularis propria, since this may increase the usually low risk of perforation during the procedure. In addition, EUS can survey for lymph node involvement. A recent meta-analysis confirmed the value of EUS in high-grade dysplasia and early adenocarcinoma with advanced disease (≥T1sm or ≥N1) detected by EUS in 14% of these patients. The number of patients needed to undergo EUS in order to identify one patient with advanced disease was 7. Furthermore, EUS identified advanced disease in 4% of patients with no endoscopically visible nodules. [62]

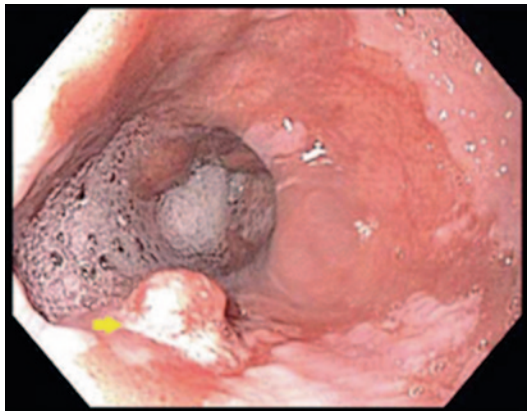

Fig. 25.8 White light endoscopy showing distal esophageal nodule (*yellow arrow*) arising in Barrett's mucosa (Courtesy Dr. Julian Abrams, Columbia University Medical Center, New York, NY)

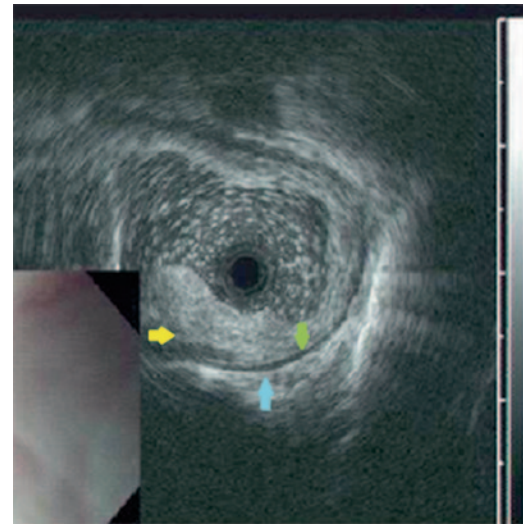

Fig. 25.9 High-frequency miniprobe ultrasound showing a hyperechoic mass (*yellow arrow*) with well-defined borders and sonographic evidence suggesting invasion into the submucosa layer (*green arrow*), but no evidence of involvement of the muscularis propria layer (*blue arrow*) (Courtesy Dr. Julian Abrams, Columbia University Medical Center, New York, NY)

Case 2 Continued

Repeat endoscopy showed Barrett's mucosa from the upper extent of the gastric folds at 40 cm from the incisors to the Z-line at 36 cm from the incisors. A nodule surrounded by irregular-appearing mucosa was seen from 37 to 39 cm, concerning for malignancy. The nodule was examined using white light endoscopy (Fig. 25.8). A 20-MHz miniprobe EUS used by filling the lumen with water showed a hyperechoic mass with well-defined borders and sonographic evidence suggesting invasion into layer 3, the submucosa (Fig. 25.9). There was no evidence of involvement of the muscularis propria. For further staging to assess for lymph node involvement, standard EUS was performed with a radial echoendoscope, which revealed localized wall thickening up to 5.7 mm of the distal esophagus. The wall layers were intact with no disruption of the muscularis propria (Fig. 25.10). Two small lymph nodes were seen in the middle paraesophageal mediastinum, which appeared benign with an irregularly shaped, hyperechoic appearance and well-defined margins (Fig. 25.11). No lymph nodes were seen in the celiac axis or porta hepatis. No lesions were visualized in the left lobe of the liver. Endoscopic mucosal resection of the nodule was performed.

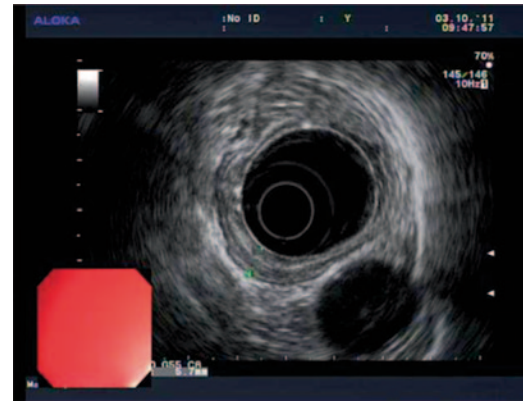

Fig. 25.10 Endoscopic ultrasound showing slight esophageal wall thickening up to 5.7 mm (*marked by green tags*) with intact layers and no disruption of the muscularis propria (Courtesy Dr. Amrita Sethi, Columbia University Medical Center, New York, NY)

Pathology revealed poorly differentiated intramucosal adenocarcinoma, arising in Barrett's mucosa with high-grade dysplasia. Malignant glands were seen extending into thickened muscularis mucosa up to 1 μm from, but not clearly invading, the submucosa. No carcinoma was identified on the deep margin (Figs. 25.12 and 25.13).

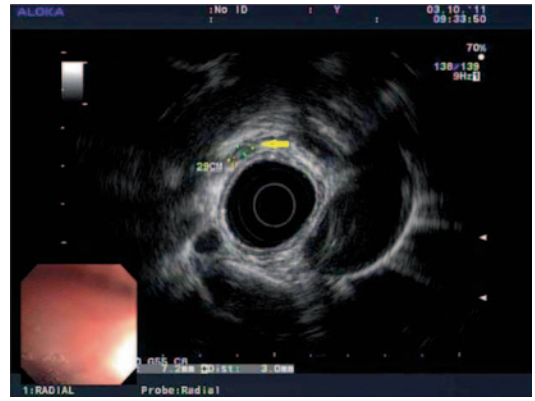

Fig. 25.11 Endoscopic ultrasound showing benign-appearing paraesophageal lymph node (*yellow arrow*) with well-defined, irregularly shaped, and hyperechoic appearance (Courtesy Dr. Amrita Sethi, Columbia University Medical Center, New York, NY)

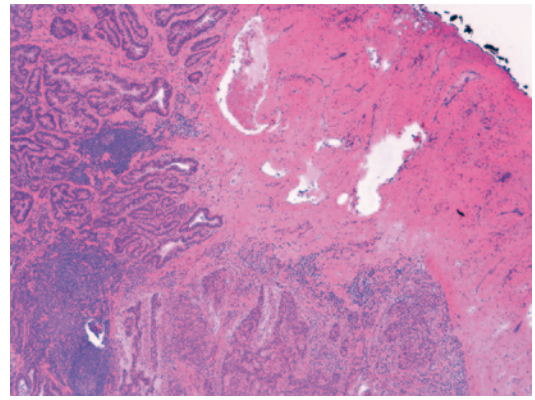

Fig. 25.12 Pathology images on low power showing extensive intramucosal carcinoma arising in a background of Barrett's with high-grade dysplasia. The carcinoma is mainly poorly differentiated and of high nuclear grade. Malignant glands extend into thickened muscularis mucosae but are not clearly invading into submucosa. Dysplastic intestinal glands are identified on one cauterized edge, and squamous mucosa is present on another. No carcinoma is identified on the deep margin (Courtesy Dr. Kathleen O'Toole and Dr. Anne Koehne de González, Columbia University Medical Center, New York, NY)

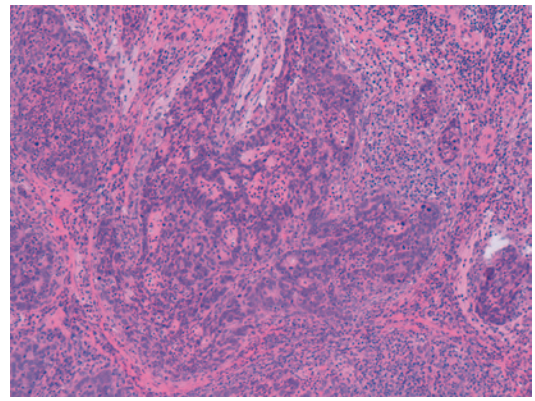

Fig. 25.13 Pathology images on medium power showing extensive intramucosal carcinoma arising in a background of Barrett's with high-grade dysplasia. The carcinoma is mainly poorly differentiated and of high nuclear grade. Malignant glands extend into thickened muscularis mucosae but are not clearly invading into submucosa. Dysplastic intestinal glands are identified on one cauterized edge, and squamous mucosa is present on another. No carcinoma is identified on the deep margin (Courtesy Dr. Kathleen O'Toole and Dr. Anne Koehne de González, Columbia University Medical Center, New York, NY)

PET/CT showed esophageal uptake but no metastatic disease.

Given the poorly differentiated histology and close to submucosal involvement, the patient was referred for consideration of esophagectomy with lymph node dissection. However, he declined surgery and elected close endoscopic management and surveillance.

Key Points

- Survival for advanced esophageal cancer is poor even with combination therapy of chemotherapy, radiation, and surgery, and these treatments may be associated with significant morbidity. Treatment does vary depending on

tumor stage; therefore, accurate cancer staging is crucial.

- CT and PET are important especially for M staging, but also N staging, of esophageal tumors.
- EUS is important for T and N staging of esophageal tumors.
- High-frequency ultrasound probes are useful for assessing T stage in obstructing lesions and superficial tumors.
- Given the limited utility of EUS for accurately staging small superficial tumors, EMR is more important for determining the T stage by depth of invasion.
- For larger tumors, EUS is important for assessing safety of EMR by evaluating involvement of the muscularis propria and for detecting the presence of lymph nodes.

Video Caption

Video 25.1 Endoscopic assessment of esophageal carcinoma arising in Barrett's esophagus and endoscopic ultrasound staging of the tumor detecting T3N1 disease

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127(12):2893–917.
2. Howlader N NA, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975–2010, National Cancer Institute. Bethesda, MD, April 2013. 2013; Available from: http://seer.cancer.gov/csr/1975_2010/.
3. Edgren G, Adami HO, Weiderpass E, Nyren O. A global assessment of the oesophageal adenocarcinoma epidemic. Gut. 2013; 62(12):1820.
4. Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, et al. Trends in esophageal adenocarcinoma incidence and mortality. Cancer. 2013;119(6):1149–58.
5. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825–31.
6. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med. 1999;130(11):883–90.
7. Shaheen N, Ransohoff DF. Gastroesophageal reflux, barrett esophagus, and esophageal cancer: scientific review. JAMA. 2002;287(15):1972–81.
8. Shaheen NJ, Crosby MA, Bozymski EM, Sandler RS. Is there publication bias in the reporting of cancer risk in Barrett's esophagus? Gastroenterology. 2000;119(2):333–8.
9. Gibbs JF, Rajput A, Chadha KS, Douglas WG, Hill H, Nwogu C, et al. The changing profile of esophageal cancer presentation and its implication for diagnosis. J Natl Med Assoc. 2007;99(6):620–6.
10. Westerterp M, Koppert LB, Buskens CJ, Tilanus HW, ten Kate FJ, Bergman JJ, et al. Outcome of surgical treatment for early adenocarcinoma of the esophagus or gastro-esophageal junction. Virchows Archiv. 2005;446(5):497–504.
11. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet. 2002;359(9319):1727–33.
12. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335(7):462–7.
13. Rice TW, Rusch VW, Ishwaran H, Blackstone EH, Worldwide Esophageal Cancer C. Cancer of the esophagus and esophagogastric junction: data-driven staging for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals. Cancer. 2010;116(16):3763–73.
14. Rice TW, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. Ann Surgi Oncol. 2010;17(7):1721–4.
15. Botet JF, Lightdale CJ, Zauber AG, Gerdes H, Urmacher C, Brennan MF. Preoperative staging of esophageal cancer: comparison of endoscopic US and dynamic CT. Radiology. 1991;181(2):419–25.
16. Tio TL, Cohen P, Coene PP, Udding J, den Hartog Jager FC, Tytgat GN. Endosonography and computed tomography of esophageal carcinoma. Preoperative classification compared to the new (1987) TNM system. Gastroenterology. 1989;96(6):1478–86.
17. Penman ID, Henry E. Advanced esophageal cancer. Gastrointest Endosc Clin N Am. [Review]. 2005;15(1):101–16, ix.
18. van Vliet EP Heijenbrok-Kal MH Hunink MG Kuipers EJ Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. British journal of cancer. 2008;98(3):547–57.
19. Kelly S, Harris KM, Berry E, Hutton J, Roderick P, Cullingworth J, et al. A systematic review of the staging performance of endoscopic ultrasound in gastro-oesophageal carcinoma. Gut. 2001;49(4):534–9.

20. Rankin SC, Taylor H, Cook GJ, Mason R. Comput tomography and positron emission tomography in the pre-operative staging of oesophageal carcinoma. Clin radiol. 1998;53(9):659–65.
21. Kato H, Miyazaki T, Nakajima M, Takita J, Kimura H, Faried A, et al. The incremental effect of positron emission tomography on diagnostic accuracy in the initial staging of esophageal carcinoma. Cancer. 2005;103(1):148–56.
22. Pfau PR, Perlman SB, Stanko P, Frick TJ, Gopal DV, Said A, et al. The role and clinical value of EUS in a multimodality esophageal carcinoma staging program with CT and positron emission tomography. Gastrointes Endosc. 2007;65(3):377–84.
23. Kato H, Kuwano H, Nakajima M, Miyazaki T, Yoshikawa M, Ojima H, et al. Comparison between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. Cancer. 2002;94(4):921–8.
24. Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Sundaresan SR, Patterson GA, et al. Staging of esophageal cancer with 18F-fluorodeoxyglucose positron emission tomography. AJR Am J Roentgenol. 1997;168(2):417–24.
25. Meltzer CC, Luketich JD, Friedman D, Charron M, Strollo D, Meehan M, et al. Whole-body FDG positron emission tomographic imaging for staging esophageal cancer comparison with computed tomography. Clin Nucl Med. [Comparative Study]. 2000;25(11):882–7.
26. Luketich JD, Friedman DM, Weigel TL, Meehan MA, Keenan RJ, Townsend DW, et al. Evaluation of distant metastases in esophageal cancer: 100 consecutive positron emission tomography scans. Ann Thorac Surg. 1999;68(4):1133–6; (discussion 6–7).
27. Block MI, Patterson GA, Sundaresan RS, Bailey MS, Flanagan FL, Dehdashti F, et al. Improvement in staging of esophageal cancer with the addition of positron emission tomography. Ann Thorac Surg. 1997;64(3):770–6; (discussion 6–7).
28. Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol. [Clinical Trial Comparative Study]. 2000;18(18):3202–10.
29. van Westreenen HL, Westerterp M, Jager PL, van Dullemen HM, Sloof GW, Comans EF, et al. Synchronous primary neoplasms detected on 18F-FDG PET in staging of patients with esophageal cancer. J Nucl Med. 2005;46(8):1321–5.
30. Karashima R, Watanabe M, Imamura Y, Ida S, Baba Y, Iwagami S, et al. Advantages of FDG-PET/CT over CT alone in the preoperative assessment of lymph node metastasis in patients with esophageal cancer. Surg Today. 2014 Jun 28.
31. Kato H, Kimura H, Nakajima M, Sakai M, Sano A, Tanaka N, et al. The additional value of integrated PET/CT over PET in initial lymph node staging of esophageal cancer. Oncol Rep. 2008;20(4):857–62.
32. Matthes K, Bounds BC, Collier K, Gutierrez A, Brugge WR. EUS staging of upper GI malignancies: results of a prospective randomized trial. Gastrointest Endosc. 2006;64(4):496–502.
33. Yasuda K, Kamaguchi M, Morikawa J, Honda M, Nakajima M. Role of endoscopic ultrasonography in the diagnosis of early esophageal carcinoma. Gastrointest Endosc Clin N Am. 2005;15(1):93–9, ix.
34. Kimmey MB, Martin RW, Haggitt RC, Wang KY, Franklin DW, Silverstein FE. Histologic correlates of gastrointestinal ultrasound images. Gastroenterology. 1989 Feb; 96(2 Pt 1):433–41.
35. Rosch T. Endosonographic staging of esophageal cancer: a review of literature results. Gastrointest Endosc Clin N Am. 1995;5(3):537–47.
36. Young PE, Gentry AB, Acosta RD, Greenwald BD, Riddle M. Endoscopic ultrasound does not accurately stage early adenocarcinoma or high-grade dysplasia of the esophagus. Clin Gastroenterol Hepatol. 2010;8(12):1037–41.
37. Lightdale CJ. Esophageal cancer. American College of Gastroenterology. The American journal of gastroenterology. 1999;94(1):20–9.
38. Catalano MF, Sivak MV, Jr., Rice T, Gragg LA, Van Dam J. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc. 1994;40(4):442–6.
39. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. Gastrointest Endosc. 1997;45(6):474–9.
40. Sandha GS, Severin D, Postema E, McEwan A, Stewart K. Is positron emission tomography useful in locoregional staging of esophageal cancer? Results of a multidisciplinary initiative comparing CT, positron emission tomography, and EUS. Gastrointest Endosc. 2008;67(3):402–9.
41. Chang KJ, Katz KD, Durbin TE, Erickson RA, Butler JA, Lin F, et al. Endoscopic ultrasound-guided fine-needle aspiration. Gastrointest Endosc. 1994;40(6):694–9.
42. Vazquez-Sequeiros E, Norton ID, Clain JE, Wang KK, Affi A, Allen M, et al. Impact of EUS-guided fine-needle aspiration on lymph node staging in patients with esophageal carcinoma. Gastrointest Endosc. 2001;53(7):751–7.
43. Eloubeidi MA, Wallace MB, Reed CE, Hadzijahic N, Lewin DN, Van Velse A, et al. The utility of EUS and EUS-guided fine needle aspiration in detecting celiac lymph node metastasis in patients with esophageal cancer: a single-center experience. Gastrointest Endosc. 2001;54(6):714–9.
44. Reed CE, Mishra G, Sahai AV, Hoffman BJ, Hawes RH. Esophageal cancer staging: improved accuracy by endoscopic ultrasound of celiac lymph nodes. Ann Thorac Surg. 1999;67(2):319–21; (discussion 322).
45. Boonstra JJ, Koppert LB, Wijnhoven BP, Tilanus HW, Van Dekken H, Tran TC, et al. Chemotherapy followed by surgery in patients with carcinoma of

the distal esophagus and celiac lymph node involvement. J Surg Oncol. 2009;100(5):407–13.
46. Eloubeidi MA, Wallace MB, Hoffman BJ, Leveen MB, Van Velse A, Hawes RH, et al. Predictors of survival for esophageal cancer patients with and without celiac axis lymphadenopathy: impact of staging endosonography. Ann Thorac Surg. 2001;72(1):212–9; (discussion 9–20).
47. Hiele M, De Leyn P, Schurmans P, Lerut A, Huys S, Geboes K, et al. Relation between endoscopic ultrasound findings and outcome of patients with tumors of the esophagus or esophagogastric junction. Gastrointest Endosc. 1997;45(5):381–6.
48. Menzel J, Hoepffner N, Nottberg H, Schulz C, Senninger N, Domschke W. Preoperative staging of esophageal carcinoma: miniprobe sonography versus conventional endoscopic ultrasound in a prospective histopathologically verified study. Endoscopy. [Clinical Trial Comparative Study]. 1999;31(4):291–7.
49. Pfau PR, Ginsberg GG, Lew RJ, Faigel DO, Smith DB, Kochman ML. Esophageal dilation for endosonographic evaluation of malignant esophageal strictures is safe and effective. Am J Gastroenterol. 2000;95(10):2813–5.
50. Wallace MB, Hawes RH, Sahai AV, Van Velse A, Hoffman BJ. Dilation of malignant esophageal stenosis to allow EUS guided fine-needle aspiration: safety and effect on patient management. Gastrointest Endosc. 2000;51(3):309–13.
51. Heinzow HS, Seifert H, Tsepetonidis S, Wolters H, Kucharzik T, Domschke W, et al. Endoscopic ultrasound in staging esophageal cancer after neoadjuvant chemotherapy–results of a multicenter cohort analysis. J Gastrointestl Surg. 2013;17(6):1050–7.
52. Catalano MF, Sivak MV, Jr., Rice TW, Van Dam J. Postoperative screening for anastomotic recurrence of esophageal carcinoma by endoscopic ultrasonography. Gastrointest Endosc. 1995;42(6):540–4.
53. Souquet JC, Napoleon B, Pujol B, Valette PJ, Chollet R, Lambert R. Endosonography-guided treatment of esophageal carcinoma. Endoscopy. 1992;24(Suppl 1):324–8.
54. Zuccaro G, Jr., Rice TW, Goldblum J, Medendorp SV, Becker M, Pimentel R, et al. Endoscopic ultrasound cannot determine suitability for esophagectomy after aggressive chemoradiotherapy for esophageal cancer. Am J Gastroenterol. 1999;94(4):906–12.
55. Rice TW, Zuccaro G, Jr., Adelstein DJ, Rybicki LA, Blackstone EH, Goldblum JR. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. Ann Thorac Surg. 1998;65(3):787–92.
56. Liu L, Hofstetter WL, Rashid A, Swisher SG, Correa AM, Ajani JA, et al. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol. 2005;29(8):1079–85.
57. Stein HJ, Feith M, Bruecher BL, Naehrig J, Sarbia M, Siewert JR. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg. 2005;242(4):566–73 (discussion 73–5).
58. Lewis JT, Wang KK, Abraham SC. Muscularis mucosae duplication and the musculo-fibrous anomaly in endoscopic mucosal resections for barrett esophagus: implications for staging of adenocarcinoma. Am J Surg Pathol. 2008;32(4):566–71.
59. Mandal RV, Forcione DG, Brugge WR, Nishioka NS, Mino-Kenudson M, Lauwers GY. Effect of tumor characteristics and duplication of the muscularis mucosae on the endoscopic staging of superficial Barrett esophagus-related neoplasia. Am J Surg Pathol. 2009;33(4):620–5.
60. Pech O, Gunter E, Dusemund F, Ell C. Value of high-frequency miniprobes and conventional radial endoscopic ultrasound in the staging of early Barrett's carcinoma. Endoscopy. 2010;42(2):98–103.
61. Chemaly M, Scalone O, Durivage G, Napoleon B, Pujol B, Lefort C, et al. Miniprobe EUS in the pretherapeutic assessment of early esophageal neoplasia. Endoscopy. 2008;40(1):2–6.
62. Qumseya BJ, Brown J, Abraham M, White D, Wolfsen H, Gupta N, Vennalaganti P, Sharma P, Wallace MB. Diagnostic performance of EUS in predicting advanced cancer among patients with Barrett's esophagus and high-grade dysplasia/early adenocarcinoma: systemic review and meta-analysis. Gastrointest Endosc 2014 Oct 24. Epub ahead of print.

Gastric Cancer and Thickened Gastric Wall

26

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Introduction

Gastric cancer remains one of the most prevalent cancers and is responsible for an estimated 989,600 new cases (8% of total cancer cases) and 738,000 deaths (10% of total cancer deaths) a year worldwide, which contrasts with the declining incidence and cancer-related deaths from gastric cancer in the USA [1, 2]. Because optimal treatment differs with each gastric cancer stage, a comprehensive strategy for cancer staging is important.

Endoscopic ultrasound (EUS) was introduced into clinical practice in the late 1970s. Along with computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET), EUS has played an important role in the diagnosis and staging of gastrointestinal (GI) malignancies. Studies have shown the excellent diagnostic accuracy of EUS in locoregional (i.e., T stage) and lymph node staging (i.e., N stage). This chapter discusses the role of EUS in gastric cancer staging.

Case Presentation

A 69-year-old female was referred to our hospital for further evaluation of a stomach lesion. Upper gastroscopy performed in another hospital had revealed chronic gastritis and a shallowly depressed lesion in the anterior wall of the distal stomach (Fig. 26.1). Biopsy of the lesion revealed moderately differentiated adenocarcinoma. CT showed neither perigastric lymphadenopathy nor metastatic lesions. EUS was planned for pretreatment staging to determine the optimal treatment for this patient.

What Techniques Improve EUS Imaging of the Stomach Wall?

EUS is performed with radial or linear echoendoscopes, some of which are equipped with special features, such as color and power Doppler [3, 4], contrast harmonic imaging [5, 6], and others [7, 8]. EUS typically produces high-frequency ultrasound between 5 and 20 MHz, which can generate a high-resolution image in the near field with a limited penetration depth ranging from 1–2 to 5–6 cm, depending on the ultrasound frequency.

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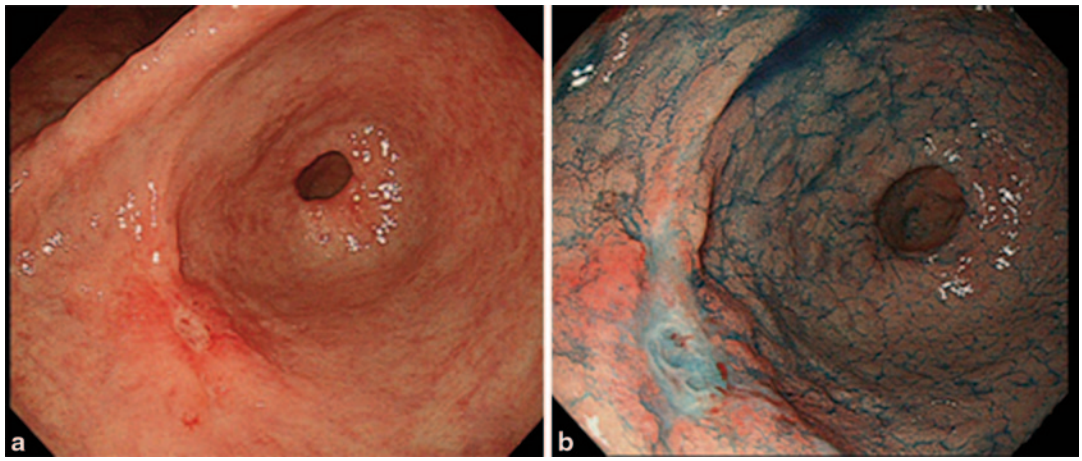

Fig. 26.1 Endoscopic images of a gastric cancer. White light **a** and chromoendoscopy with indigo carmine **b** show a shallow depressed lesion in the anterior wall of the antrum

In general, gastric EUS is performed with the patient in the left lateral position, usually under conscious sedation with benzodiazepines in conjunction with a central analgesic. Propofol has been used recently and is associated with very low complication rates [9–11]. Radial echoendoscopes generate radial images of 360° and are oriented perpendicular to the shaft axis of the instrument. In contrast, linear echoendoscopes produce images directed parallel to the shaft axis of the endoscope, allowing effective and safe performance of EUS-guided fine-needle aspiration (EUS-FNA). In our personal experience, radial imaging offers a better view of the gastrointestinal wall and the structures surrounding the stomach, and it provides a complete scan, unlike the linear echoendoscope that requires rotating the scope manually 360 degrees to get a complete view. This is a matter of personal preference, and some endosonographers (especially in the Western Hemisphere) may prefer the linear instrument for initial staging with the idea that any lymph nodes or other lesions that need EUS-FNA can be targeted immediately without changing the scope. EUS with high-frequency ultrasound probes is especially useful for early gastric cancer as opposed to the radial or linear echoendoscopes that are used in imaging advanced gastric cancer. Therefore, the choice of staging method—echoendoscope or miniature probe EUS—may first depend on the estimation of tumor depth (T stage) from findings on upper endoscopy or other imaging modalities [12, 13].

Adherence to the following principles during EUS will help ensure clear images.

1. **Clean out the stomach for a better view**. Stomach contents and mucus on the stomach wall should be removed as much as possible because floating debris will worsen the quality of the images and subsequently complicate interpretation of EUS images. For this purpose, upper endoscopy should be performed before EUS. Upper endoscopy also can help to define the gross appearance of the upper GI tract and confirm the location of the lesion.
2. **Instill water during EUS**. Acoustic coupling of the ultrasound transducer to the GI wall requires application of fluid as an interface between the transducer and the wall. This can be accomplished either by using a water-filled balloon around the tip of the echoendoscope or by instilling water into the gastric lumen. Water should be de-aired because air bubbles will interfere with the acoustic shadow. In the standard left lateral position during endoscopy, the stomach is initially collapsed by aspiration, followed by instillation of 200–400 mL of water into the lumen up to the fundus. The examination is begun from the antrum, while the instrument is slowly withdrawn, and

all areas of the gastric circumference are visualized as far as possible with perpendicular scanning.

3. **Sustain the position**. Scanning should be performed perpendicular to the target lesions because an oblique image may be unclear and can over- or underestimate disease depth. The appropriate distance between target lesions and the transducer is 0.5–1.0 cm.
4. **Use high frequency for shallow lesions and low frequency for deeper lesions**. High-frequency EUS (e.g., using a miniature 20-MHz probe) can provide high-resolution images. This is especially useful in evaluating shallow lesions that may be located within the mucosa or submucosa. On the other hand, high-frequency EUS cannot penetrate the stomach wall and is not compatible for evaluation of deep lesions or perigastric lesions (e.g., lymph nodes, ascites). Low-frequency EUS, both radial and linear, can evaluate lesions that lie in deep parts of the stomach wall as well as perigastric lesions.
5. **Utilize positioning during EUS to obtain better images**. EUS of the stomach can be difficult, especially in the prepylorus, fundus, and angle of the stomach. Maintaining the water level and keeping the probe scanning perpendicular to the wall is sometimes difficult to achieve. In these instances, rotating the patient may help keep the water level constant, and pushing the scope in, pulling it out, and then rotating it may help achieve a perpendicular position. For a lesion in the upper body or fundus of the stomach, slight rotation to the prone position from the left lateral position may be helpful. With a lesion around the angle of the stomach, a supine position may facilitate visualization. With a lesion in the prepylorus, a right lateral position may help obtain clear EUS images.

Normal Gastric Wall Anatomy as Viewed by EUS

The gastric wall typically consists of five distinct layers by EUS using the echoendoscopes with 7.5–12 MHz [14–16]. The first two inner layers with high and low echogenicity represent the interface/superficial mucosa and deep mucosa/muscularis mucosa. The third hyperechoic layer corresponds to the submucosa, the fourth hypoechoic layer to the muscularis propria, and the fifth hyperechoic layer to the serosa, which usually is not easily distinguishable from the surrounding echo-rich tissue. Using higher frequency EUS miniprobes (12 to 20 MHz) and under optimal conditions, up to nine gastric wall layers can be identified. The surrounding organs, vessels, and other structures are important for diagnosis as well as for orientation (e.g., to determine tumor infiltration depth). These organs and other structures include the pancreatic body and tail, parts of the liver (especially the left lobe), parts of the left kidney and spleen, and vessels such as the aorta, vena cava (proximal stomach), celiac trunk, and the splenic and left renal veins. In everyday practice, both the water filling the lumen and balloon inflation methods can be combined for improved imaging.

Gastric Cancer Staging with EUS

What is the TNM Staging System for Gastric Cancer?

The classification systems of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) are the staging classifications used most often in the USA and commonly used in Asian countries. The AJCC/UICC system is based on TNM: tumor (T), lymph node (N), and metastasis (M) (Table 26.1) [17].

The final pathological staging will be determined by the surgically resected specimen. However, the initial staging is critical because of its importance in determining treatment strategy. Early stage patients may be eligible for endoscopic resection, which is discussed in more detail in the following section. Patients in stages I to III by preoperative staging may be good candidates for surgical resection [18–20]. Furthermore, patients with higher stage (T2 and above) tumors or suspected nodal involvement may benefit from neoadjuvant (preoperative) and/or adjuvant

Table 26.1 AJCC (American Joint Committee on Cancer)/UICC (International Union Against Cancer) TNM classification

Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ: intraepithelial tumor without invasion of the lamina propria		
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa		
T1a	Tumor invades lamina propria or muscularis mucosae		
T1b	Tumor invades submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor penetrates subserosal connective tissue without invading visceral peritoneum or adjacent structures		
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures		
T4a	Tumor invades serosa (visceral peritoneum)		
T4b	Tumor invades adjacent structures		
Regional lymph nodes (N)			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph node metastasis◊		
N1	Metastasis in 1–2 regional lymph nodes		
N2	Metastasis in 3–6 regional lymph nodes		
N3	Metastasis in 7 or more regional lymph nodes		
N3a	Metastasis in 7–15 regional lymph nodes		
N3b	Metastasis in 16 or more regional lymph nodes		
Distant metastasis (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0	M0
	T4b	N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2	M0
	T4b	N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1

(postoperative) therapies in addition to surgery. Therefore, multidisciplinary evaluation is necessary to identify the best treatment strategy. On the other hand, patients with distant metastasis will receive less benefit from surgical resection than patients in earlier stages. Systemic therapy and/or palliative therapy may be indicated for these patients.

What Are the Indications for Endoscopic Resection?

It is also important to understand the indications for endoscopic treatment, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) for early-stage gastric cancer. According to Japanese gastric cancer treatment guidelines established in 2010, patients who have a T1a (mucosal) lesion and meet the following criteria discussed below can be managed endoscopically because the risk of lymph node metastasis is low and the prognosis is similar to patients who undergo surgical resection [19].

Definite Indication for Endoscopic Resection of Gastric Cancer In Japan, EMR or ESD is a standard treatment for differentiated adenocarcinoma without ulcerative findings [UL (-)], a depth of invasion clinically diagnosed as T1a, and a tumor diameter less than 2 cm.

Expanded Indication for Endoscopic Treatment for Gastric Cancer Tumors in the following categories have a very low probability of lymph node metastasis. Endoscopic resection for these tumors is regarded as an investigational treatment. ESD, but *not* EMR, should be employed. Tumors clinically diagnosed as T1a and one of the following characteristics: (a) differentiated, UL (-), but more than 2 cm in diameter; (b) differentiated, UL (-), and less than 3 cm in diameter; and (c) undifferentiated, UL (-), and less than 2 cm in diameter.

T staging by EUS

EUS can determine T staging by detecting tumor infiltration in the deepest part of the affected gastric wall. In general, gastric cancer has less echogenicity than does the surrounding normal tissue. Depending on the tumor stage, as the cancer grows, it destroys the normal gastric wall structure from the mucosal layer and eventually infiltrates other structures (Fig. 26.2).

T1: Tumor within the mucosa (a) and submucosa (b). The tumor usually has less echogenicity than the surrounding normal tissue. As a result, hypoechoic wall thickening of the first and second mucosal layer and/or the submucosa (third layer), and an intact muscularis propria (fourth layer) is observed (Figs. 26.3, 26.4 and 26.5).

T2: Tumor infiltrates the muscularis propria and subserosa (Fig. 26.6 and Video 26.1).

T3: Tumor penetrates subserosal connective tissue without invading the visceral peritoneum or adjacent structures (Fig. 26.7).

T4: Tumor invades the serosa (visceral peritoneum) (T4a, Fig. 26.8) or adjacent structures (T4b).

N staging by EUS

For N staging of gastric cancer, the number of malignant regional lymph nodes can be assessed at the same time as the T stage of the primary lesion. EUS characteristics of malignant lymph nodes include (1) lymph node size greater than 10 mm, (2) sharp and distinct margin, (3) homogenous hypoechoic pattern, and (4) round shape (Fig. 26.9) [20–23]. However, a diagnosis made on the basis of these echo features is not reliable because the accuracy of predicting malignant lymph nodes is about 80% even when all four of these features occur in the same lymph node. Additionally, only 25% of all malignant lymph nodes present with all four of these malignant features. Therefore, EUS-FNA is recommended for a definitive cytopathological diagnosis [24–26]

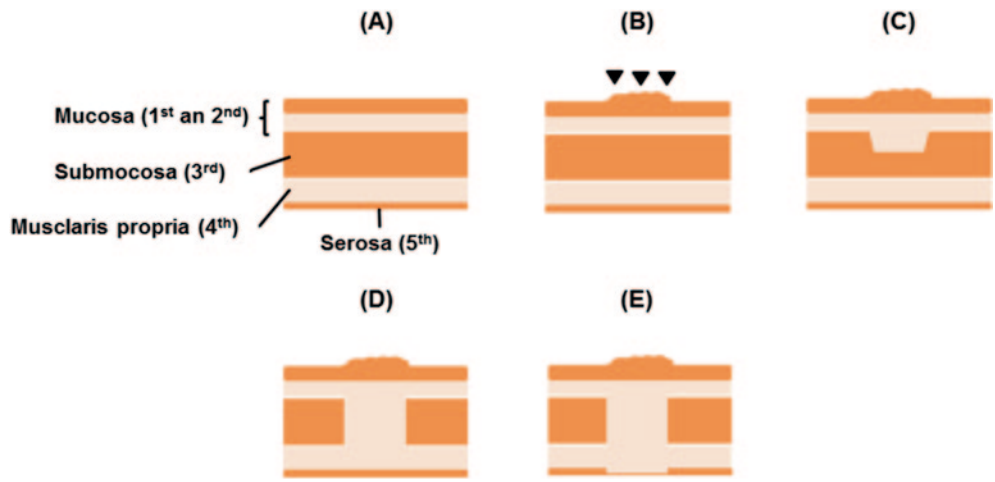

Fig. 26.2 Endoscopic ultrasound evaluation of the depth of gastric cancer. **a** Normal gastric wall consists of five distinct layers. **b** Cancers limited to the mucosa show irregularity in the first and second layers, but the third layer is intact. **c** Submucosal invasion displays irregularity of the third layer. **d** Muscularis propria invasion shows interruption of the third layer. **e** Interruption of the fifth layer indicates that the invasion is deeper than the subserosal layer

When confronted with multiple regional lymph nodes, it may not be practical or feasible to perform EUS-FNA on every single lymph node. In such circumstances, we recommend EUS-FNA of 1–2 lymph nodes that appear highly suspicious for malignancy based on the echo features. If these are malignant, we would consider all other lymph nodes with similar echo features to be malignant. In challenging cases when EUS and EUS-FNA are inconclusive or difficult to perform, results from other diagnostic studies discussed later in this chapter should be comprehensively analyzed.

Recently, contrast-enhanced EUS (CE-EUS) has been reported as useful in predicting malignant lymph nodes in various cancers. Kanamori et al. utilized an intravenous contrast agent (Levovist, Nihon Schering Co., Ltd., Tokyo, Japan) to evaluate patients with mediastinal or abdominal lymphadenopathy using surgery or EUS-FNA as the gold standard. They described three enhancement patterns of lymph nodes following contrast injection: diffuse or uniform enhancement of the entire lymph node, no enhancement, and filling defect with spotty or heterogeneous filling of the node. All malignant lymph nodes displayed the filling defect pattern of enhancement, while the majority of benign lymph nodes enhanced homogeneously. Although no comparative study of CE-EUS and EUS-FNA has been published, the sensitivity of CE-EUS for predicting malignant lymph nodes was reported to be as high as 100% with 81.8% specificity and 92.0% accuracy [5, 6]. Therefore, CE-EUS may potentially be a complementary technique along with EUS-FNA for N staging, especially if multiple lymph nodes are found in a particular patient.

How Accurate is T and N Staging by EUS?

Recently, two meta-analyses have reported data on the staging performance of EUS in gastric cancer. Mocellin et al. examined 66 studies that enrolled a total of 7747 patients with gastric cancer who were undergoing staging EUS. Their results suggest that EUS has a high diagnostic yield in distinguishing T1–2 from T3–4 gastric cancer with a sensitivity of 0.86 [95% confidence interval (CI), 0.81–0.90] and a specificity of 0.90 (95% CI, 0.87–0.93). T1 tumors were also distinguished from T2 tumors accurately with 0.85 (95% CI 0.78-0.91) sensitivity and 0.90 (95% CI

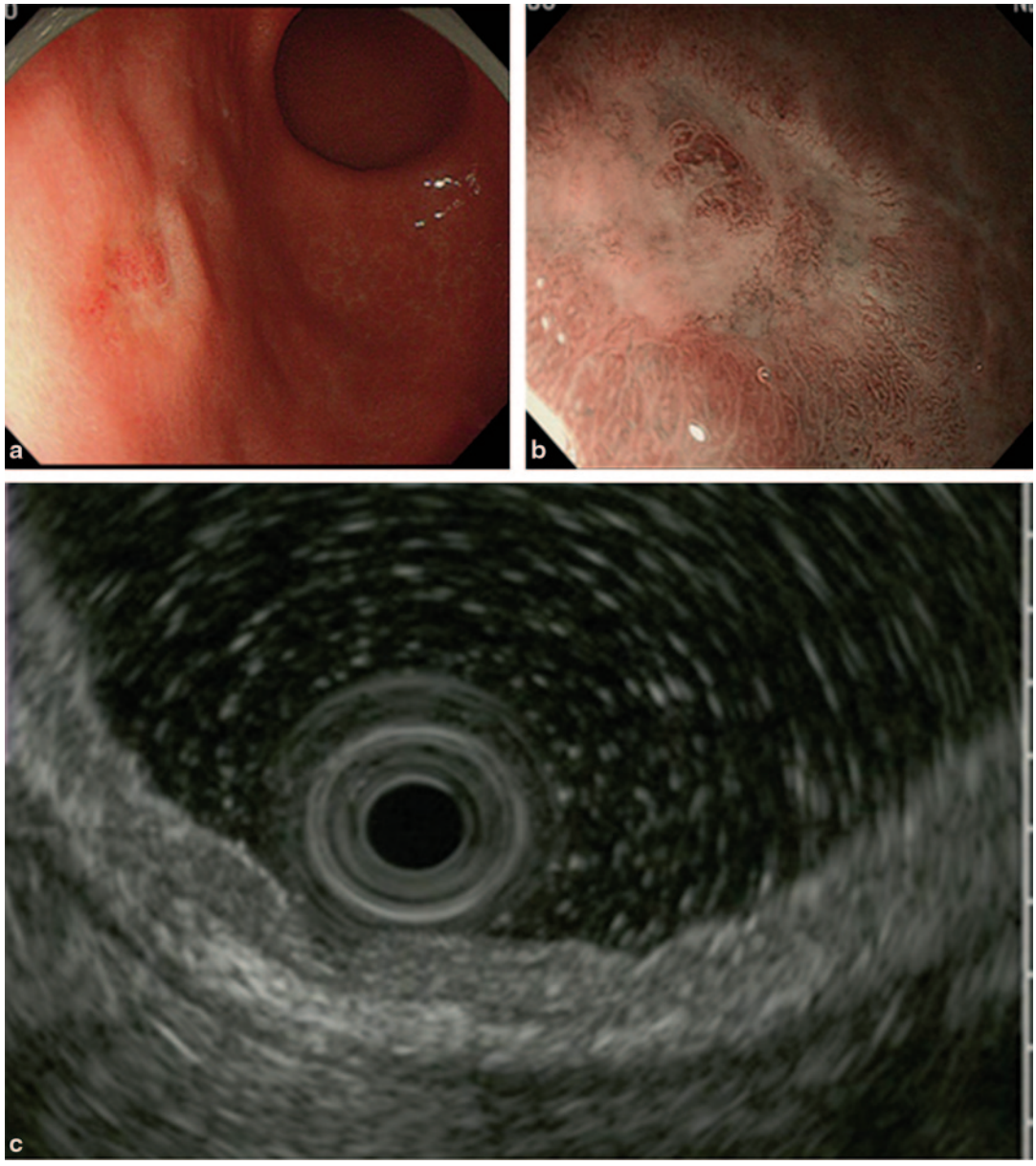

Fig. 26.3 Endoscopy and EUS images of mucosal (T1a) gastric cancer. **a–b** Gastroscopy indicates a shallow depressed lesion on the antrum. Narrow band image shows irregular microvasculature, suggesting an undifferentiated type of cancer. **c** EUS image reveals a shallow depressed lesion in the thickened first and second layers. No irregularity in the third layer suggests a mucosal lesion

0.85-0.93) specificity. Compared to the diagnostic accuracy for T1 tumors as a whole, EUS is less reliable in identifying T1a tumors because of lower specificity [0.75 (95% CI, 0.62-0.84)]. Regarding N staging, overall sensitivity was 0.83 (95% CI, 0.79-0.87) with specificity 0.67 (95% CI, 0.61-0.72) [27].

Another meta-analysis by Cardoso et al. reported the same trend, finding that EUS is a moderately accurate technique for gastric cancer staging with 75% accuracy for T staging and 64% accuracy for N staging. EUS is particularly helpful with advanced T stage (T3 and T4) as opposed to less advanced T stage or N stage. Diagnostic

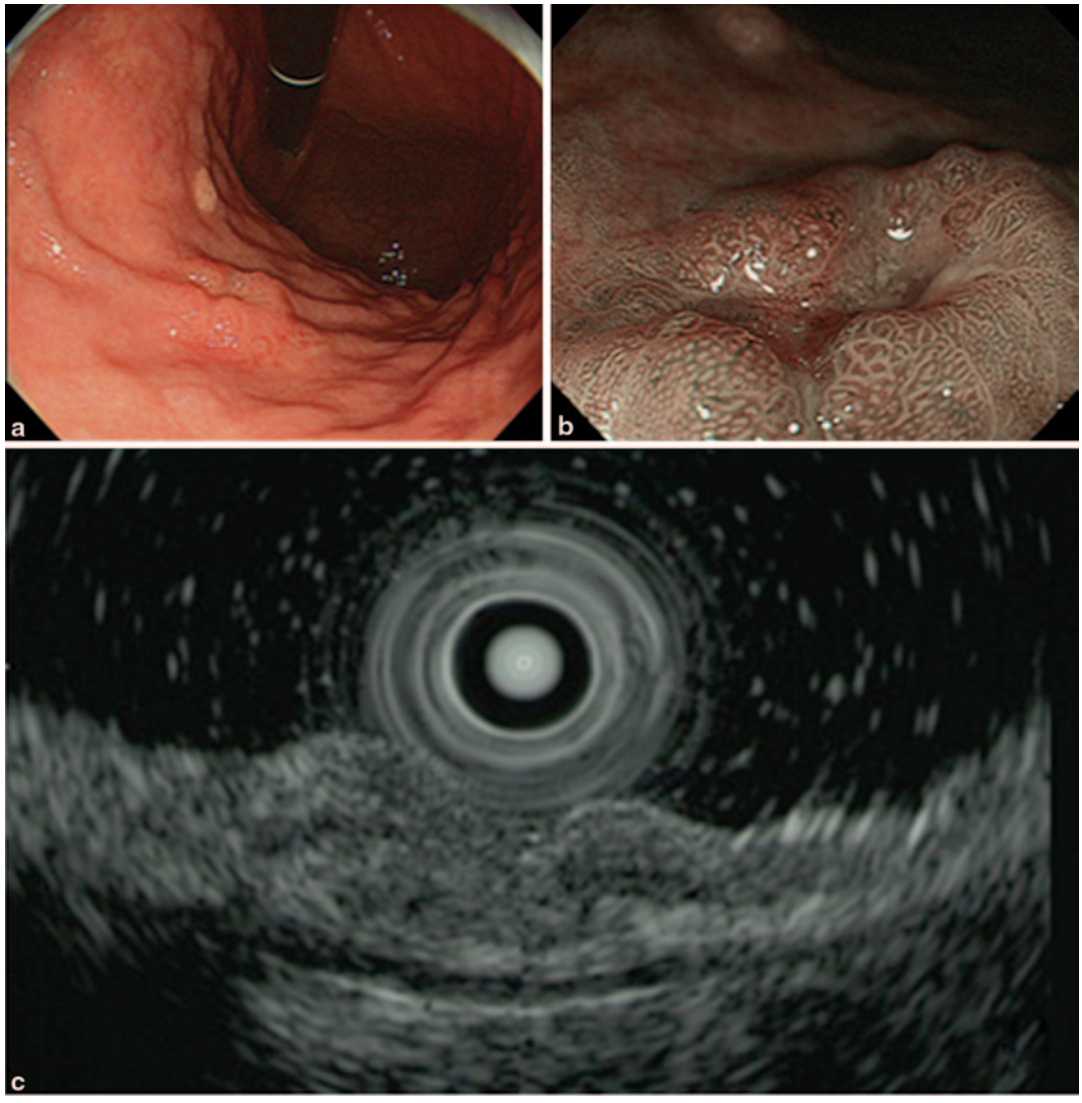

Fig. 26.4 Endoscopic and EUS images of submucosal (T1b) gastric cancer. **a–b** Gastroscopy shows a depressed lesion in the anterior wall of the gastric upper body. **c** EUS reveals irregularly thickened first and second layers. An irregularity in the hyperechoic third layer suggests cancer invasion into the submucosal layer

accuracy for each T stage is as follows: T1 77%, T2 65%, T3 85%, and T4 79%, and these differences were not statistically significant [28].

The above data suggest that EUS is a useful modality, especially for T staging. Extrapolating from the data for esophageal and rectal cancer staging, N staging accuracy likely improves with the addition of EUS-FNA rather than relying on EUS imaging alone. It should be noted that EUS is often used to evaluate gastric cancers that are undifferentiated or large, and may incorrectly diagnose tumor invasion depth by either over- or understaging the tumor [29]. In these circumstances, staging should be complemented with other imaging modalities.

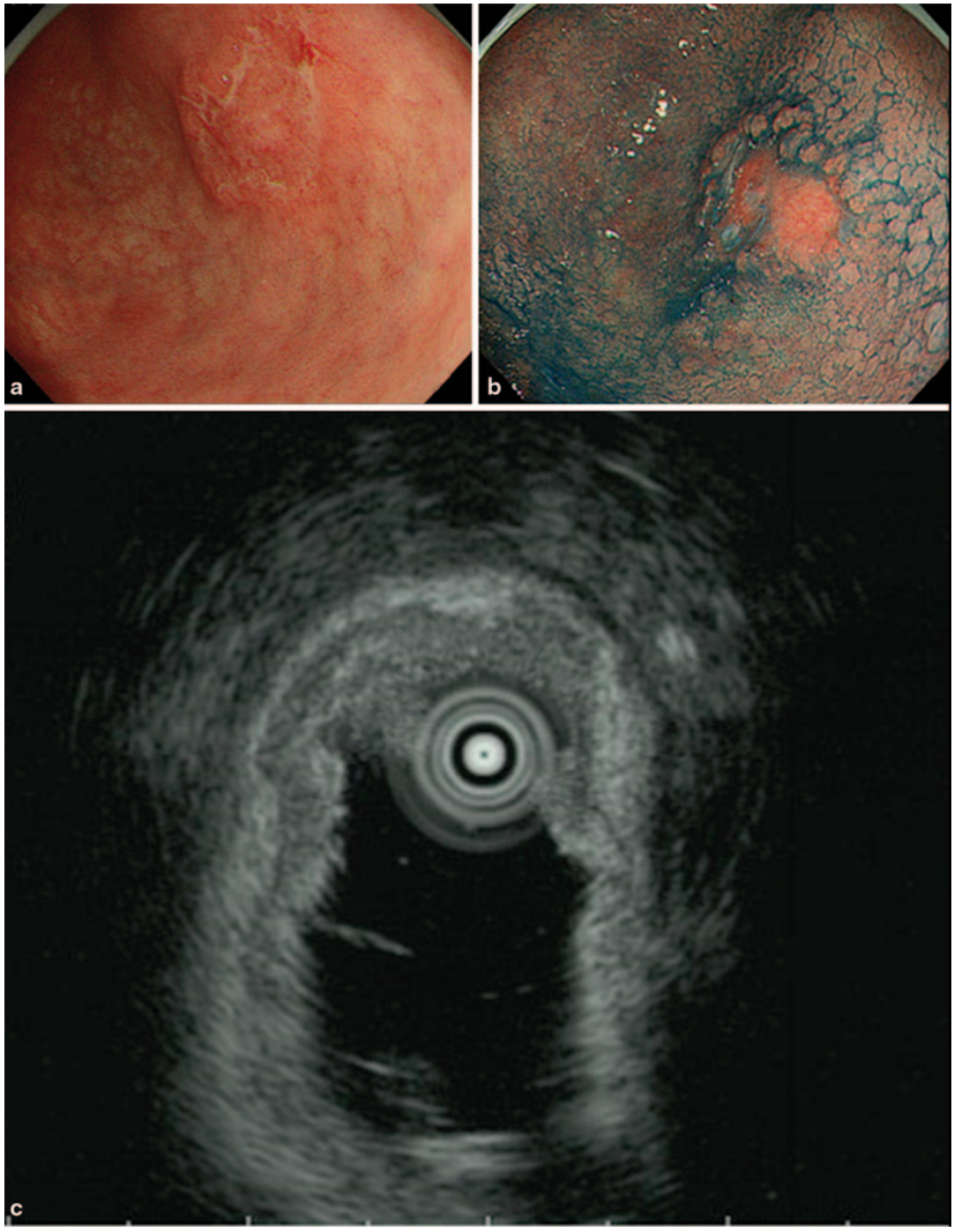

Fig. 26.5 Endoscopic and EUS images of submucosal (T1b) gastric cancer. **a–b** Gastroscopy shows a depressed lesion on the posterior wall of the gastric antrum. **c** EUS reveals irregularly thickened first and second layers. An irregularity in the hyperechoic third layer suggests cancer invasion into the submucosal layer

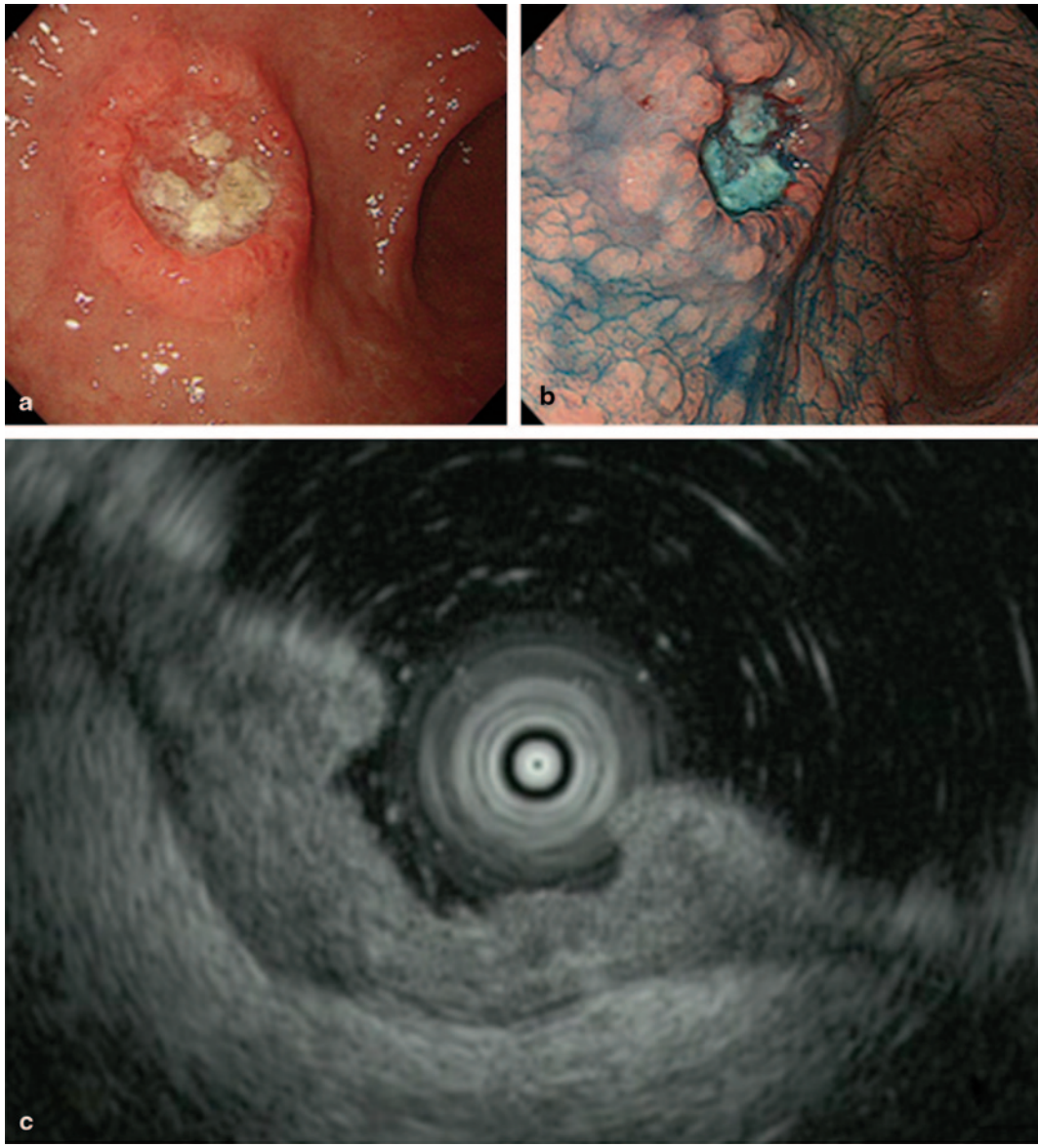

Fig. 26.6 Endoscopic and EUS images of gastric cancer with invasion of the muscularis propria (T2). **a**–**b** Gastroscopy shows a depressed lesion on the anterior wall of the gastric antrum. **c** EUS reveals a thickened gastric wall from the first to the third layer. The structure of the third layer is completely destroyed, suggesting cancer invasion into the muscularis propria

Case Presentation (continued)

We chose to use a miniprobe EUS with 20 MHz because the endoscopic findings had suggested an early gastric cancer. The EUS image shows five distinct layers: (1–2) mucosal layer, (3) submucosal layer, (4) muscularis propria, and (5) serosa. A hypoechoic mass with a depression has destroyed the normal layer pattern between the first and third layers, just below the EUS probe. This finding suggested gastric cancer with submucosal invasion (T1b). Because of the high likelihood of lymph node metastasis, endoscopic treatment was not indicated, and the patient underwent surgical resection.

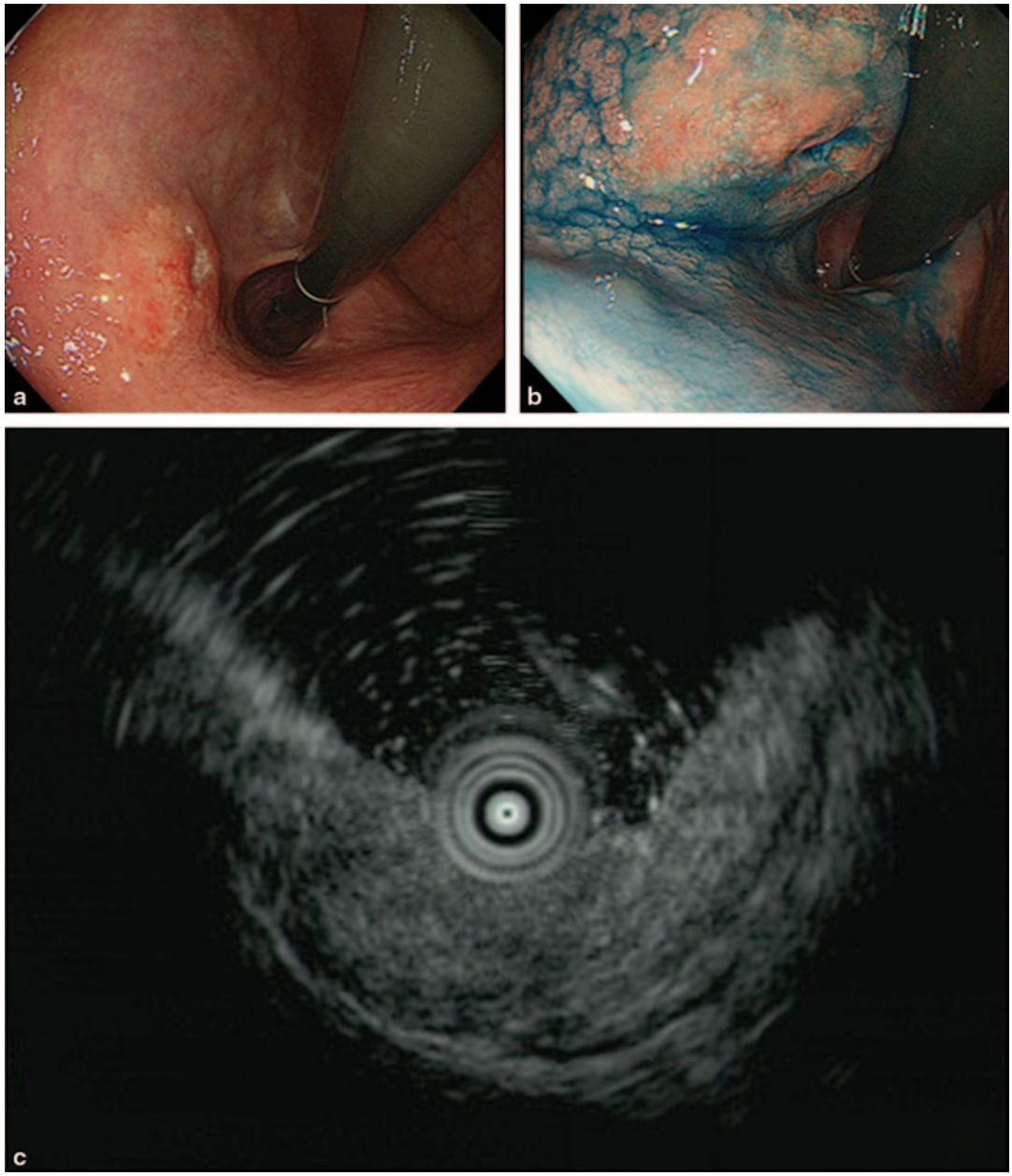

Fig. 26.7 Endoscopic and EUS images of gastric cancer with subserosal invasion (T3). **a–b** Gastroscopy shows a depressed lesion in the gastric cardia. **c** EUS reveals a heterogeneously thickened gastric wall from the first to the fourth layer. Also, the fifth layer is intact but irregular, suggesting cancer invasion deeper than the subserosal layer

How Does EUS Compare to Other Staging Modalities?

It is important to understand the advantages and disadvantages of using EUS in gastric cancer staging as opposed to other available techniques. These modalities include multidetector-row computed tomography (MDCT), magnetic resonance imaging (MRI), and positron emission tomography (PET). A recent systematic review of gastric cancer T staging by EUS, MDCT, and MRI showed similar diagnostic accuracy among

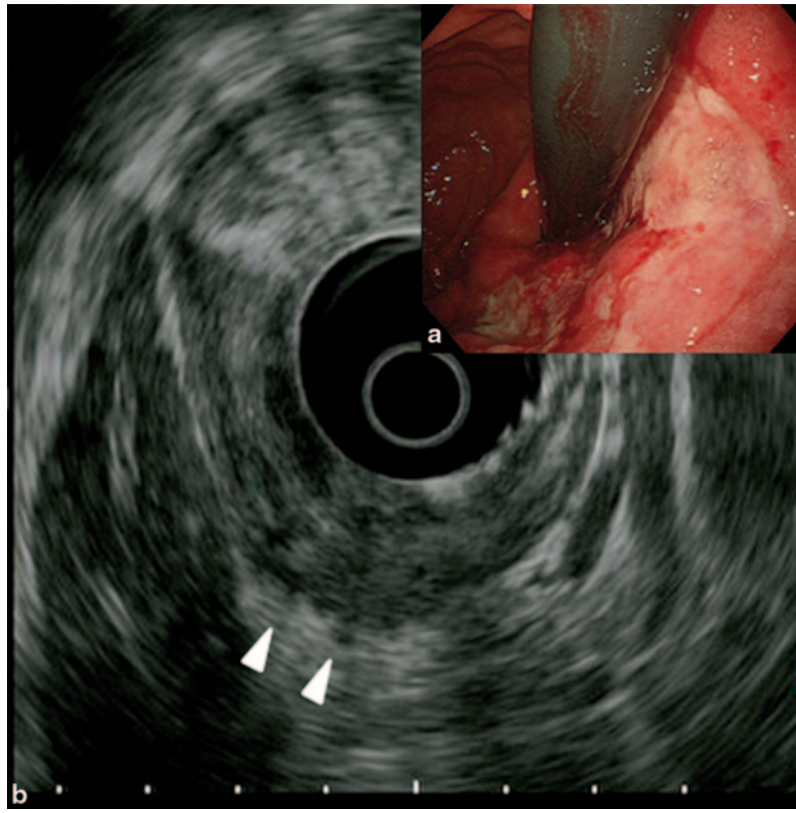

Fig. 26.8 Endoscopic and EUS images of gastric cancer with serosal invasion (T4a). **a** Gastroscopy shows an ulcerative lesion in the gastric cardia. **b** EUS shows a thickened gastric wall from the first through the fifth layer, with serrated extensions beyond the wall (*arrowheads*), consistent with serosal invasion

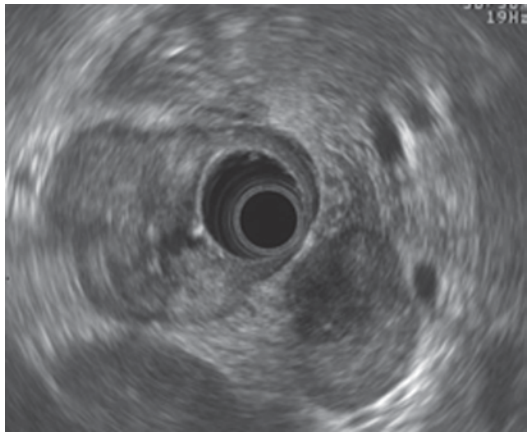

Fig. 26.9 EUS reveals a lymph node adjacent to a gastric cancer in the antrum of stomach with characteristics of a malignant lymph node including size greater than 10 mm, sharp and distinct margin, homogenous hypoechoic pattern, and round shape

the three techniques (65–92.1%, 77.1–88.9%, and 71.4–82.6%, respectively). However, the authors suggested that EUS should be the first choice for T staging because most of the experience with gastric cancer staging has been with EUS (23 studies) compared with MDCT (6 studies) and MRI (3 studies) [30]. This of course assumes local availability of EUS expertise. If unavailable, MDCT is a reasonable alternative.

With regard to N staging, the diagnostic yields of EUS and CT are similar. The sensitivity and specificity of EUS in detecting lymph node involvement range from 16.7 to 90.7% and 48.4 to 100%, respectively; the sensitivity and specificity of CT for assessing lymph node involvement are 62.5−91.9% and 50.0−87.9%, respectively [31–35]. The advantage of EUS is the ability to perform EUS-FNA to evaluate suspicious nodes, which increases the accuracy of nodal staging.

Table 26.2 Etiology of giant gastric folds

Malignancy	Gastric adenocarcinoma, linitis plastica, lymphoma, gastric metastasis
Infection	*Helicobacter pylori*, secondary syphilis, syphilis, tuberculosis, CMV, HSV, anisakiasis
Infiltration/inflammation	Crohn's disease, sarcoidosis, amyloidosis, eosinophilic or lymphocytic gastritis
Vascular lesion	Portal hypertensive gastropathy, gastric varices
Miscellaneous causes	Menetrier's disease, Zollinger–Ellison syndrome

Table 26.3 Gastric wall layers primarily involved by etiology of giant gastric folds

Etiology	Layer
Gastric cancer, linitis plastica	2nd−4th
Gastric lymphoma	2nd
H. pylori infection	2nd
Gastric varices	3rd
Lymphoma	2nd−4th
Menetrier's disease	2nd

The role of EUS in M staging is questionable because of the limited field of vision with the echoendoscope. However, EUS can occasionally detect ascites or liver metastases missed by radiology imaging. As a result, EUS can complement radiology imaging. Therefore, in the overall approach to staging for gastric cancer, we recommend initial MDCT scan to evaluate for distant metastases. If metastatic disease is not identified, EUS should be performed for locoregional staging where this expertise is available.

Another Use for Gastric EUS: Giant Gastric Folds

The diagnosis of giant gastric folds is generally suspected when gastric folds do not flatten despite sufficient air insufflation. Values for the normal thickness of the gastrointestinal wall have not been established, but 2–4 mm is usually considered in the normal range with a 1:1:1 relationship among the mucosa, submucosa, and muscularis propria although the muscularis propria may be thicker in the antrum [36–38]. A gastric wall greater than 4 mm thick is considered abnormal. The etiology of giant gastric folds varies and includes malignancies, infections, infiltration or inflammation, vascular abnormalities, and benign conditions (Table 26.2). EUS is useful in establishing a differential diagnosis of giant gastric folds by detecting veiled lesions under the mucosal layer and evaluating the wall layers involved by the lesions (Table 26.3) [39, 40]. For lesions localized in the mucosal and submucosal layer of the stomach wall, endoscopic biopsy would be the first choice for tissue sampling, considering its safety and convenience. EUS-FNA can be useful especially for lesions lying deep within the wall of the stomach (e.g., submucosa and muscularis propria), and 19-gauge needles or core biopsy needles may increase diagnostic yield. Endoscopic snaring and EMR of giant gastric folds should be considered when biopsy and EUS-FNA are nondiagnostic.

Key Points

- High frequency EUS should be used for shallow gastric lesions and low frequency for deeper lesions.
- Endoscopic resection with EMR and ESD is indicated for differentiated gastric adenocarcinoma without ulceration, diameter less than 2 cm and T1a stage.
- Accuracy of EUS for T and N staging appear comparable with multidetector-row CT and MRI.
- EUS is less accurate for differentiating early stage gastric tumors.
- EUS may help diagnose the etiology of thickened gastric folds with the aid of forceps biopsy for lesions limited to the mucosa and submucosa layers and fine needle aspiration or biopsy for deeper lesions in the submucosa and muscularis propria.

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Video Caption

Video 26.1 T2 gastric cancer with muscularis propria invasion

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63:11–30.
2. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
3. Lee YT, Sung JJ, Yung MY, et al. Use of color Doppler EUS in assessing azygos blood flow for patients with portal hypertension. Gastrointest Endosc. 1999;50:47–52.
4. Becker D, Strobel D, Bernatik T, et al. Echo-enhanced color- and power-doppler EUS for the discrimination between focal pancreatitis and pancreatic carcinoma. Gastrointest Endosc. 2001;53:784–9.
5. Hocke M, Menges M, Topalidis T, et al. Contrast-enhanced endoscopic ultrasound in discrimination between benign and malignant mediastinal and abdominal lymph nodes. J Cancer Res Clin Oncol. 2008;134:473–80.
6. Kanamori A, Hirooka Y, Itoh A, et al. Usefulness of contrast-enhanced endoscopic ultrasonography in the differentiation between malignant and benign lymphadenopathy. Am J Gastroenterol. 2006;101:45–51.
7. Saftoiu A, Vilmann P, Ciurea T, et al. Dynamic analysis of EUS used for the differentiation of benign and malignant lymph nodes. Gastrointest Endosc. 2007;66:291–300.
8. Xu W, Shi J, Zeng X, et al. EUS elastography for the differentiation of benign and malignant lymph nodes: a meta-analysis. Gastrointest Endosc. 2011;74:1001-9; quiz 1115 e1–4.
9. Dewitt J, McGreevy K, Sherman S, et al. Nurse-administered propofol sedation compared with midazolam and meperidine for EUS: a prospective, randomized trial. Gastrointest Endosc. 2008;68:499–509.
10. Vargo JJ, Zuccaro G, Jr., Dumot JA, et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. Gastroenterology. 2002;123:8–16.
11. Fanti L, Agostoni M, Arcidiacono PG, et al. Target-controlled infusion during monitored anesthesia care in patients undergoing EUS: propofol alone versus midazolam plus propofol. A prospective double-blind randomised controlled trial. Dig Liver Dis. 2007;39:81–6.
12. Choi J, Kim SG, Im JP, et al. Comparison of endoscopic ultrasonography and conventional endoscopy for prediction of depth of tumor invasion in early gastric cancer. Endoscopy. 2010;42:705–13.
13. Sano T, Okuyama Y, Kobori O, et al. Early gastric cancer. Endoscopic diagnosis of depth of invasion. Dig Dis Sci 1990;35:1340–4.
14. Yanai H, Matsumoto Y, Harada T, et al. Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. Gastrointest Endosc. 1997;46:212–6.
15. Akahoshi K, Misawa T, Fujishima H, et al. Preoperative evaluation of gastric cancer by endoscopic ultrasound. Gut. 1991;32:479–82.
16. Murata Y, Suzuki S, Hashimoto H. Endoscopic ultrasonography of the upper gastrointestinal tract. Surg Endosc. 1988;2:180–3.
17. Sobin LH, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumors. 7th ed. New York: Wiley-Blackwell; 2010.
18. Okines A, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v50–4.
19. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer. 2011;14:101–12.
20. Ajani JA, Bentrem DJ, Besh S, et al. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw. 2013;11:531–46.
21. Catalano MF, Sivak MV, Jr., Rice T, et al. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc. 1994;40:442–6.
22. Bhutani MS, Hawes RH, Hoffman BJ. A comparison of the accuracy of echo features during endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration for diagnosis of malignant lymph node invasion. Gastrointest Endosc. 1997;45:474–9.
23. de Melo SW, Jr., Panjala C, Crespo S, et al. Interobserver agreement on the endosonographic features of lymph nodes in aerodigestive malignancies. Dig Dis Sci. 2011;56:3204–8.
24. Eloubeidi MA, Wallace MB, Reed CE, et al. The utility of EUS and EUS-guided fine needle aspiration in detecting celiac lymph node metastasis in patients with esophageal cancer: a single-center experience. Gastrointest Endosc. 2001;54:714–9.
25. Nakahara O, Yamao K, Bhatia V, et al. Usefulness of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) for undiagnosed intra-abdominal lymphadenopathy. J Gastroenterol. 2009;44:562–7.
26. Eloubeidi MA, Vilmann P, Wiersema MJ. Endoscopic ultrasound-guided fine-needle aspiration of celiac lymph nodes. Endoscopy. 2004;36:901–8.
27. Mocellin S, Pasquali S. Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer.

Cochrane Database Syst Rev. 2015;2:CD009944 (Epub ahead of print).
28. Cardoso R, Coburn N, Seevaratnam R, et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. Gastric Cancer. 2012;15(Suppl 1):S19–26.
29. Kim JH, Song KS, Youn YH, et al. Clinicopathologic factors influence accurate endosonographic assessment for early gastric cancer. Gastrointest Endosc. 2007;66:901–8.
30. Kwee RM, Kwee TC. Imaging in local staging of gastric cancer: a systematic review. J Clin Oncol. 2007;25:2107–16.
31. Yun M, Lim JS, Noh SH, et al. Lymph node staging of gastric cancer using (18)F-FDG PET: a comparison study with CT. J Nucl Med. 2005;46:1582–8.
32. Bhandari S, Shim CS, Kim JH, et al. Usefulness of three-dimensional, multidetector row CT (virtual gastroscopy and multiplanar reconstruction) in the evaluation of gastric cancer: a comparison with conventional endoscopy, EUS, and histopathology. Gastrointest Endosc. 2004;59:619–26.
33. Polkowski M, Palucki J, Wronska E, et al. Endosonography versus helical computed tomography for locoregional staging of gastric cancer. Endoscopy. 2004;36:617–23.
34. Ahn HS, Lee HJ, Yoo MW, et al. Diagnostic accuracy of T and N stages with endoscopy, stomach protocol CT, and endoscopic ultrasonography in early gastric cancer. J Surg Oncol. 2009;99:20–7.
35. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer. Gastric Cancer. 2009;12:6–22.
36. Sabbagh LC. The gut: esophagus, stomach, and rectum. Gastrointest Endosc. 2009;69:S90–2.
37. Gordon SJ, Rifkin MD, Goldberg BB. Endosonographic evaluation of mural abnormalities of the upper gastrointestinal tract. Gastrointest Endosc. 1986;32:193–8.
38. Botet JF, Lightdale C. Endoscopic sonography of the upper gastrointestinal tract. AJR Am J Roentgenol. 1991;156:63–8.
39. Caletti G, Fusaroli P, Togliani T, et al. Endosonography in gastric lymphoma and large gastric folds. Eur J Ultrasound. 2000;11:31–40.
40. Komorowski RA, Caya JG, Geenen JE. The morphologic spectrum of large gastric folds: utility of the snare biopsy. Gastrointest Endosc. 1986;32:190–2.

Rectal Cancer and Anal Sphincter Disorders

27

Ferga C. Gleeson and Michael J. Levy

Introduction

In 2015 within the USA, it is estimated that 40,000 new cases of primary de novo rectal cancer will be diagnosed [1]. Their prognosis is most impacted by the extent of primary tumor invasion (T stage), the presence and number of lymph nodes involved (N stage), involvement of the circumferential resection margin (CRM), and the presence of distant metastasis (M stage). Staging and therapy depend on presurgical imaging modalities that include computed tomography (CT), magnetic resonance imaging (MRI), and EUS. The determined stage is the key in deciding which patients may benefit from neoadjuvant therapy as well as the most appropriate surgical approach (Fig. 27.1).

The diagnostic accuracy of EUS in rectal cancer staging has recently been questioned and criticized as clinical practice and literature do not appear to support the early very positive reports. A German multicenter, prospective, quality assurance study evaluated 7000 patients between 2000 and 2008 and compared radial EUS findings to surgical pathology T stage without the use of neoadjuvant therapy [2]. While the T stage concordance was only 65 %, increasing procedure volumes improved their results. The frequency of under- and overstaging was 18 and 17 %, respectively. Another report from a US center conducted between 1993 and 2007 revealed that EUS nodal evaluation with imaging alone without FNA did not reliably identify patients with nodal disease. Their opinion was based on the finding of a 29 % false-positive rate and because 23 % of patients were understaged when compared to surgical pathology as the gold standard [3]. The conclusions of both reports have uncertain applicability to current practice, given that they evaluated radial EUS alone using technology dating back to the early 1990s. Current practice routinely incorporates linear imaging, FNA assessment of indeterminate nodes, and improved ultrasound technology.

The objective of this chapter was to provide a comprehensive overview using historical and current data to help understand the incremental benefit of EUS versus alternative imaging modalities for assessing patients with primary de novo rectal cancer, following neoadjuvant therapy and during postoperative disease surveillance utility. We also explore potential novel interventions.

Case Study

Initial Presentation

A 62-year-old male presented with a 2-week history of intermittent hematochezia. A digital rectal examination identified the distal border of a

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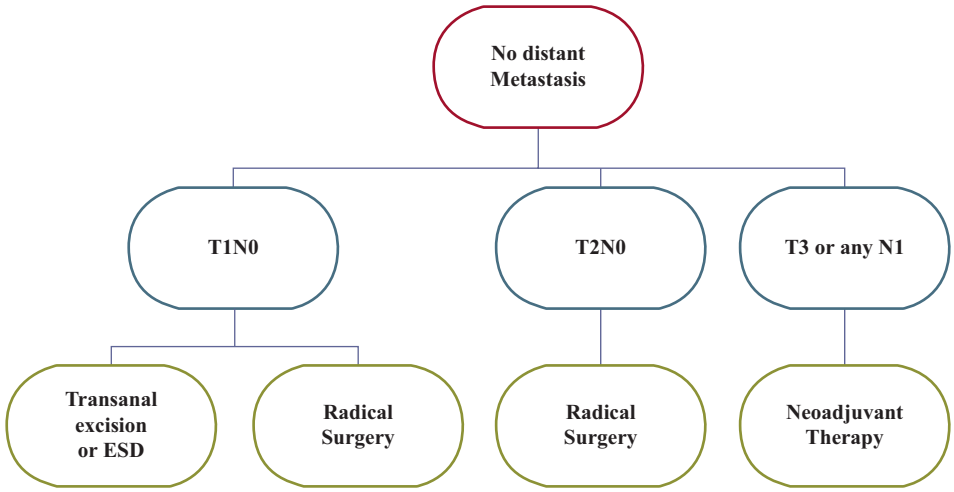

Fig. 27.1 Management algorithm for nonmetastatic primary rectal cancer (*ESD* endoscopic submucosal dissection)

posterior lateral wall ulcerated mass. Endoscopic examination revealed a traversable 4-cm friable ulcerated polypoid mass with its distal border located at the distal valve of Houston, occupying 75% of the luminal circumference. Mucosal biopsies confirmed the presence of adenocarcinoma. Abdominal CT revealed no evidence of metastatic disease. Pelvic MRI identified an enhancing 4-cm mass located approximately 7 cm from the anal verge with questionable extension through the muscularis propria and into the mesorectal fat. There was no involvement of the mesorectal fascia, with a 6 mm distance to the circumferential resection margin, and no evidence for invasion into adjacent structures. In addition, indeterminate 3- to 5-mm lymph nodes were found within the mesorectal fat. A rectal EUS examination was recommended.

What Are Useful Pearls for Initial Primary Rectal Cancer Assessment?

Anorectal Anatomy

The rectum extends from the upper end of the anal canal to the rectosigmoid junction and is approximately 12 cm in length [4]. It is subdivided into proximal, middle, and distal thirds. The surgically defined anal canal measures 2.5–4 cm in length with two-third above the dentate line and one-third below the dentate line [5]. The anatomic anal canal corresponds to the distal one-third of the surgical anal canal and spans from the dentate line to the anorectal verge. Above the dentate line, the anal canal is lined by columnar epithelium, whereas it is lined by squamous epithelium distal to the dentate line. The anal transitional zone corresponds to an approximately 10-mm-long segment between the columnar and squamous epithelial zones where the mucosa is of variable histology [6].

The rectal wall is composed of mucosa, submucosa, and muscularis propria. The mucosa comprises two wall layers: an outer hyperechoic layer (the interface between mucosa and the ultrasound probe) and an inner hypoechoic wall layer. The third wall layer is hyperechoic and represents the submucosa. The muscularis propria or fourth wall layer is composed of an outer longitudinal and inner circular smooth muscle layer. The inner circular smooth muscle becomes thickened distally and continues as the internal anal sphincter and the outer longitudinal muscle fuses with fibers from the levator ani [5]. The outermost layer of the sphincter complex is formed by striated muscles, the levator ani, and puborectalis muscles superiorly and by the inferior part of the external anal sphincter inferiorly.

The rectum is surrounded by mesorectal fat containing lymph nodes, superior hemorrhoidal

vessels, and fibrous tissue collectively known as the mesorectum. The mesorectum is continuous with the fat of the sigmoid mesocolon superiorly and usually thicker along the posterior rectum in its intraperitoneal portion and on occasion is absent anteriorly. It is bound circumferentially by the mesorectal fascia. This fascia extends inferiorly and coalesces with Denonvilliers' fascia in men anteriorly, and anterior to this fascia are the seminal vesicles and prostate gland. Conversely in women, the anterior mesorectal fascia coalesces with rectovaginal fascia, anterior to which is the vagina. The mesorectal fascia forms an important barrier to the radial spread of upper and middle third rectal tumors and forms the plane of dissection used in total mesorectal excision (TME).

Nodal drainage of the rectum occurs initially to the perirectal lymph nodes within the mesorectum [7]. The majority of nodes follow the rectal blood supply and are located superiorly and posteriorly. The common path of nodal spread is along the superior rectal artery into the apical mesorectum and the inferior mesenteric artery into the sigmoid mesocolon. The middle rectal artery arises from the internal iliac artery directly and the inferior rectal artery arises from the internal pudendal artery, a branch of the anterior division of the internal iliac artery. The inferior and middle rectal arteries anastomose at the anorectal junction and, although uncommon, distal rectal cancers can spread to the nodes along the internal pudendal and internal iliac arteries.

Table 27.1 The 2010 American Joint Committee on Cancer (AJCC) staging system for primary rectal cancer

TNM	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Nx	Regional lymph nodes cannot be assessed
N0	No regional nodal metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or non peritonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Mx	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (i.e., liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

What Is the TNM Staging System for Rectal Cancer?

The tumor node metastasis (TNM) system of the American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC) has become the worldwide standard for staging colorectal cancer [8, 9]. The TNM system classifies the primary tumor (T) stage based on the depth of tumor invasion into and through the rectal wall. Nodal substations classified as regional lymph nodes for rectal cancer are perirectal, inferior mesenteric, sigmoid mesenteric, lateral sacral, presacral, sacral promontory, internal pudendal, internal iliac, superior rectal, middle rectal, and inferior rectal. Involvement of lymph nodes outside these groups, such as in the external or common iliac substations, is considered to be distant metastases (M stage) (Table 27.1).

EUS Technique

The examination is performed following a full colonoscopy preparation or 2 Fleets enemas and flexible sigmoidoscopy with a patient lying in the

left lateral decubitus position to facilitate optimal visualization. The necessary features to document for endoscopic evaluation are highlighted in Fig. 27.2. The middle valve of Houston is thought to be a surrogate marker for the anterior peritoneal reflection, and the location of a tumor, if proximal or distal to the anterior peritoneal reflection, has important surgical planning implications.

Following advancement of the echoendoscope to the sigmoid colon, air or CO_2 is aspirated as the echoendoscope is withdrawn in order to improve acoustic coupling. The use of either a radial or a linear echoendoscope is a personal preference. Starting with a radial echoendoscope is very reasonable to readily visualize the rectal wall layers and assess for lymph nodes. In addition to aspirating air, water will likely be needed to fill the rectum to enhance imaging. The patient can be rotated to shift the water and allow it to submerge the mass. Care must be taken to establish the relationship of the distal tumor border to the seminal vesicles in men and the cervix in females. The presence or absence of adjacent organ involvement to include the prostate, bladder, and seminal vesicles in men, and the bladder, vagina, and cervix in women should also be noted. In addition, the perirectal and perisigmoid space should be evaluated for the presence of lymph nodes or omental lesions, irrespective of whether a radial or a linear echoendoscope is used. The advantage of beginning with the linear echoendoscope is the ability to image and FNA using the same instrument.

Endosonographically, the rectal wall is seen as five alternating hyper- and hypoechoic layers. A tumor that extends no deeper than the mucosa or submucosa is classified as a T1 lesion (Video 27.1). If the lesion enters the muscularis propria (hypoechoic fourth layer) but does not breach through, it is a T2 lesion (Fig. 27.3). Deeper penetration through the muscularis propria layer, extending beyond the rectal wall and into the surrounding perirectal fat, is consistent with a T3 lesion (Fig. 27.4). Finally, a T4 lesion implies direct invasion into an adjacent organ, i.e., the prostate gland, vagina, and bladder (Fig. 27.5).

EUS evaluation of this 4-cm distal rectal cancer revealed hypoechoic wall thickening to 11 mm with pseudopodia formation and 2-mm infiltration beyond the muscularis propria.

What Are the T Staging Pitfalls?

In published studies, the accuracy of EUS T stage ranges from 80 to 95% compared with 65–75% for CT and 75–85% for MRI [10–12]. With respect to T stage, one particular problem for EUS is the overstaging of T2 tumors due to the difficulty in differentiating peritumoral inflammation and/or fibrosis from the cancer itself (Fig. 27.6) [13]. This tumor meets criteria for a T3 tumor because it did extend through the entire thickness of the muscularis propria into the perirectal fat and obliterated the well-defined fat–muscle interface by neoplastic pseudopodia. Accuracy of specifically T2 staging was examined in a retrospective study because this represents one major decision point in management of rectal cancers with higher T stage tumors receiving neoadjuvant therapy [14]. Both overstaging and understaging of actual T1 or T3 tumors occurred in 16% to yield a negative predictive value for identifying tumor depth of T2 or less of 84% and absence of nodal disease of 87%. Incorrect EUS staging impacted management in 23% of patients.

It is thought that all T3 rectal tumors are not clinically equivalent, with minimally invasive disease carrying a more favorable prognosis [15]. Therefore, by discriminating minimally invasive from advanced T3 disease (invasion $\leq$2 mm or >3 mm beyond the muscularis propria), preoperative EUS may provide important prognostic information. However, the challenge is that overstaging is noted more commonly in minimally invasive T3 (50%) when compared to advanced T3 disease [16]. The maximum tumor thickness of T3 cancers is also an independent prognostic factor for local and overall recurrence [17] using a cutoff value of $\geq$19 mm.

Understaging, conversely, may result from a failure to detect microscopic cancer infiltration owing to the limits of EUS resolution. Spatial resolution is improved by increasing ultrasound frequency, but at the expense of reduced depth of penetration that may compromise inspection of deeper structures. Other variables that influence the accuracy of tumor staging include operator experience and the location of the tumor within the rectum, with reduced accuracy for

DRE (digital rectal exam):

- Tumor palpated (yes/ no)
- Location (anterior, posterior)
- Fixed or mobile

Endoscopic Tumor Characteristics:

- Proximal and distal border (cm) from anal verge
- Where is the distal border in relation to the middle value of Houston?
- Circumference – 1-25%, 26-50%, 51-75%, 76-100%
- Anterior, Posterior, right or left lateral wall (circle all that apply)
- Ulceration: yes/ no
- Polypoid or sessile
- Obstruction: No, Partial (permit endoscope but not echoendoscope), Complete (no scope traverses)
- Mucosal tumor biopsies performed: yes/ no
- Tattoo placement: yes/ no

EUS (uTNM) Characteristics:

- Where is the distal border located in relation to the seminal vesicles or cervix? Above, Same level, Below
- T Stage:
  - Maximal wall thickness (mm)
  - If T3: depth of invasion beyond the muscularis propria (mm)
    minimal disease (< 3mm) or extensive disease (≥3mm)
- N Stage:
  - Peri iliac vessel, perisigmoid or perirectal node (circle all that apply)
  - Long and short axis dimensions (for all lymph nodes undergoing FNA or for most concerning appearing if FNA not performed)
  - Echogenicity, border, shape (for all lymph nodes undergoing FNA or for most concerning appearing if FNA not performed)
  - Impression of extra capsular spread: yes/ no
  - FNA: site, number of lymph nodes and number of passes per node
- **Extramural or Omental deposits**: yes/ no;
  - Size; number of deposits & number of FNA passes per deposit
  - Ascites: yes/no
  - FNA performed: yes/no, site
- **Internal Anal Sphincter involvement**: yes/ no
- **External Anal Sphincter involvement**: yes/ no
- **Other organ involvement**: yes/no, site

Fig. 27.2 Endoscopic and EUS features to be evaluated during the examination

more distal tumors [13, 18–20]. A meta-analysis of 42 studies ($n = 5039$; 1980–2008) reviewed the published data for EUS accuracy by the T stages, suggesting that EUS sensitivity is greatest for advanced disease (T3 or T4) rather than for early (T1 or T2) disease (Table 27.2) [21].

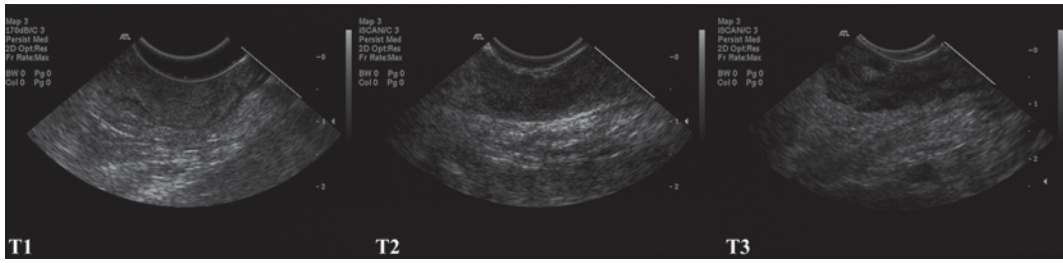

Fig. 27.3 Comparative images of the rectal wall reflecting the mural changes between T1, T2, and T3 lesions

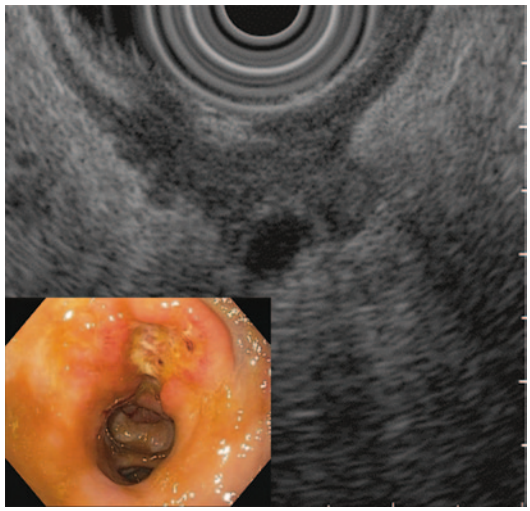

Fig. 27.4 An ulcerated friable mid-rectal T3 cancer penetrating through the muscularis propria layer, extending beyond the rectal wall and into the surrounding perirectal fat

EUS revealed a superficial T3 lesion, 3 round hypoechoic peritumoral lymph nodes as well as a 9 × 7 mm left common iliac artery lymph node. FNA of this node was performed.

What Are the Nodal (N) Staging Pitfalls?

EUS features that accurately predict nodal metastasis have been identified in patients with esophageal cancer [22]. These conventional echo features that correlate with malignancy include an enlarged node (≥1 cm in short axis), hypoechoic appearance, round shape, and smooth border (Table 27.3). For patients with esophageal cancer, if all four abnormal morphological features are present, the accuracy for malignant invasion is 80%. However, all four features of malignant involvement are present in only 25% of malignant lymph nodes (Fig. 27.7). Unfortunately, the standard conventional EUS nodal criteria have proven inaccurate for staging many nonesophageal cancers [22–24]. No one criterion is predictive of malignancy in patients with lung, esophageal, and pancreatic cancer.

The N stage accuracy for EUS imaging in the setting of any malignancy is only 70–75% and was recently reported to be as low as 42% [25, 26]. It was previously assumed that EUS was incapable, or only seldom able, to detect benign perirectal lymph nodes. Therefore, in patients with rectal cancer, mere visualization of lymph nodes was deemed an accurate surrogate marker of nodal metastasis, thereby obviating the need for FNA. A meta-analysis [35 studies (n = 2732; 1966–2008)] of the EUS N stage accuracy in rectal cancer found that the sensitivity and specificity of EUS are moderate (approximately 75%) and concluded that further refinement in diagnostic criteria is needed to improve the diagnostic accuracy [27]. An important limitation of their analysis was the dependence on mostly studies that imaged using radial instruments alone without FNA.

Prior transrectal ultrasound studies identified a nodal size of ≥7 mm as an optimal size cutoff for predicting nodal metastases in rectal cancer, with an accuracy of 83% when compared with surgical pathology [28]. A dedicated FNA study, based on a perception that metastatic loco-regional nodes only minimally differ in morphological appearance from benign nodes, noted that the number

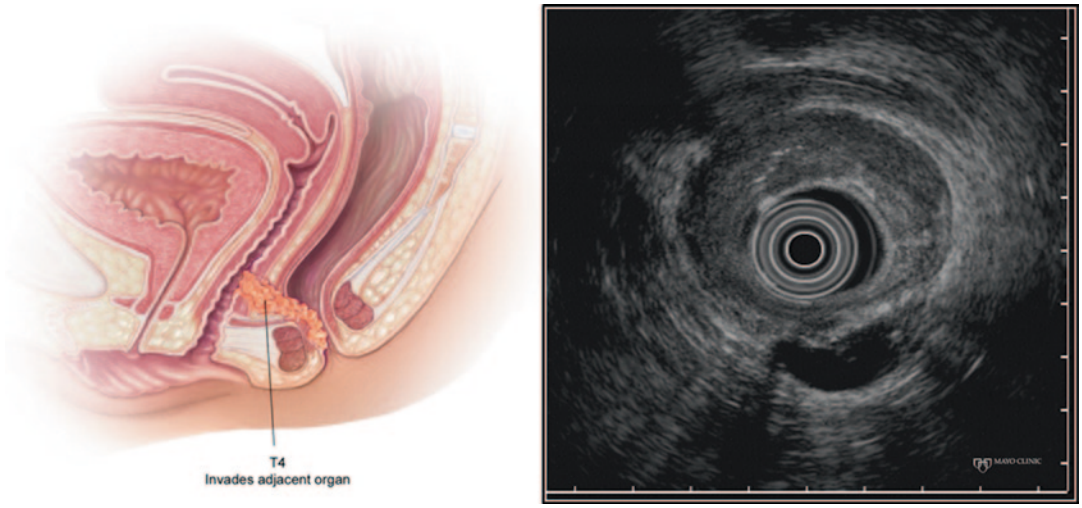

Fig. 27.5 A radial EUS examination revealing infiltration anteriorly into the vaginal wall establishing a T4 lesion

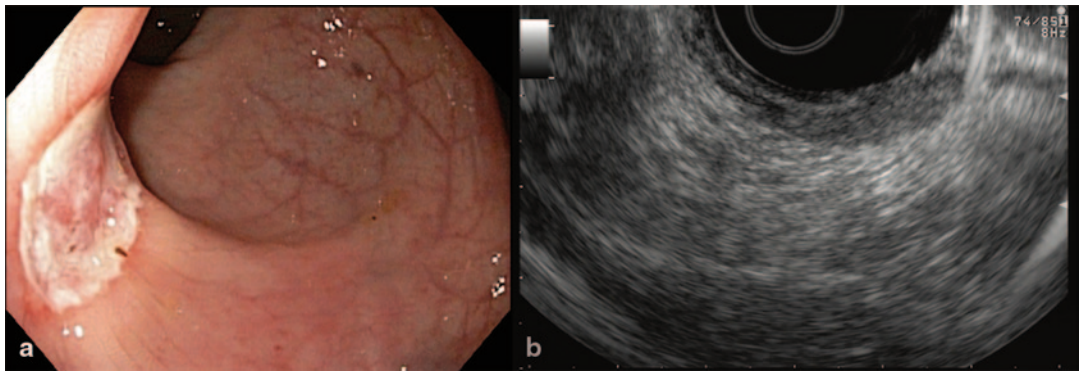

Fig. 27.6 **a** Postpolypectomy for malignancy with superficial ulceration secondary to cautery effect. **b** There is discrete mural hypoechoic change on EUS which cannot distinguish malignant from inflammatory change unless sampled by FNA

Table 27.2 EUS imaging T stage data

T stage	Sensitivity (%)	Specificity (%)
T1	88	98
T2	80	96
T3	96	91
T4	95	98

Table 27.3 EUS morphological features of benign and malignant lymph nodes

EUS features	Benign LN features	Malignant LN features
Echogenicity	Hyperechoic	Hypoechoic
Shape	Irregular	Round
Border	Irregular	Smooth
Size (short axis)	<10 mm	≥ 10 mm

of conventional malignant echo features present per lymph node did not accurately differentiate benign from malignant nodes, unless all four features were present (Table 27.4) [29]. The accuracy for each of the four conventional criteria (short axis ≥ 10 mm, hypoechoic appearance, round shape, and smooth border) for detecting malignancy is as follows: 61, 65, 51, and 51%, respectively. A lymph node short-axis length ≥ 5 mm or a hypoechoic appearance was the only

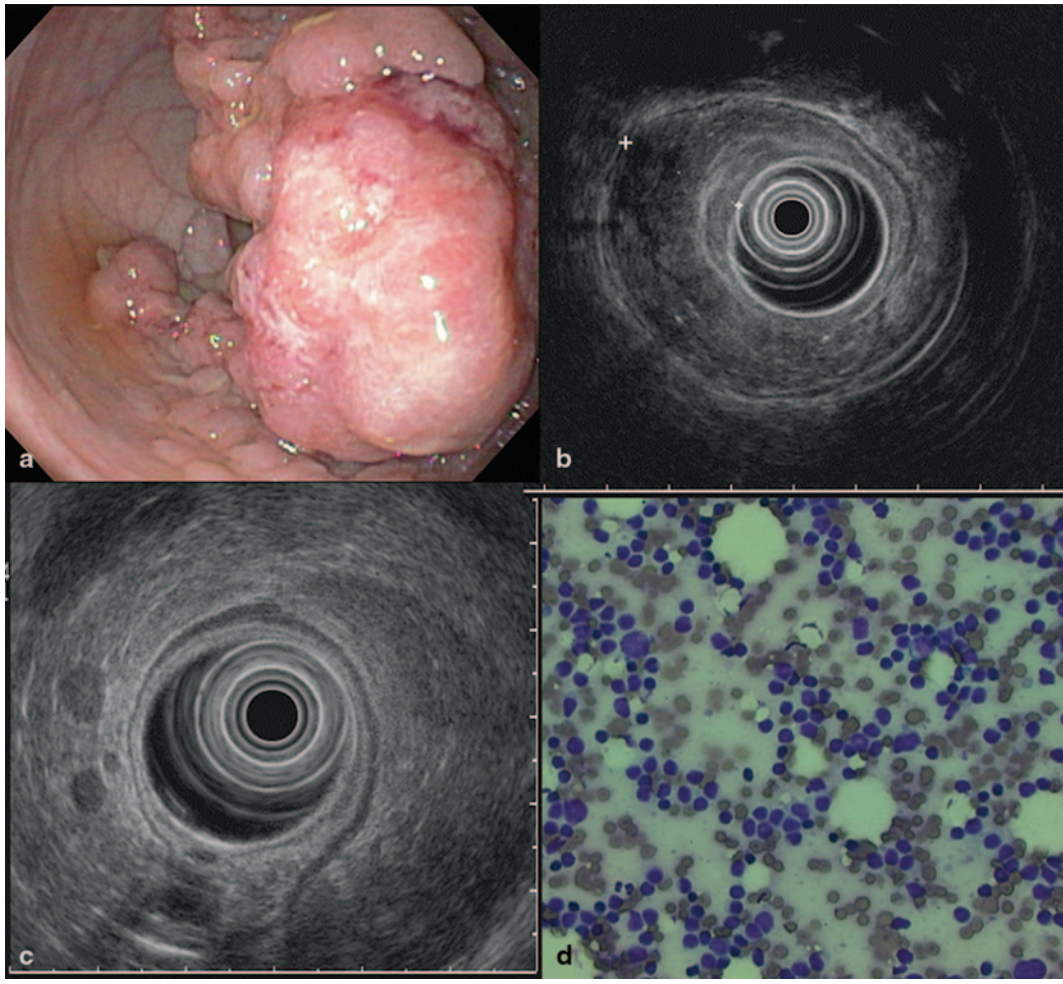

Fig. 27.7 **a**, **b** A bulky T2N1 tumor with **c** nonperitumoral lymph nodes confirmed **d** malignant by FNA

Table 27.4 Performance characteristics relative to the number of malignant EUS nodal features

	≥2 features	≥3 features	4 features
Sensitivity %	77	68	23
Specificity %	29	52	100
PPV %	53	60	100
NPV %	55	61	55
Accuracy %	54	61	61

PPV positive predictive value, *NPV* negative predictive value

EUS feature predictive of malignant infiltration. Optimum short- and long-axis lengths of 6 and 9 mm, respectively, yielded the best power distinction for malignancy (Fig. 27.8).

Using surgical histopathology specimens, Knight and colleagues assessed the performance characteristics of EUS-FNA in the setting of primary or metastatic colorectal carcinoma of perirectal masses, lymph nodes, and distant metasta-

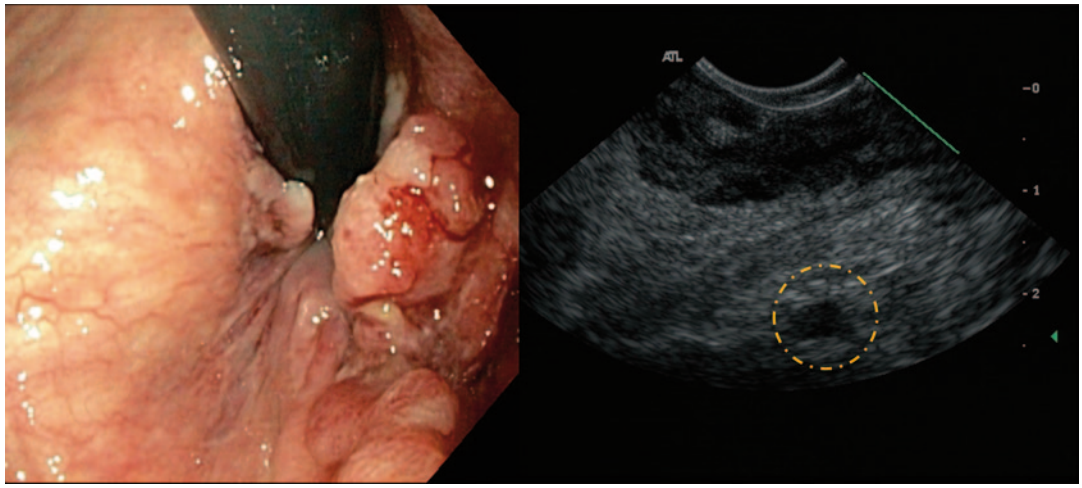

Fig. 27.8 A distal T3N1 lesion in a 54-year-old male who proceeded to neoadjuvant therapy followed by surgery. The highlighted node is perilesional and therefore not amenable to FNA. It has a hypoechoic appearance and short axis > 5mm but oval in shape with an irregular border

ses. The overall sensitivity, specificity, and positive and negative predictive values were reported as 89, 79, 89 and 79%, respectively [30].

The preoperative EUS-FNA identification of extramesenteric lymph node metastases upstages 7% of primary rectal cancers. This is important because, for example, external iliac artery lymph node infiltration is outside the standard operative field for total mesorectal excision (TME). Nodal metastasis to this site typically impacts medical and surgical planning by extending the radiation fields and may indicate the need to extend the TME resection to include an extensive lymph node dissection [31]. Other markers that are associated with such metastases include serum CEA level, tumor length ≥4 cm, tumor annularity ≥50%, sessile morphology, and lymph node size. Unfortunately, these potential surrogate markers are insufficiently accurate, and EUS-FNA is necessary to identify metastasis to these nodal stations.

These findings clearly indicate the need for EUS-FNA to verify nodal status, rather than relying on nodal morphology alone, when making critical decisions regarding the use of neoadjuvant therapy. Failure to do so risks stage inappropriate therapy and in turn inappropriate patient outcomes. We now favor routine FNA because (1) improved technology allows visualization of benign lymph nodes in virtually all patients, (2) most malignant nodes in the setting of rectal cancer are less than 1 cm in size, and (3) the predictive value of imaging alone for distinguishing benign from malignant nodes remains poor.

A note of caution is that luminal fluid cytology may be positive for malignancy in 48% of luminal cancers, including rectal cancer, but is not affected by performing FNA [32]. These translocated cells may contaminate the FNA specimen and lead to false-positive FNA results. In addition, endosonographer technique and cytological misinterpretation also contribute to false-positive EUS-FNA cytology [33].

EUS-FNA of solid lesions in the lower GI tract is considered a low-risk procedure for infectious complications and does not warrant prophylactic administration of antibiotics for the prevention of bacterial endocarditis [34]. Perirectal cystic structures are considered a relative contraindication to FNA given the risk of abscess formation requiring percutaneous drainage, which has occurred despite the administration of prophylactic antibiotics [35]. If FNA is contemplated, we encourage discussion of the need and potential risks with the patients' medical and surgical staff. A recent large single-center study of 502 patients undergoing EUS-FNA of lower GI lesions, over

80 % of which were for rectal cancer, highlighted that risk factors for adverse events included pre-procedural pain, FNA of a site other than a lymph node or gut wall, and malignant cytology [36].

Case Follow-Up

The final interpretation of EUS was a superficial T3 tumor with indeterminate peritumoral nodes, but a malignant left common iliac artery lymph node, thus establishing a distal T3N1M1a rectal cancer. The patient proceeded to neoadjuvant therapy including expansion of the pelvic radiation fields. An abdominoperineal resection with an extended lymphadenectomy was subsequently performed.

Utility of EUS Compared to Other Staging Modalities

MRI Versus EUS Assessment

The role of MRI using an endorectal coil has been well established for local staging of rectal cancer [37–39]. It offers several theoretical advantages over EUS as it reveals a larger field of view and permits the study of stenotic, nontraversable tumors [18, 40, 41]. Recently, the identification of the anterior peritoneal reflection on MRI in 74 % of patients in one study is important given the impact of this landmark on surgical planning [42]. A meta-analysis of 90 articles (1995–2002) compared the utility of MRI, radial EUS without FNA, and CT for staging with histopathology correlation as the gold standard and came to the following conclusions: For T1/T2 lesions, EUS and MRI had similar sensitivity, but specificity was higher in EUS (86 vs. 69 %); for T3 tumors, the sensitivity of EUS was significantly higher than that of MRI or CT [43]. A more recent prospective study comparing radial EUS to MRI revealed that MRI was unable to visualize any T1 tumor, whereas EUS understaged all T4 tumors [44]. Furthermore, the presence of luminal stenosis and polypoid morphology was inversely associated with accuracy for either EUS or MRI.

MRI may also be used to evaluate mesorectal nodal involvement as lymph nodes may be assessed using size criteria as well as specific nodal imaging. The most reliable MRI criteria for lymph node metastasis when correlated with histological findings are an irregular contour and inhomogeneous signal [45, 46]. Many studies have evaluated the performance of MRI for assessing lymph node involvement. A meta-analysis from 2004 revealed that the sensitivity and specificity of MRI were 66 and 76 %, respectively, compared with 67 and 78 % for radial EUS without FNA and 55 and 74 % for CT [39, 43]. In another meta-analysis, there was similarly no significant difference in N staging between MRI and EUS, although EUS had a slight advantage in diagnostic specificity [47].

CT and PET-CT Versus EUS Assessment

The traditional role of CT is to identify metastatic disease as its resolution is inadequate to allow accurate distinction of the various layers, thereby limiting T stage evaluation [48, 49]. More recently, however, multislice CT has been shown useful for determining mesorectal fascia involvement, especially for tumors located in the proximal and mid-rectum with 76 % sensitivity and 96 % specificity. However, the accuracy for predicting mesorectal fascia involvement in a distal rectal cancer remains suboptimal with 66 % sensitivity and 82 % specificity [50, 51]. The CT lymph node size threshold value yielding the greatest negative predictive value for predicting nodal metastasis is 7 mm [52]. Currently, while CT combined with EUS is considered the most cost-effective staging strategy for nonmetastatic proximal rectal cancer, the emerging utility of MRI is likely to change this approach [53].

PET-CT often provides additional information beyond conventional staging in primary rectal cancer and is proposed for selective use in more advanced stages and when indeterminate findings exist with conventional staging [54]. Contrast-enhanced PET-CT is superior to nonenhanced PET-CT for precise definition of regional nodal status and enhances the staging/

therapy in one-third of patients [55, 56]. Some authorities suggest that the SUV_{max} value following neoadjuvant therapy predicts downstaging and a complete pathological response [57, 58]. No EUS-FNA versus PET-CT comparative study has been reported to date.

What Is the Utility of EUS Assessment Following Neoadjuvant Therapy?

Tumor response to neoadjuvant therapy is a strong predictor of disease-free survival. However, the accuracy of EUS for staging rectal cancer following such therapy is reduced markedly due to the secondary effects of postradiation edema, inflammation, necrosis, and fibrosis [59, 60]. Although few data exist, routine EUS staging following neoadjuvant therapy is discouraged [61]. The T stage accuracy following neoadjuvant therapy is 50 % [62–67]. As outcome is most accurately predicted by final pathologic stage, restaging tumors following neoadjuvant therapy is limited, and clinical correlation is most important to dictate operative and postoperative management modalities. However, FNA of nonperitumoral lymph nodes in this setting may establish the presence of residual nodal malignancy, which may offer useful information to guide further management decisions.

Is There a Role for EUS Surveillance Following Radical or Local Surgery in Rectal Cancer?

A positive CRM, serosal involvement, lymphovascular invasion, extramural venous invasion, and poor histological differentiation are important independent predictive factors for the development of local recurrence (LR) [68]. The combination of neoadjuvant therapy and total mesorectal excision has significantly reduced the incidence of LR to less than 10 %, which is greatest within the first 2 years following surgery [69, 70]. Early detection of a recurrent local tumor may result in earlier treatment and improved survival. As LR often occurs in the extraluminal region (i.e., deep to the mucosa), follow-up with forward-viewing endoscopy may fail to detect LR at a sufficiently early stage. Even EUS may be unable to visually distinguish recurrence from postoperative change related to fibrosis or inflammation, and images may be obscured by artifacts from surgically placed clips or sutures. However, FNA of the residual rectal wall or perirectal space (91 % sensitivity and 93 % specificity) may offer a diagnosis which is superior to clinical evaluation or EUS imaging alone.

There is no clear strategy for early detection of local recurrence. Two prospective studies demonstrated that EUS was superior to CT for local recurrence detection of rectal cancer [71, 72]. The sensitivity of EUS was higher (100 %) in both studies compared to CT (82–85 %). EUS was also more sensitive than digital rectal examination, CT, and CEA levels to detect LR in asymptomatic patients [73]. The optimal interval for EUS surveillance following surgical intervention is unknown. However, performing EUS every 6 months for the first 2 years following a low anterior resection may be a reasonable surveillance strategy to detect recurrent rectal cancer [74].

Local excision is an alternative management approach for superficial rectal cancers and for patients unfit for radical oncologic surgery. However, it is associated with a high local recurrence rate. Mucosal scar biopsy and EUS-FNA of either a lymph node or the deep rectal wall are methods to establish local recurrence in these patients (Fig. 27.9) [75]. In addition, EUS-FNA ± trucut biopsy (TCB) may be useful in the diagnostic evaluation of patients with extraluminal perirectal lesions to guide management [76].

Rectal implantation cysts occurring at the anastomosis following low anterior resection for rectal cancer need to be distinguished from locally recurrent rectal cancer. EUS may reveal cystic lesions at the anastomotic site with heterogeneous wall thickening, and FNA may reveal mucin containing some inflammatory cells in the absence of malignant cells [77]. EUS-FNA and TCB are sensitive for the diagnosis of malignancy in pelvic masses but carry a 7 % adverse event rate if cystic pelvic masses are sampled; there-

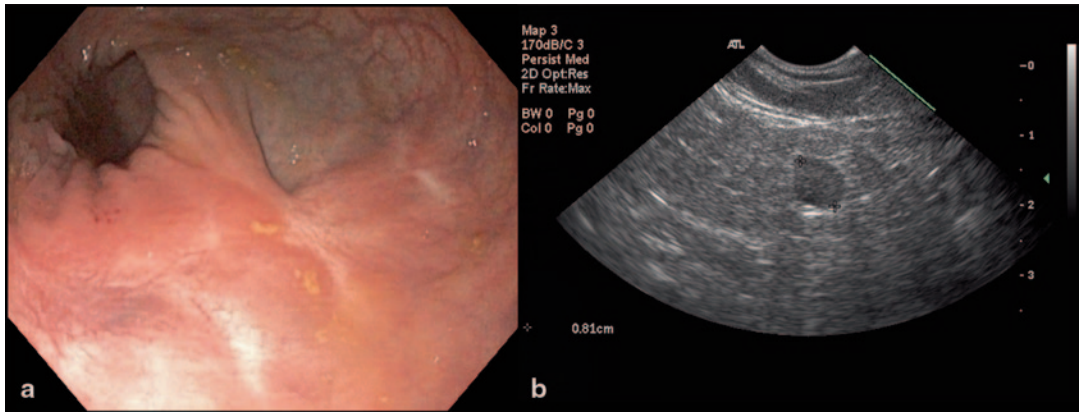

Fig. 27.9 **a** Posttransanal excision scar 18 months following local therapy. **b** EUS detected an enlarged hypoechoic non-perilesional lymph node which was positive for malignancy

fore, aspirating predominantly cystic structures is generally discouraged [78, 79].

EUS for Rectal Wall Metastases

Distant cancers rarely metastasize to the gastrointestinal wall. Such findings are estimated to account for 0.03 % of upper GI endoscopies and 0.05 % of colonoscopies [80]. The EUS appearance without FNA of secondary rectal linitis plastica is that of circumferential wall thickening affecting predominantly the submucosal and muscularis propria layers similar to primary gastric linitis plastica (Fig. 27.10) [81]. The role of FNA in the diagnosis of rectal linitis plastica secondary to prostate cancer has been reported [82]. The EUS appearance of rectal linitis plastica contrasts with processes such as rectal endometriotic implants that are either hypoechoic or heterogeneous deposits involving the fourth and fifth layer with intact mucosal layers and with local rectal cancer recurrence which usually presents in an extraluminal site [83, 84]. EUS-FNA ± TCB may confirm the diagnosis and identify the primary malignancy for metastatic lesions, which to date has included cancers originating from the bladder, breast, stomach, and cutaneous melanoma [85].

Is There a Role for EUS in Perianal Disease and Sphincter Disorders?

Perianal Fistulae and Abscess Formation

EUS is an informative imaging modality with significant impact on the treatment of Crohn's disease-associated perianal fistulae [86]. A fistula appears as a hyperechoic track within a hypoechoic region which represents air bubbles within an inflamed region. The patient's options are an endoscopic examination with either a radial or a linear echoendoscope or a nonendoscopic rigid rectal probe. A prospective blinded study compared EUS, pelvic MRI, and evaluation under anesthesia (EUA) and assessed cost-effectiveness. It revealed good agreement for the studies ($EUS = 91\,\%$; $MRI = 87\,\%$; $EUA = 91\,\%$) when compared to a surgical gold standard [87]. Examination using a 360° anorectal transducer containing a built-in three-dimensional (D) acquisition system with a gel-filled balloon with a patient in the lithotomy position is probably a superior method. In addition, MRI has emerged as an important imaging modality as it provides evaluation of the fistula within the anal canal and its relationship to the sphincter complex, other pelvic floor anatomical structures, and associated complications, i.e., abscess formation. In fact, MRI has replaced EUS in this setting

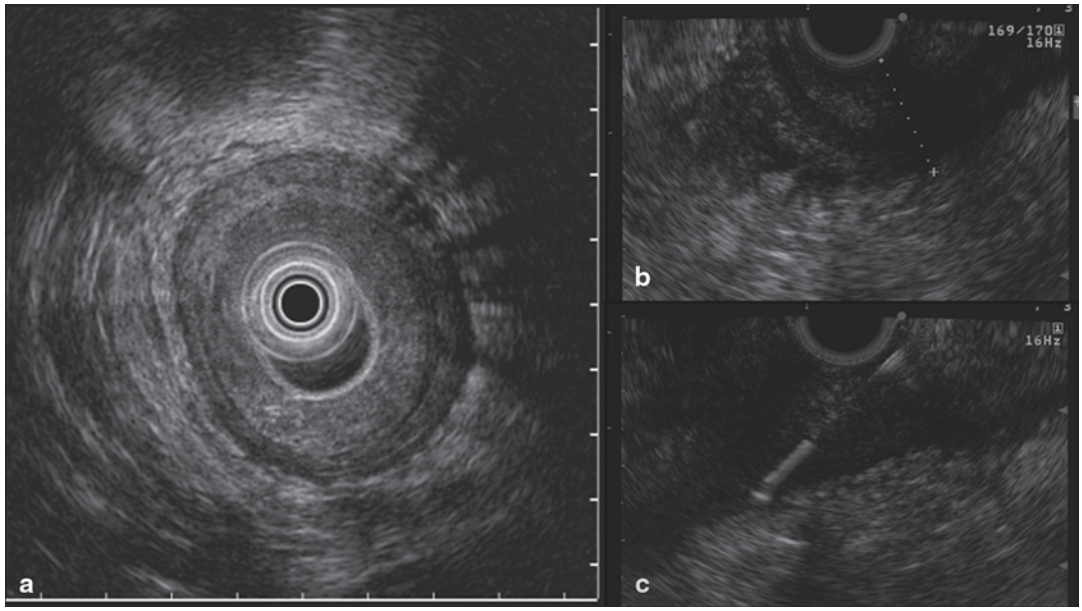

Fig. 27.10 **a**, **b** Circumferential hypoechoic mural thickening (*10 mm*) with unremarkable mucosal biopsy results. **c** However, EUS-FNA confirmed metastasis from a transitional cell cancer of the bladder, diagnosed 2 years previously

in most centers given the technical difficulty of EUS in such patients and due to surgeon preference for reviewing MRI to aid their surgical approach.

Injury to Anal Sphincter

EUS is better tolerated than electromyography, which requires needle placement directly into the sphincter complex. At 5 months postpartum, the prevalence of obstetric anal sphincter injuries in a cohort of primiparous women was 28 % [88]. The defects in the internal and external anal sphincter have different appearances on EUS. The former appears as a hyperechoic break in the normally hypoechoic ring, and the latter appears as a hypoechoic area within the normally hyperechoic ring. However, 2D and 3D transperineal sonography tools are used with increasing frequency and are becoming the gold standard to evaluate the anal sphincter complex in a proctology practice.

What Are Innovative Interventions for the Future?

EUS-guided drainage and stenting provide another option for the management of postoperative pelvic fluid collections [89]. EUS-guided drainage of abdominopelvic abscesses unrelated to diverticular disease may be another future therapeutic indication [90]. EUS fine-needle injection (FNI) with ethanol for persistent malignant pelvic lymph nodes following therapy in nonsurgical candidates has also been reported in addition to EUS-guided coil and glue placement for bleeding rectal varices [91, 92].

Key Points

- Rectal cancer T stage accuracy of EUS has room for improvement.
- FNA has emerged as an essential component of loco-regional clinical staging.

- FNA can identify M1a disease and may upstage 7% of patients presenting for evaluation.
- Staging with EUS following neoadjuvant therapy should be approached with caution.
- EUS-FNA of the rectal wall or extramural perirectal space is useful to establish local disease recurrence in the postoperative surveillance period.

Conflict of Interest The authors declare no conflict of interest.

Financial Disclosures None

Video Caption

Video 27.1 A T1 lesion with a surgical pathology gold standard revealing invasive grade 3 (of 4) adenocarcinoma ($2.7 \times 2.0 \times 0.5$ cm) invading into the submucosa but not into the muscularis propria with a negative surgical resection margin. However, a single (1 of 39) regional lymph node was positive for metastatic adenocarcinoma

References

1. http://www.cancer.gov/cancertopics/types/colon-and-rectal
2. Marusch F, Ptok H, Sahm M, et al. Endorectal ultrasound in rectal carcinoma–do the literature results really correspond to the realities of routine clinical care? Endoscopy. 2011;43(5):425–31.
3. Shapiro R, Ali UA, Lavery IC, Kiran RP. Endorectal ultrasound does not reliably identify patients with uT3 rectal cancer who can avoid neoadjuvant chemoradiotherapy. Int J Colorectal Dis. 2013;28:993–1000. [Epub ahead of print].
4. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst. 2001;93:583–96.
5. Wexner SD, Jorge JMN. Anatomy and embryology of the anus, rectum, and colon. In: Corman ML, editor. Colon and rectal surgery. Philadelphia: Lippincott-Raven; 1998. p. 1–26.
6. Kaiser AM, Ortega AE. Anorectal anatomy. Surg Clin North Am. 2002;82(6):1125–38.
7. Canessa CE, Badia F, Fierro S, et al. Anatomic study of the lymph nodes of the mesorectum. Dis Colon Rectum. 2001;44:1333–6.
8. Greene FL, Page DL, Fleming ID, et al. (eds). AJCC cancer staging manual. 7th ed. NewYork: Springer; 2010.
9. Sobin LH, Wittekind C (eds). TNM: classification of malignant tumours. 6th ed. NewYork: Wiley-Liss; 2002.
10. Golfieri R, Giampalma E, Leo P et al. Comparison of magnetic resonance (0, 5 T), computed tomography, and endorectal ultrasonography in the preoperative staging of neoplasms of the rectum-sigma. Correlation with surgical and anatomopathologic findings. Radiol Med. 1993;85(6):773–83.
11. Kim NK, Kim MJ, Yun SH, Sohn SK, Min JS. Comparative study of transrectal ultrasonography, pelvic computerized tomography, and magnetic resonance imaging in preoperative staging of rectal cancer. Dis Colon Rectum. 1999;42(6):770–5.
12. Halefoglu AM, Yildirim S, Avlanmis O, Sakiz D, Baykan A. Endorectal ultrasonography versus phased-array magnetic resonance imaging for preoperative staging of rectal cancer. World J Gastroenterol. 2008;14(22):3504–10.
13. Kauer WK, Prantl L, Dittler HJ, Siewert JR. The value of endosonographic rectal carcinoma staging in routine diagnostics: a 10-year analysis. Surg Endosc. 2004;18(7):1075–8.
14. Ahuja NK, Sauer BG, Wang AY, White GE, Zabolotsky A, Koons A, Leung W, Sarkaria S, Kahaleh M, Waxman I, Siddiqui AA, Shami VM. Performance of endoscopic ultrasound in staging rectal adenocarcinoma appropriate for primary surgical resection. Clin Gastroenterol Hepatol. 2014. doi:10.1016/j.cgh.2014.07.013. [epub ahead of print].
15. Harewood GC, Kumar KS, Clain JE, Levy MJ, Nelson H. J Clinical implications of quantification of mesorectal tumor invasion by endoscopic ultrasound: all T3 rectal cancers are not equal. Gastroenterol Hepatol. 2004;19(7):750–5.
16. Jürgensen C, Teubner A, Habeck JO, Diener F, Scherübl H, Stölzel U. Staging of rectal cancer by EUS: depth of infiltration in T3 cancers is important. Gastrointest Endosc. 2011;73(2):325–8.
17. Esclapez P, Garcia-Granero E, Flor B, et al. Prognostic heterogeneity of endosonographic T3 rectal cancer. Dis Colon Rectum. 2009;52(4):685–91.
18. Orrom WJ, Wong WD, Rothenberger DA, Jensen LL, Goldberg SM. Endorectal ultrasound in the preoperative staging of rectal tumors. A learning experience. Dis Colon Rectum. 1990;33(8):654–9.
19. Solomon MJ, McLeod RS, Cohen EK, Simons ME, Wilson S. Reliability and validity studies of endoluminal ultrasonography for anorectal disorders. Dis Colon Rectum. 1994;37(6):546–51.
20. Sailer M, Leppert R, Bussen D, Fuchs KH, Thiede A. Influence of tumor position on accuracy of endorectal ultrasound staging. Dis Colon Rectum. 1997;40(10):1180–6.
21. Puli SR, Bechtold ML, Reddy JB, Choudhary A, Antillon MR, Brugge WR. How good is endoscopic ultrasound in differentiating various T stages of rectal cancer? Meta-analysis and systematic review. Ann Surg Oncol. 2009;16(2):254–65.
22. Catalano MF, Sivak MV, Rice T, et al. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc. 1994;40:442–6.

23. Murata Y, Muroi M, Yoshida M, et al. Endoscopic ultrasonography in the diagnosis of esophageal carcinoma. Surg Endosc. 1987;1:11–6.
24. Tio TL, Coene PP, Luiken GJ, et al. Endosonography in the clinical staging of esophagogastric carcinoma. Gastrointest Endosc. 1990;36(Suppl 2): S2–10.
25. Rosen LS, Bilchik AJ, Beart RW Jr, et al. New approaches to assessing and treating early-stage colon and rectal cancer: summary statement from 2007 Santa Monica conference. Clin Cancer Res 2007;13: 6853–6s.
26. Tsendsuren T, Jun SM, Mian XH. Usefulness of endoscopic ultrasonography in preoperative TNM staging of gastric cancer. World J Gastroenterol. 2006;12:43–7.
27. Puli SR, Reddy JB, Bechtold ML, Choudhary A, Antillon MR, Brugge WR. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta-analysis and systematic review. Ann Surg Oncol. 2009;16(5):1255–65.
28. Heneghan JP, Salem RR, Lange RC, et al. Transrectal sonography in staging rectal carcinoma: the role of gray-scale, color-flow, and Doppler imaging analysis. AJR Am J Roentgenol 1997;169:1247–52.
29. Gleeson FC, Clain JE, Papachristou GI, et al. Prospective assessment of EUS criteria for lymphadenopathy associated with rectal cancer. Gastrointest Endosc. 2009;69(4):896–903.
30. 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. 2011. doi:10.1002/dc.21804. [Epub ahead of print]
31. Gleeson FC, Clain JE, Rajan E, Topazian MD, Wang KK, Levy MJ. EUS-FNA assessment of extramesenteric lymph node status in primary rectal cancer. Gastrointest Endosc. 2011;74(4):897–905.
32. Levy MJ, Gleeson FC, Campion MB, et al. Prospective cytological assessment of gastrointestinal luminal fluid acquired during EUS: a potential source of false-positive FNA and needle tract seeding. Am J Gastroenterol. 2010;105(6):1311–8.
33. Gleeson FC, Kipp BR, Caudill JL, et al. False positive endoscopic ultrasound fine needle aspiration cytology: incidence and risk factors. Gut. 2010;59(5):586–93.
34. 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(6):684–9.
35. Mohamadnejad M, Al-Haddad MA, Sherman S, McHenry L, Leblanc JK, DeWitt J. Utility of EUS-guided biopsy of extramural pelvic masses. Gastrointest Endosc. 2012;75(1):146–51.
36. Levy MJ, Abu Dayyeh BK, Fujii LL, et al. Prospective evaluation of adverse events following lower gastrointestinal tract EUS FNA. Am J Gastroenterol. 2014;109(5):676–85.
37. Brown G, Richards CJ, Bourne MW, et al. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology 2003;227:371–7.
38. Gualdi GF, Casciani E., Guadalaxara A, et al. Local staging of rectal cancer with transrectal ultrasound and endorectal magnetic resonance imaging: comparison with histologic findings, Dis Colon Rectum. 2000;43:338–45.
39. Bianchi P, Ceriani C, Palmisano A, et al. A prospective comparison of endorectal ultrasound and pelvic magnetic resonance in the preoperative staging of rectal cancer. Ann Ital Chir. 2006;77(1):41–6.
40. Hulsmans FJ, Tio TL, Fockens P, et al. Assessment of tumor infiltration depth in rectal cancer with transrectal sonography: caution is necessary. Radiology. 1994;190(3):715–20.
41. Hildebrandt U, Feifel G. Preoperative staging of rectal cancer by intrarectal ultrasound. Dis Colon Rectum. 1985;28(1):42–6.
42. Gollub MJ, Maas M, Weiser M, Beets GL, Goodman K, Berkers L, Beets-Tan RG. Recognition of the anterior peritoneal reflection at rectal MRI. AJR Am J Roentgenol. 2013;200(1):97–101.
43. Bipat S, Glas AS, Slors FJ, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging, a meta-analysis. Radiology 2004;232:773–83.
44. Fernández-Esparrach G, Ayuso-Colella JR, Sendino O et al. EUS and magnetic resonance imaging in the staging of rectal cancer: a prospective and comparative study. Gastrointest Endosc. 2011;74(2):347–54.
45. Brown G, Richards CJ, Bourne MW. Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. Radiology. 2003;227(2):371–7.
46. Brown G, Kirkham A, Williams GT, et al. High-resolution MRI of the anatomy important in total mesorectal excision of the rectum. AJR Am J Roentgenol. 2004;182(2):431–9.
47. Lahaye MJ, Engelen SM, Kessels AG, et al. USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer: predictive criteria. Radiology. 2008;246(3):804–11.
48. Heriot AG, Grundy A, Kumar D. Preoperative staging of rectal carcinoma. Br J Surg. 1999;86:17–28.
49. Kim NK, Kim MJ, Yun SH, Sohn SK, Min JS. Comparative study of transrectal ultrasonography, pelvic computerized tomography, and magnetic resonance imaging in preoperative staging of rectal cancer. Dis Colon Rectum. 42:770–5.
50. Wolberink SV, Beets-Tan RG, de Haas-Kock DF, van de Jagt EJ, Span MM, Wiggers T. Multislice CT as a primary screening tool for the prediction of an involved mesorectal fascia and distant metastases in primary rectal cancer: a multicenter study. Dis Colon Rectum. 2009;52(5):928–34.
51. Vliegen R, Dresen R, Beets G, Daniels-Gooszen A, et al. The accuracy of Multi-detector row CT for the assessment of tumor invasion of the mesorectal fascia in primary rectal cancer. Abdom Imaging. 2008;33(5):604–10.

52. Pomerri F, Maretto I, Pucciarelli S et al. Prediction of rectal lymph node metastasis by pelvic computed tomography measurement. Eur J Surg Oncol. 2009;35(2):168–73.
53. Harewood GC, Wiersema MJ. Cost-effectiveness of endoscopic ultrasonography in the evaluation of proximal rectal cancer. Am J Gastroenterol. 2002;97(4):874–82.
54. Eglinton T, Luck A, Bartholomeusz D, Varghese R, Lawrence M. Positron-emission tomography/computed tomography (PET/CT) in the initial staging of primary rectal cancer. Colorectal Dis. 2010;12(7):667–73.
55. Davey K, Heriot AG, Mackay J et al. The impact of 18-fluorodeoxyglucose positron emission tomography-computed tomography on the staging and management of primary rectal cancer. Dis Colon Rectum. 2008;51(7):997–1003.
56. Tateishi U, Maeda T, Morimoto T, Miyake M, Arai Y, Kim EE. Non-enhanced CT versus contrast-enhanced CT in integrated PET/CT studies for nodal staging of rectal cancer. Eur J Nucl Med Mol Imaging. 2007;34(10):1627–34.
57. Kim JW, Kim HC, Park JW et al. Predictive value of (18) FDG PET-CT for tumour response in patients with locally advanced rectal cancer treated by preoperative chemoradiotherapy. Int J Colorectal Dis. 2013;28(9):1217–4.
58. Bampo C, Alessi A, Fantini S et al. Is the standardized uptake value of FDG-PET/CT predictive of pathological complete response in locally advanced rectal cancer treated with capecitabine-based neoadjuvant chemoradiation? Oncology. 2013;84(4):191–9.
59. Siddiqui AA, Fayiga Y, Huerta S. The role of endoscopic ultrasound in the evaluation of rectal cancer. Int Semin Surg Oncol. 2006;3:36.
60. Williamson PR, Hellinger MD, Larach SW, Ferrara A. Endorectal ultrasound of T3 and T4 rectal cancers after preoperative chemoradiation. Dis Colon Rectum. 1996;39(1):45–9.
61. Marone P, de Bellis M, Avallone A et al. Accuracy of endoscopic ultrasound in staging and restaging patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation. Clin Res Hepatol Gastroenterol. 2011;35(10):666–70.
62. Vanagunas A, Lin DE, Stryker SJ. Accuracy of endoscopic ultrasound for restaging rectal cancer following neoadjuvant chemoradiation therapy. Am J Gastroenterol. 2004;99(1):109–12.
63. Romagnuolo J, Parent J, Vuong T, Bélanger M, Michel RP, Belliveau PJ, Trudel JL. Predicting residual rectal adenocarcinoma in the surgical specimen after preoperative brachytherapy with endoscopic ultrasound. Can J Gastroenterol. 2004;18(7):435–40.
64. Rau B, Hunerbein M, Barth C et al. Accuracy of endorectal ultrasound after preoperative radiochemotherapy in locally advanced rectal cancer. Surg Endosc. 1999;13:980–4.
65. Maor Y, Nadler M, Barshack I et al. Endoscopic ultrasound staging of rectal cancer: diagnostic value before and following chemoradiation. J Gastroenterol Hepatol. 2006;21(2):454.
66. Napoleon B, Pujol B, Berger F, Valette PJ, Gerard JP, Souquet JC. Accuracy of endosonography in the staging of rectal cancer treated by radiotherapy. Br J Surg. 1991;78:785–8.
67. Ramirez JM, Mortensen NJ, Takeuchi N, Humphreys MM. Endoluminal ultrasonography in the follow-up of patients with rectal cancer. Br J Surg. 1994;81:692–4.
68. Dresen RC, Peters EE, Rutten HJ et al. Local recurrence in rectal cancer can be predicted by histopathological factors. Eur J Surg Oncol. 2009;35(10):1071–7.
69. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg. 2004;240(2):260–8.
70. Jörgren F, Johansson R, Damber L, Lindmark G. Risk factors of rectal cancer local recurrence: population-based survey and validation of the Swedish rectal cancer registry. Colorectal Dis. 2010;12(10):977–86.
71. Novell F, Pascual S, Viella P, Trias M. Endorectal ultrasonography in the follow-up of rectal cancer. Is it a better way to detect early local recurrence? Int J Colorectal Dis. 1997;12:78–81.
72. Lohnert M, Dohrmann P, Stoffregen C, Hamelmann H. Value of endorectal sonography in the follow-up of patients treated surgically for rectum carcinoma. Zentralbl Chir. 1991;116:461–4.
73. Mellgren A, Sirivongs P, Rothenberger DA, Madoff RD, Garcia-Aguilar J. Is local excision adequate therapy for early rectal cancer? Dis Colon Rectum. 2000;43:1064–71.
74. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the american cancer society and the us multi-society task force on colorectal cancer. Gastroenterology. 2006;130(6):1865–71.
75. Gleeson FC, Larson DW, Dozois EJ et al. Recurrence detection following transanal excision facilitated by EUS-FNA. Hepatogastroenterology. 2012;59(116):1102–7.
76. Boo SJ, Byeon JS, Park do H et al. EUS-guided fine needle aspiration and trucut needle biopsy for examination of rectal and perirectal lesions. Scand J Gastroenterol. 2011;46(12):1510–8.
77. Honda K, Akahoshi K, Matsui N et al. Role of EUS and EUS-guided FNA in the diagnosis of rectal implantation cyst at an anastomosis site after a previous low anterior resection for a rectal cancer without evidence of cancer recurrence. Gastrointest Endosc. 2008;68(4):782–5.
78. Mohamadnejad M, Al-Haddad MA, Sherman S, McHenry L, Leblanc JK, DeWitt J. Utility of EUS-guided biopsy of extramural pelvic masses. Gastrointest Endosc. 2012;75(1):146–51.

79. Puri R, Eloubeidi MA, Sud R, Kumar M, Jain P. Endoscopic ultrasound-guided drainage of pelvic abscess without fluoroscopy guidance. J Gastroenterol Hepatol. 2010;25(8):1416–9.
80. Wei SC, Su WC, Chang MC, Chang YT, Wang CY, Wong JM. Incidence, endoscopic morphology and distribution of metastatic lesions in the gastrointestinal tract. J Gastroenterol Hepatol. 2007;22(6):827–31.
81. Dumontier I, Roseau G, Palazzo L, Barbier JP, Couturier D. Endoscopic ultrasonography in rectal linitis plastica. Gastrointest Endosc. 1997;46(6):532–6.
82. Bhutani MS. EUS and EUS-guided fine-needle aspiration for the diagnosis of rectal linitis plastica secondary to prostate carcinoma. Gastrointest Endosc. 1999;50(1):117–9.
83. Pishvaian AC, Ahlawat SK, Garvin D, Haddad NG. Role of EUS and EUS-guided FNA in the diagnosis of symptomatic rectosigmoid endometriosis. Gastrointest Endosc. 2006;63(2):331–5.
84. Mascagni D, Corbellini L, Urciuoli P, Di Matteo G. Endoluminal ultrasound for early detection of local recurrence of rectal cancer. Br J Surg. 1989;76(11):1176–80.
85. Gleeson FC, Clain JE, Rajan E et al. Secondary linitis plastica of the rectum: EUS features and tissue diagnosis (with video). Gastrointest Endosc. 2008;68(3):591–6.
86. Lahat A, Assulin Y, Beer-Gabel M, Chowers Y. Endoscopic ultrasound for perianal Crohn's disease: disease and fistula characteristics, and impact on therapy. J Crohns Colitis. 2012;6(3):311–6.
87. Schwartz DA, Wiersema MJ, Dudiak KM et al. A comparison of endoscopic ultrasound, magnetic resonance imaging, and exam under anesthesia for evaluation of Crohn's perianal fistulas. Gastroenterology. 2001;121(5):1064–72.
88. Guzmán Rojas RA, Shek KL, Langer SM, Dietz HP. The prevalence of anal sphincter injury in primiparous women. Ultrasound Obstet Gynecol. 2013. doi:10.1002/uog.12481. [Epub ahead of print].
89. Ulla-Rocha JL, Vilar-Cao Z, Sardina-Ferreiro R. EUS-guided drainage and stent placement for postoperative intra-abdominal and pelvic fluid collections in oncological surgery. Therap Adv Gastroenterol. 2012;5(2):95–102.
90. Ramesh J, Bang JY, Trevino J, Varadarajulu S. Comparison of outcomes between EUS-guided trans-colonic and trans-rectal drainage of abdominopelvic abscesses. J Gastroenterol Hepatol. 2013;28(4):620–5.
91. DeWitt J, Mohamadnejad M. EUS-guided alcohol ablation of metastatic pelvic lymph nodes after endoscopic resection of polypoid rectal cancer: the need for long-term surveillance. Gastrointest Endosc. 2011;74(2):446–7.
92. Weilert F, Shah JN, Marson FP, Binmoeller KF. EUS-guided coil and glue for bleeding rectal varix. Gastrointest Endosc. 2012;76(4):915–6.

Subepithelial Lesions

28

Christopher S. Huang and John R. Saltzman

Introduction

The term "subepithelial lesion" (or "submucosal lesion") is used to describe any gastrointestinal tract mass or polyp with normal-appearing overlying mucosa. These lesions are often incidentally detected during upper endoscopy or colonoscopy, and are identified by the presence of a smooth bulge protruding into the lumen. They can represent non-neoplastic intramural lesions, intramural neoplasms (both benign and those with malignant potential), as well as extrinsic compression from adjacent structures (normal and abnormal). Endoscopic ultrasound (EUS) is typically necessary to further evaluate subepithelial lesions and determine which ones require additional tissue sampling, follow-up, or resection. This chapter will cover the diagnosis and management of the most common subepithelial lesions likely to be encountered by practicing gastroenterologists.

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Case Presentation

A 54-year-old woman with a history of a T3N0M0 moderately differentiated mucinous adenocarcinoma of the sigmoid colon, status-post sigmoid colectomy 5 years ago, was referred for surveillance colonoscopy. The patient was asymptomatic, but had a mildly elevated CEA level. The most recent surveillance colonoscopy 3 years ago was unremarkable other than post-surgical changes. The current examination was notable for a prominent 3-cm bulge with smooth, normal-appearing overlying mucosa located 11 cm from the anal verge (Fig. 28.1).

What is the Differential Diagnosis of Subepithelial Lesions?

The differential diagnosis of subepithelial lesions encompasses a spectrum of processes, including non-neoplastic intramural lesions, a wide variety of benign and potentially malignant intramural neoplasms, and extrinsic compression from adjacent structures (Table 28.1). When encountering a subepithelial lesion, the endoscopist should be aware of the most common diagnoses based on the lesion's endoscopic appearance and location, placing them in the context of the patient's medical and surgical history. For example, a lobulated subepithelial lesion located in the gastric fundus in a patient with cirrhosis or prior bouts of acute pancreatitis should immediately raise the suspicion for gastric varices (Fig. 28.2).

L. S. Lee (ed.), *ERCP and EUS,* DOI 10.1007/978-1-4939-2320-5_28,

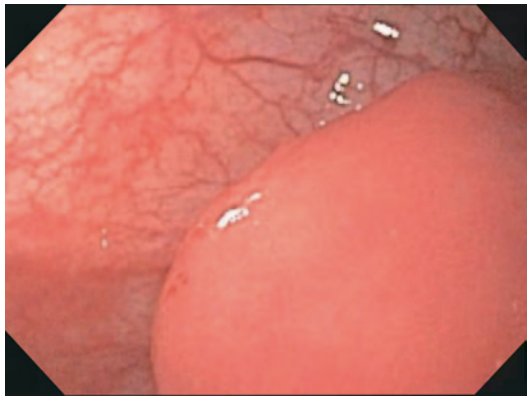

Fig. 28.1 A subepithelial lesion identified in the proximal rectum in a patient with a prior history of sigmoid colon cancer

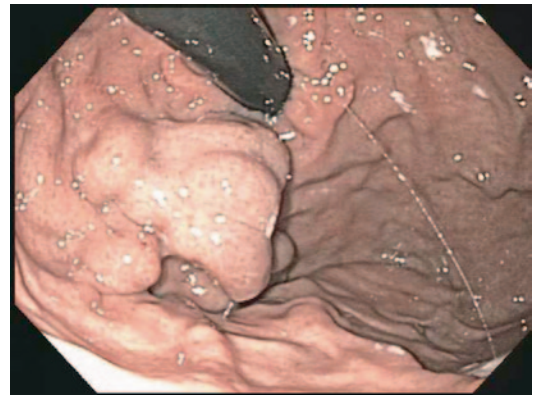

Fig. 28.2 Endoscopic appearance of gastric varices located in the fundus

The differential can be narrowed somewhat based on the location of the lesion [1–3]. The most common subepithelial lesions of the esophagus are leiomyomas, granular cell tumors, and cysts (duplication or bronchogenic). In the stomach, gastrointestinal stromal tumors (GISTs) and pancreatic rests are most common. Duodenal subepithelial lesions are encountered less commonly, but GISTs, carcinoids, lipomas, and duplication cysts can be found with similar frequency. In the colon and rectum, the most common lesions are carcinoids, lipomas, and GISTs. In women, one must also consider the possibility of endometriosis or even extrinsic compression of the rectum caused by a tampon in the vagina [4, 5].

A Stepwise Approach to the Evaluation of Subepithelial Lesions of the Gastrointestinal Tract

Initial Endoscopic Evaluation: What Endoscopic Techniques Diagnose Subepithelial Lesions?

The initial evaluation of subepithelial lesions can be performed using standard endoscopic equipment and techniques [6, 7]. The first step is to visually assess the following features: size, location, shape, color, surface characteristics, presence of pulsation, and change in appearance with patient repositioning and with air insufflation. Subepithelial lesions generally have normal-appearing overlying mucosa, but surface characteristics (e.g., focal ulceration or umbilication) and color

Table 28.1 Differential diagnosis of gastrointestinal subepithelial lesions

Benign intramural lesions	Malignant (or potentially malignant) intramural lesions	Extrinsic compression
Duplication cyst	Carcinoid	Normal intra-abdominal structures (pancreas, liver, spleen, gallbladder, etc.)
Granular cell tumor	Gastrointestinal stromal tumor	Abnormal intra-abdominal structures
Inflammatory fibroid tumor	Glomus tumor	(pancreatic/hepatic/renal cysts, aneurysms, lymph nodes, abscesses, tumors)
Leiomyoma	Lymphoma	
Lipoma	Metastatic carcinoma	
Lymphangioma		
Pancreatic rest		
Schwannoma		
Varices		

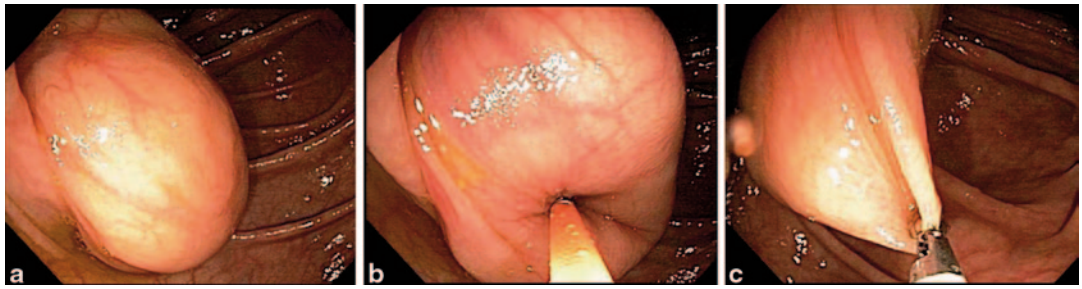

Fig. 28.3 Endoscopic features of lipomas. **a** Endoscopic appearance of a colonic lipoma in the ascending colon. **b** Positive "pillow" or "cushion" sign, characterized by indentation of the lipoma using a closed biopsy forceps. **c** Grasping the overlying mucosa and pulling it away from the underlying lipoma demonstrates the "tent sign"

(e.g., bluish, yellowish, translucent) should be evaluated, as these features may provide clues to the nature of the underlying lesion. Distinguishing intramural lesions from extrinsic compression can be difficult with endoscopy alone [8], but a significant change in the appearance of a lesion with alterations in patient position and degree of lumen distension suggests an extrinsic source.

A closed biopsy forceps can be used to probe the lesion, assessing its mobility and consistency. The presence of the "pillow/cushion" sign, characterized by the ability to indent the lesion with the biopsy forceps, is a feature that is highly specific for lipomas. Lipomas may also demonstrate the "tent sign," described as the ability to grasp the overlying mucosa with a forceps and easily pull the mucosa away from the underlying lesion (Fig. 28.3).

For lesions that do not appear vascular (bluish coloration) or cystic (translucent) and do not demonstrate the "pillow sign," biopsies may then be obtained to rule out an epithelial lesion as well as attempt to sample the underlying lesion. Unlike most other subepithelial lesions, carcinoid tumors can frequently be diagnosed using standard biopsy technique since they often arise from the deep mucosal layer. Areas of ulceration, if present, should be targeted to improve diagnostic yield [9]. "Stacked" (bite-on-bite, or tunneled) biopsies can be obtained using conventional, large-capacity, or jumbo biopsy forceps, although the reported yield of this technique is fairly low and variable depending on the forceps size (17%−42% for conventional and large-capacity, 67% for jumbo forceps) [10–13]. For jumbo forceps, significant bleeding occurred in nearly 35% of patients. Using jumbo forceps or a snare to "unroof" the overlying mucosa may expose the underlying lesion and allow for high-yield targeted biopsies, but also carries an increased risk for bleeding (Fig. 28.4) [13–16].

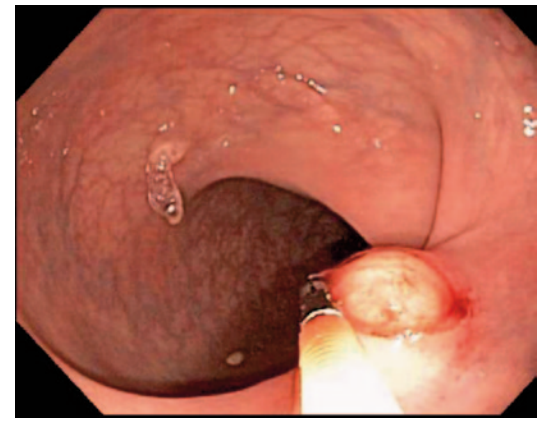

Fig. 28.4 Unroofing technique. The overlying mucosa was unroofed using a large capacity biopsy forceps, revealing the underlying lesion (lipoma)

At this stage of the evaluation, if the diagnosis has not been established, EUS should be performed.

EUS—Technical Tips to Enhance EUS Imaging

Subepithelial lesions can be imaged using radial scanning or linear array echoendoscopes,

as well as catheter ultrasound probes. Factors such as the size and location of the target lesion, its visibility from within the lumen, and the anticipated need to perform EUS-guided tissue acquisition may guide the selection of equipment to be used in any particular procedure. For example, catheter ultrasound probes may be more suitable for evaluating small (< 1 cm) subepithelial lesions due to the higher imaging frequency, which produces finer detail at the expense of depth of penetration. A radial echoendoscope may be preferred to initially localize a lesion that creates little-to-no visible bulge within the lumen. A linear array echoendoscope should be used initially if the lesion is readily localizable and EUS-guided tissue acquisition is definitely planned, obviating the need for radial examination and thereby reducing the number of endoscope insertions required.

When performing the EUS examination, the lumen of the gastrointestinal tract should be maximally deflated of air, and if possible, the target lesion should be submerged in water to achieve optimal imaging of the lesion. This may be impossible or unsafe due to lesion location and risk for aspiration (especially for lesions in the esophagus), in which case the balloon around the transducer should be filled with a very small volume of water to achieve acoustic coupling. The endoscopist should avoid overfilling the balloon, which may distort or compress very small lesions. Another approach to imaging small lesions in the esophagus is the "condom technique," whereby a condom is attached to the tip of a double-channel endoscope and filled with water, and the examination is performed with a catheter ultrasound probe advanced through the endoscope channel into the contained column of water [17].

Other locations can also introduce challenges during EUS examination, such as the gastric antrum, where it may be difficult to submerge the lesion in water. Repositioning the patient on to his or her back, and keeping the head of the bed elevated to at least 45° may allow for the safe instillation of more water into the gastric lumen. Lesions in the high gastric fundus or cardia may also be difficult to image, and it may be necessary to keep the endoscope tip in the distal esophagus and scan through multiple wall layers (from the outside-in). Slightly rotating the patient toward the prone position may help as well.

For colorectal lesions, the bowel should be prepared with enemas or oral purge, depending on the location of the lesion. In general, EUS of lesions proximal to the sigmoid colon should not be attempted with standard echoendoscopes given the technical difficulties of navigating an oblique-viewing scope through the colon. If available, a catheter ultrasound probe or a forward-viewing echoendoscope can be used in these situations.

At times, it can be challenging to accurately determine a lesion's layer of origin, particularly if the lesion is bulky. It may be helpful to carefully focus on the edges of the lesion where there is a transition from normal to abnormal tissue, rather than at the center. In addition, as in any EUS examination, it is important to make sure that the scanning is perpendicular to the target, as opposed to tangential scanning which can lead to distortion of the echolayers of the gut wall and misinterpretation of layer of origin.

How Accurate is EUS Imaging for Diagnosing Subepithelial Lesions?

Endoscopic ultrasound is the modality of choice for distinguishing intramural lesions from extrinsic compression and for diagnosing the nature of subepithelial lesions. Differentiating extrinsic compression from an intramural lesion by EUS is highly accurate at 100 % in one study [18]. For intramural lesions, EUS can determine the layer of origin and characterize the endosonographic features, which in some cases (e.g., lipomas) can establish a certain diagnosis even without the need to obtain tissue. Table 28.2 summarizes the typical EUS characteristics of the most commonly encountered subepithelial lesions. However, the diagnostic accuracy of EUS imaging alone is approximately 50 % overall, and only 30 % for lesions proven to be neoplastic in nature, with the majority of incorrect diagnoses occurring

Table 28.2 Endosonographic features of intramural subepithelial lesions

Subepithelial lesion	Echogenicity/appearance	EUS layer of origin
Carcinoid	Hypoechoic	2 or 3
Granular cell tumor	Hypoechoic	2 or 3
Varices	Anechoic, serpiginous structures	2 or 3
Inflammatory Fibroid Polyp	Hypoechoic, indistinct margins	2 or 3
Leiomyoma	Hypoechoic	2 or 4
Pancreatic rest	Hypoechoic/mixed; may contain anechoic tubular spaces	2, 3 or 4
Lipoma	Intensely hyperechoic	3
Gastrointestinal stromal tumor	Hypoechoic; may contain echogenic foci or anechoic spaces	4
Duplication cyst	Anechoic, compressible; 3- or 5-layer wall may be visible	Any, or extramural

Layer 2 = deep mucosa; layer 3 = submucosa; layer 4 = muscularis propria

with hypoechoic lesions arising from the third and fourth echolayers of the gut wall [8, 19, 20]. Interobserver variability also limits the accuracy of EUS imaging for lesions other than lipomas, cystic lesions, and extrinsic compression [21]. Therefore, tissue acquisition of hypoechoic lesions larger than 1 cm in size is generally recommended to establish a firm diagnosis, unless the lesion requires resection regardless of histology (e.g., patient is experiencing symptoms or complications related to the lesion such as gastrointestinal bleeding).

Tissue Acquisition: What Are the Pros and Cons of the Various Techniques?

There are several options for obtaining tissue from subepithelial lesions, including stacked biopsies/unroofing techniques (discussed above), EUS-guided fine needle aspiration (EUS-FNA), EUS-guided fine needle biopsy (EUS-FNB), endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). The choice of which technique to use depends on factors such as lesion size, location, layer of origin, as well as the availability of necessary equipment and expertise.

Endoscopic Ultrasound-Guided Fine Needle Aspiration

The technical aspects of EUS-FNA are covered in detail in Chap. 23.

Several studies have demonstrated that EUS-FNA is a safe and accurate means of diagnosing subepithelial lesions of the gastrointestinal tract, particularly GISTs, with overall accuracy rates ranging from 67 to 98 % (Video 28.1) [2, 9, 22–30]. In the largest relevant study published to date, comprising 141 patients with gastric subepithelial lesions, the overall accuracy rate of EUS-FNA was 96 % based on criterion standard (surgical histopathologic results, or follow-up course for inoperable cases) [23]. However, diagnostic yield of EUS-FNA may be somewhat limited with EUS-FNA being diagnostic in 43–68 % of cases [31].

Factors that may enhance the diagnostic yield of EUS-FNA include the presence of an on-site cytopathologist, higher number of needle passes (five are recommended), and availability of immunohistochemical staining. Needle diameter has not been definitively shown to significantly impact the diagnostic accuracy of EUS-FNA for subepithelial lesions [32, 33], but 25-gauge needles may more easily puncture small, mobile lesions, as well as those within or adjacent to the duodenum when the scope tip may be acutely angulated.

Endoscopic Ultrasound with Fine Needle Biopsy

In cases where tissue architectural details and immunohistochemical staining are required, obtaining a core-tissue specimen via EUS-FNB may be

advantageous [34]. Another potential advantage of obtaining tissue cores is that specimen adequacy can be determined by the endoscopist, whereas FNA samples require an on-site cytopathologist. Combining EUS-FNA with FNB may be superior to either tissue sampling technique alone, [35] although this approach has not been extensively studied in patients with subepithelial lesions.

Endoscopic Mucosal Resection and Endoscopic Submucosal Dissection

In select cases, EMR or ESD of subepithelial lesions may be performed to simultaneously obtain a histologic diagnosis as well as provide definitive treatment. This approach may be considered for situations in which FNA or FNB is likely to be low yield (e.g., very small lesions, suspected symptomatic pancreatic rest) or when previous stacked biopsies were diagnostic for a lesion that warrants resection (e.g., carcinoid tumor, granular cell tumor). Although associated with an increased risk for complications, endoscopic resection of lesions arising from the submucosa and even muscularis propria is increasingly performed and has a high diagnostic yield (87–94 %) [10, 16, 36–41]. It is necessary to identify the layer of origin with EUS before attempting resection because the risks are directly related to the depth of the tumor. Traditional saline-assisted polypectomy and cap-assisted EMR may be used to resect lesions. A relatively simple and elegant way of resecting small lesions that arise from the deep mucosa or submucosa (without sonographic evidence of involvement of the muscularis propria) is endoscopic band ligation with snare polypectomy. This technique is frequently employed for the resection of rectal carcinoids smaller than 1 cm in diameter, and has been shown to be superior to conventional polypectomy in terms of achieving complete resection with negative margins [42, 43]. Band ligation with or without electrosurgical resection has also been employed as a promisingly safe and effective method of treating small subepithelial lesions arising from the muscularis propria, including GISTs [37, 44–46]. In the so-called "ligate and let-go" technique, snare resection is not performed at the time of band ligation, thereby avoiding the risks of bleeding and perforation. Rather, the lesion is allowed to undergo ischemic necrosis and spontaneously slough off over time. The long-term effectiveness of this technique as a treatment option remains to be shown and a downside to this technique is the lack of a complete specimen for histologic examination.

Case Continued

Rectal endoscopic ultrasound was performed to further evaluate the subepithelial lesion found during colonoscopy. A linear echoendoscope was selected for this examination because tissue sampling was anticipated. The examination demonstrated a hypoechoic, heterogeneous 3-cm lesion involving the submucosa, muscularis propria, and perirectal fat with an irregular outer border (Fig. 28.5). Fine needle aspiration was performed using a 22-gauge needle. Cytologic examination was positive for malignancy consistent with mucinous adenocarcinoma.

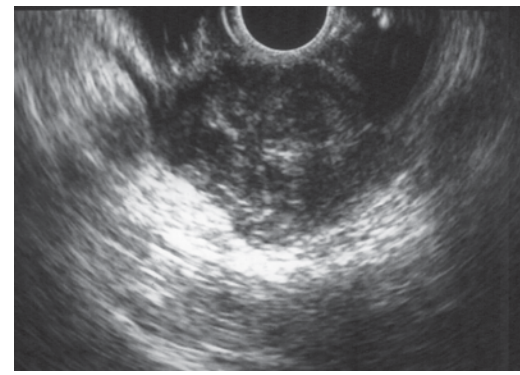

Fig. 28.5 Endoscopic ultrasound examination of a subepithelial lesion located in the proximal rectum of the patient with a prior history of sigmoid colon cancer.

Diagnosis and Management of Specific Gastrointestinal Subepithelial Lesions

Gastrointestinal Stromal Tumor (GIST): What EUS Features Predict Malignancy and How are Incidental GISTs Managed?

GISTs are the most common intramural subepithelial lesion encountered in the gastrointestinal tract, with approximately 4000–6000 new cases diagnosed each year and an estimated prevalence of 129 cases per million [47, 48]. They are most commonly located in the stomach (60–70%), followed by the small bowel (20–30%), colon and rectum (5%), and esophagus (<5%) [49]. GISTs may also arise from outside the gastrointestinal tract, in locations such as the mesentery, omentum, and retroperitoneum.

The clinical presentation of GISTs is quite variable, and related primarily to tumor size and location. Small GISTs are frequently asymptomatic, detected incidentally during endoscopic or radiographic studies performed for unrelated reasons. Symptomatic GISTs most commonly present with acute or chronic bleeding due to tumor ulceration. Other presenting signs or symptoms include abdominal pain, early satiety, dysphagia, gastric outlet obstruction, palpable masses, or acute abdomen (secondary to intra-abdominal hemorrhage) [50–52].

Endoscopic and Endosonographic Features

GISTs typically are round/oval, firm lesions with smooth contour and normal overlying mucosa, although ulceration may be present with larger tumors (Fig. 28.6). Endosonographically, GISTs are typically hypoechoic and most commonly originate from the fourth EUS layer (muscularis propria). Important features to assess by EUS include the size, regularity of the outer border, and presence of echogenic foci and cystic spaces. Large tumor size (>3 cm) and irregular border are the most reliable predictors of malignant behavior; other less consistent predictors include heterogeneous echotexture, cystic spaces, extraluminal growth, and hypervascularity [53–57].

Diagnosis and Management

GISTs were originally considered smooth muscle tumors, but are now known to arise from the interstitial cells of Cajal, which are the pacemaker cells of the gastrointestinal tract. Histologically, the majority of GISTs are composed of spindle cells arranged in interlacing, short fascicles or in a storiform pattern of growth (Fig. 28.6). A smaller proportion of GISTs are composed of epithelioid cells or a mixed cellular composition. The hallmark immunohistochemical feature of GISTs that distinguishes them from other mesenchymal/spindle cell tumors is positive staining for CD117 (c-KIT), which is expressed in over 90% of GISTs [58–60]. A novel marker known as DOG1 (discovered on gastrointestinal stromal tumors 1) is comparable to CD117 in terms of sensitivity and specificity, and may be especially useful in diagnosing cases of CD117-negative GISTs [61, 62]. Other markers that may be expressed include CD34 (60–80%), and less commonly smooth muscle actin (SMA) and S100. [58]. While these markers are generally unhelpful in confirming a diagnosis of GIST, they are useful in the diagnosis or exclusion of other gastrointestinal mesenchymal tumors [63].

Patients with GISTs should ideally be managed by a multidisciplinary team with expertise in sarcomas or tumors of the gastrointestinal tract [64, 65]. Gastroenterologists, working in conjunction with pathologists, are usually responsible for establishing the diagnosis and facilitating the appropriate referrals. Surgeons and medical oncologists are primarily responsible for developing a comprehensive treatment plan based on the resectability of the primary tumor, the aggressiveness of the tumor (Table 28.3), and the extent of any possible metastases.

Treatment of Localized GISTs

Surgical resection is the mainstay of therapy for patients with localized GIST, and should be the initial treatment if the tumor is technically resectable and the patient is a surgical candidate. However, the management of small, incidentally detected GISTs is controversial, and surgical resection of all such lesions may not be feasible or in the patient's best interest. The National

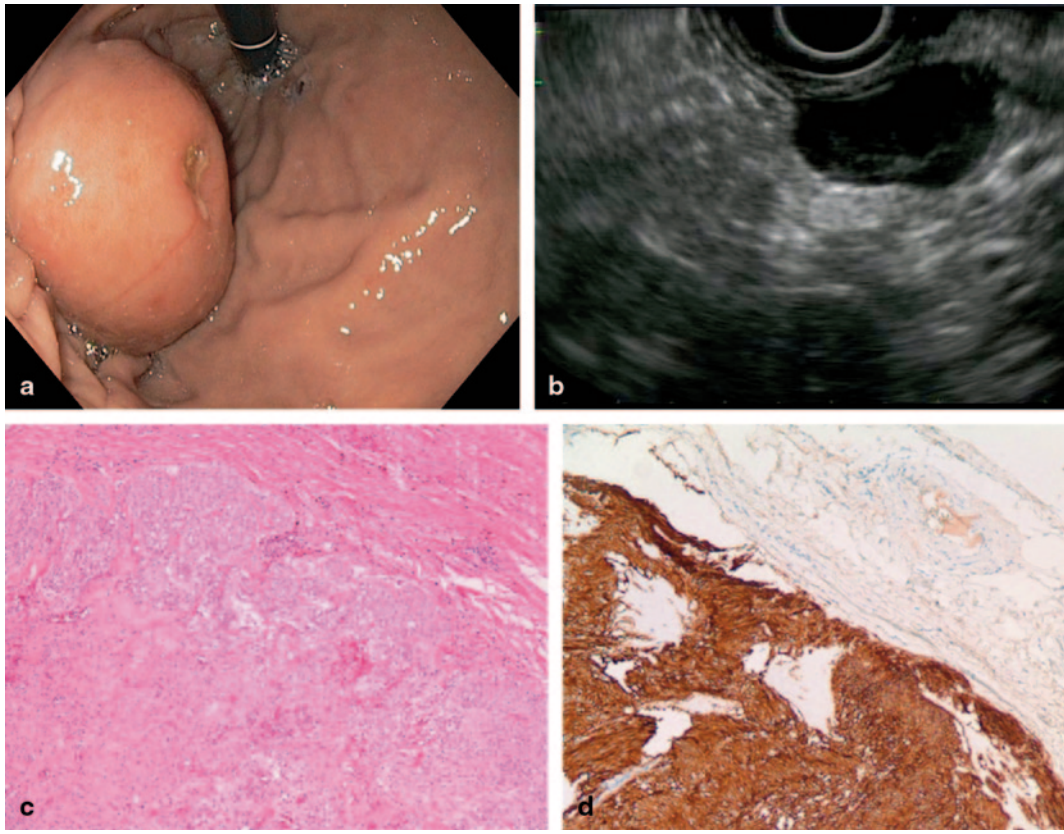

Fig. 28.6 Gastrointestinal stromal tumor (GIST). **a** Endoscopic appearance of a gastric GIST, featuring a focal surface ulceration. **b** Endosonographic appearance of a gastric GIST, characterized as a hypoechoic round lesion arising from the muscularis propria. **c** Histologic features of GISTs include spindle cells arranged in interlacing, short fascicles. **d** Immunohistochemical stain for CD117 (c-KIT) is strongly and diffusely positive

Table 28.3 Proposed modification of NIH consensus classification for assessing risk of aggressive behavior in gastrointestinal stromal tumors

Risk category	Tumor size (cm)	Mitotic index (per 50 HPF)	Primary tumor site/integrity
Very low	<2	≤5	Any site
Low	2–5	≤5	Any site
Intermediate	<5	6–10	Any site
	2–5	>5	Gastric
	5–10	≤5	Gastric
High	>10	Any mitotic rate	Any site
	Any size	>10	Any site
	>5	>5	Any site
	2–5	>5	Non-gastric
	5–10	≤5	Non-gastric
	Any size	Any mitotic rate	Tumor rupture

Adapted from Joensuu [123]

Comprehensive Cancer Network and the European Society for Medical Oncology recommend that all GISTs 2 cm or larger should be resected [64, 66], whereas the American Gastroenterolog-

ical Association's recommended size threshold for resection is 3 cm (as well as tumors < 3 cm with concerning EUS features) [7]. Studies examining the natural history of small, asymptomatic gastrointestinal subepithelial lesions arising from the muscularis propria suggest that the vast majority do not change significantly over time [67–71]. Therefore, surveillance may be a safe approach for the management of such lesions, provided they do not display suspicious EUS features. Surveillance may also be appropriate for patients with significant comorbidities, advanced age, or high surgical risk [72]. It is important that all patients being considered for surveillance understand the possible malignant potential of all GISTs, as well as the risks and benefits of serial EUS examinations versus surgical resection. The optimal surveillance interval has not been established, but 6- to 12-month intervals are generally considered appropriate [64, 72].

While not commonly performed, endoscopic resection of GISTs has been described using a variety of techniques, such as EMR, ESD, band ligation-assisted resection, and endoscopic enucleation/excavation [37, 40, 44, 46, 73, 74]. Because GISTs typically arise from the muscularis propria, endoscopic resection carries a considerable risk for complications, especially bleeding and perforation. In one of the largest published studies on this topic, 97 patients with gastric GISTs less than 3.5 cm in size underwent attempted resection using a technique termed "endoscopic excavation." In this technique, the overlying mucosa is incised in a cross pattern to expose the tumor, which is then separated from the surrounding tissue by injection of a solution of saline, indigo carmine, and epinephrine. After achieving adequate exposure, the tumor is excavated from the muscularis propria layer using a snare, insulated-tip knife or hook knife, and the gastric wall defect is closed using hemostatic clips. Using this modified ESD technique, resection was successful in 91 patients (94%), with a perforation rate of 24% [73]. Another option is the band "ligate and let-go" technique, which is technically simple and likely safe for resection of GISTs less than 1 cm in size, although the adequacy of resection remains questionable. Therefore, given the current concerns regarding safety and long-term efficacy, endoscopic resection of GISTs cannot be routinely recommended at this time.

Leiomyoma: What is the Recommended Management?

Leiomyomas are benign smooth muscle tumors that arise from either the muscularis mucosae or muscularis propria. Although quite rare, they are the most common mesenchymal tumor found in the esophagus, and can also occur infrequently in the colon (predominately in the rectum or sigmoid colon), stomach, or small bowel.

Leiomyomas are classically very slow growing, and as such are frequently asymptomatic. They can present at any age, with a peak incidence in the third to fifth decades. The most common symptoms of esophageal lesions are dysphagia or chest discomfort [75]. Rarely, leiomyomas may ulcerate and bleed. Malignant transformation is extremely uncommon.

Endoscopic and Endosonographic Features

Esophageal leiomyomas most commonly occur in the mid- to distal esophagus, correlating with the muscular composition of the esophagus. They usually appear as a solitary smooth flat or hemispheric bulge with intact overlying mucosa (Fig. 28.7) [76]. Some may be annular and encircle the esophagus. In the colon, they appear as smooth polypoid lesions that have a firm consistency. Endosonographically, leiomyomas appear hypoechoic, homogeneous, and well-circumscribed arising from the muscularis propria or muscularis mucosae.

Diagnosis and Management

Histologically, leiomyomas are characterized by fascicles of spindle cells, with low-to-moderate cellularity and absent or low mitotic activity (Fig. 28.7). On immunohistochemical testing, leiomyomas stain positive for smooth muscle actin (SMA) and desmin, but negative for CD117, CD34, and S100.

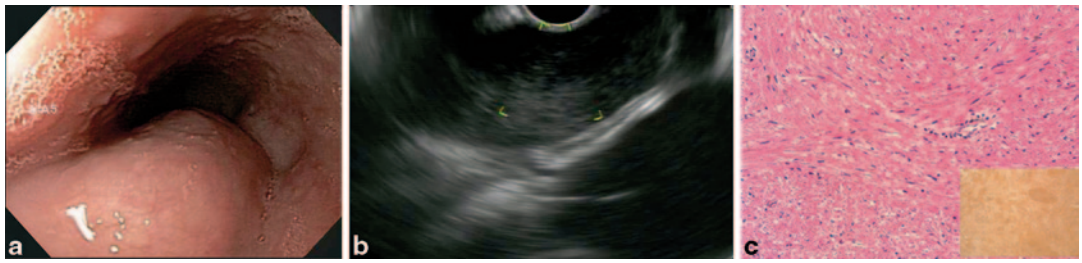

Fig. 28.7 Esophageal leiomyoma. **a** Endoscopic appearance of an esophageal leiomyoma resulting in mild compression of the esophagus. **b** Endosonographic examination demonstrates a homogenous, hypoechoic mass. **c** Histologic features include spindle cells arranged in fascicles with absent or low mitotic activity. Immunohistochemical stain for smooth muscle actin (inset lower right corner) is diffusely positive

Asymptomatic leiomyomas generally do not require intervention, but rather expectant observation and periodic surveillance by radiography, endoscopy, or EUS [77]. The natural history of most asymptomatic esophageal leiomyomas is usually benign, with most tumors remaining stable in size for many years; thus, a non-surgical approach is justified. Indications for resection include unremitting symptoms, increase in tumor size, large size, mucosal ulceration, and the need to obtain definite histopathologic diagnosis. Surgical resection is the traditional treatment of choice for esophageal leiomyomas, most commonly via thoracotomy (or more recently, thoracoscopy) with transthoracic extramucosal enucleation. Endoscopic resection via EMR or ESD techniques can be considered for small lesions that arise from the muscularis mucosae [78]. As with GISTs, there is growing experience with endoscopic resection of leiomyomas arising from the muscularis propria [38, 40, 45, 73, 74, 79], but this approach has not been widely embraced in the United States.

Lipoma: What Endoscopic and EUS Features are Diagnostic?

Lipomas are benign tumors composed of mature adipocytes. In the gastrointestinal tract, they are most commonly found in the colon, and only rarely in the upper gastrointestinal tract or small bowel. Gastrointestinal tract lipomas are usually asymptomatic, but depending on size and location, may result in complications or symptoms such as abdominal pain, change in bowel habits, bleeding or obstruction from intussusception.

Endoscopic and Endosonographic Features

Endoscopically, lipomas are characterized by a yellowish hue and soft consistency with a positive "pillow/cushion sign" which is 98 % specific, but only 40 % sensitive for lipomas [8]. In addition, grasping the overlying mucosa with a biopsy forceps easily pulls the mucosa away from the underlying lesion ("tent sign"). Stacked biopsies may occasionally produce an extrusion of fatty tissue ("naked fat sign"). Lesions that lack these characteristic endoscopic features should be investigated further with EUS. The finding of an intensely hyperechoic, well-circumscribed mass arising from the submucosal layer is diagnostic, making further diagnostic testing or tissue acquisition unnecessary (Fig. 28.8).

Diagnosis and Management

The diagnosis of lipomas can be made based on the characteristic endoscopic and EUS features. Asymptomatic lipomas require no treatment, whereas symptomatic lipomas should be resected, traditionally via surgery. Endoscopic resection can be considered in circumstances when the clinical situation allows for elective resection. Although endoscopic resection of lipomas larger than 2 cm was initially discouraged

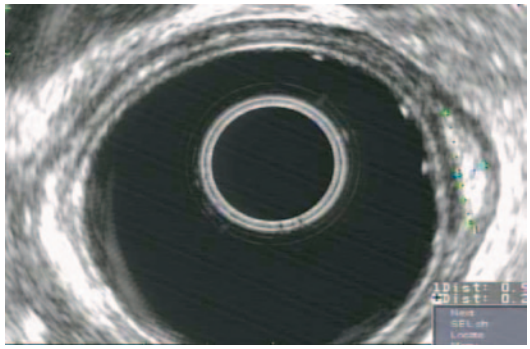

Fig. 28.8 Endosonographic appearance of a small gastric lipoma, characterized by an intensely hyperechoic lesion within the submucosa

due to increased risk of perforation, several case reports have described safe resection techniques even for large lesions. The spectrum of techniques includes saline/epinephrine-lift with snare resection, ligation of the base with a detachable loop prior to snare resection or as a stand-alone therapy to induce ischemic necrosis and spontaneous separation from the wall ("loop and let go"), and unroofing techniques [80–85]. On a practical note, endoscopists who endeavor to perform snare resection of large lipomas should be aware that fatty tissue conducts electrosurgical current inefficiently, so careful assessment of snare placement is necessary to avoid inadvertent application of cautery through the tumor itself.

Carcinoid Tumor: When is Endoscopic Resection Indicated?

Carcinoid tumors constitute a heterogeneous group of tumors that arise from neuroendocrine cells of the gastrointestinal tract. They can arise in any portion of the gut, most commonly in the small intestine and in the rectum [86–88]. Gastric carcinoids, which represent approximately 6% of all carcinoids, are categorized into three types: (1) Type I carcinoids (most common) are associated with chronic atrophic gastritis, achlorhydria, hypergastrinemia and often pernicious anemia; (2) Type II carcinoids occur in the setting of Zollinger–Ellison syndrome and MEN-I; and (3) Type III carcinoids (sporadic) are usually solitary, large tumors that develop in normal gastric mucosa without hypergastrinemia; these tend to display aggressive local behavior and have a high incidence of metastasis.

Most carcinoids are non-functioning tumors and do not create symptoms from excess hormone production and release. Presenting features may include non-specific symptoms such as pain, nausea, and vomiting from local invasion, bowel obstruction, or mesenteric ischemia. The carcinoid syndrome, characterized by the well-known features of flushing, wheezing, and diarrhea, occurs in approximately 20–30% of well-differentiated midgut carcinoids (small bowel to the proximal colon), but rarely, if ever, occurs with foregut and hindgut tumors. Carcinoid syndrome is usually due to release of vasoactive compounds such as serotonin and tachykinins from hepatic metastases, but may also occur if there is direct retroperitoneal involvement, with venous drainage that bypasses the liver.

Endoscopic and Endosonographic Features

Endoscopically, carcinoids usually appear smooth, round, and yellowish. They tend to have a firm consistency, and may have a central depression or ulceration (Fig. 28.9) [89]. On EUS, carcinoids appear as hypoechoic, homogeneous lesions with smooth margins, typically arising from the deep mucosa or submucosa.

Diagnosis and Management

Unlike most other subepithelial lesions, carcinoids can usually be diagnosed using standard biopsy forceps because they often originate from the deep mucosal layer. Histologically, they are characterized by small, round, or polygonal, uniform cells arranged in nests, trabecular, or gyriform patterns. Immunohistochemical stains for synaptophysin and chromogranin are strongly and diffusely positive, establishing the diagnosis (Fig. 28.9).

The treatment of widespread disease and syndromes associated with hormonal hypersecretion is beyond the scope of this chapter. The

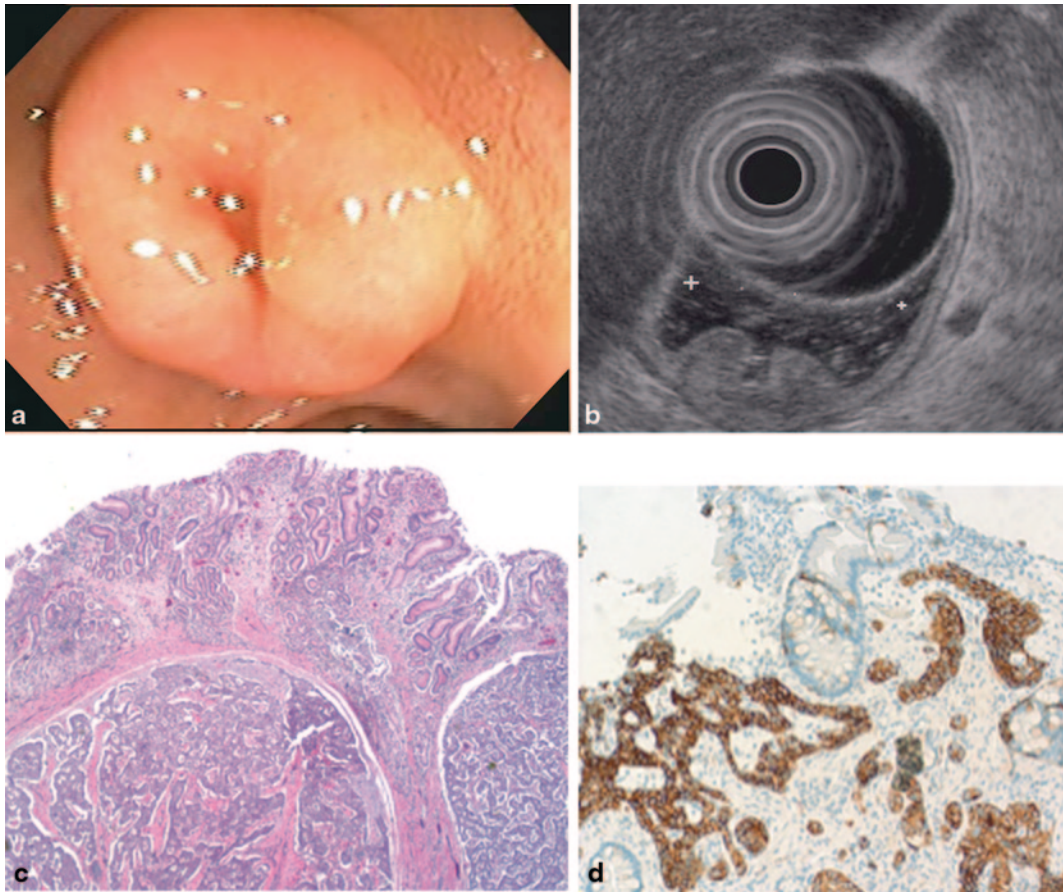

Fig. 28.9 Duodenal carcinoid tumor. **a** Endoscopic appearance of a carcinoid in the duodenal bulb, demonstrating a central depression. **b** Endosonographic appearance of a duodenal carcinoid. **c** Histologic features of gastric carcinoid. **d** Immunohistochemical stains for chromogranin A are positive

management of localized carcinoids depends on tumor location and size. Surgical resection of the primary tumor and local lymph nodes is considered the only potentially curative treatment [87, 90, 91]. Type I and II gastric carcinoids that are smaller than 1 cm in size may be managed by annual endoscopic surveillance alone given their extremely low risk of local invasion and metastasis. Endoscopic resection can be considered for type I and type II gastric carcinoids that are 1–2 cm in size and do not invade the muscularis propria on EUS imaging [7, 92, 93]. Whenever possible, surgical resection and lymph node dissection should be performed for Type III gastric carcinoids given their more aggressive nature. Rectal carcinoids smaller than 1 cm in size can also be adequately treated by endoscopic resection, with little risk for local or distant recurrence (Fig. 28.10) [94]. There is debate concerning the adequacy of endoscopic resection of rectal lesions 1–2 cm in size, and rectal carcinoids larger than 2 cm should be resected surgically [87]. Both small intestine and colon carcinoids should be surgically resected due to their more aggressive nature.

From a practical standpoint, band-ligation EMR is probably the most technically simple, safe, and effective approach to resection of suitable carcinoid tumors [95]. Endoscopic submucosal dissection may also be considered, depending on local expertise and experience.

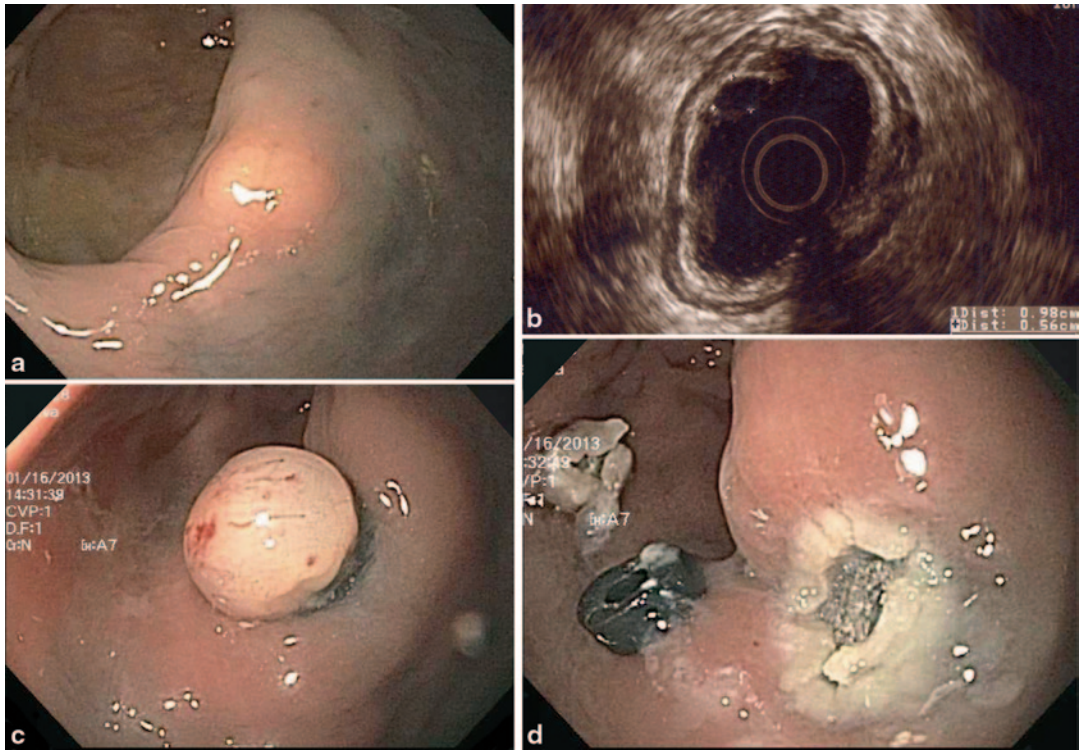

Fig. 28.10 Band ligation-endoscopic mucosal resection of a small rectal carcinoid. **a** Endoscopic appearance of rectal carcinoid. **b** Endosonographic examination of the rectal carcinoid confirms the absence of involvement of the muscularis propria, and size under 1 cm. **c** Band ligation of the rectal carcinoid. **d** Complete resection of the rectal carcinoid achieved by endoscopic resection

Pancreatic Rest: What Endoscopic and EUS Features Are Characteristic?

Pancreatic rests represent ectopic pancreatic tissue within the wall of the gastrointestinal tract. They are most commonly detected in the gastric antrum, but also may occur in the duodenum or proximal jejunum. The majority of these lesions are asymptomatic with no clinical significance, but rare complications have been reported, including ulceration, bleeding, gastric outlet obstruction, pancreatitis, and even malignancy [96].

Endoscopic and Endosonographic Features

Endoscopically, pancreatic rests typically are soft, malleable round/oval subepithelial nodules, often with a central umbilication that represents the orifice of a draining duct (Fig. 28.11). They are most commonly located in the 3 o'clock to 7 o'clock position of the antrum along the posterior wall of the greater curvature. On EUS, they usually appear hypoechoic or heterogeneous with indistinct margins, and may contain anechoic tubular areas (duct structures), and localize within the second, third, or fourth echolayers [97, 98].

Diagnosis and Management

The diagnosis of pancreatic rest can usually be confidently established based on the endoscopic and EUS features. Histologic confirmation, although not usually necessary, may occasionally be obtained by inserting biopsy forceps within the central umbilication, or most effectively by band-ligation EMR or cap-assisted EMR techniques [10, 36, 99]. Histologic examination of resected specimens would be expected to reveal

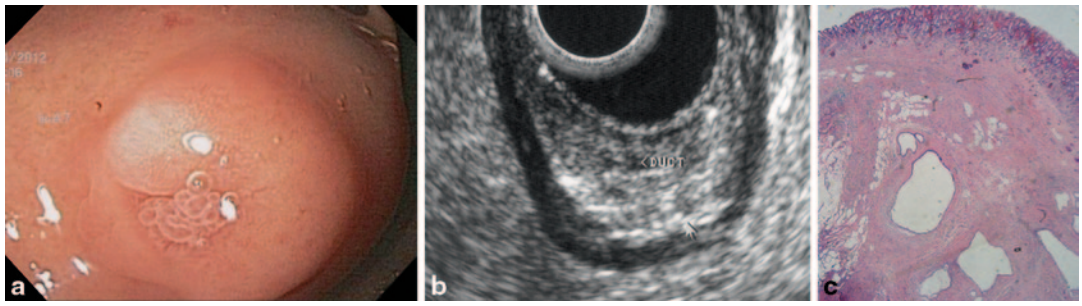

Fig. 28.11 Pancreatic rest. **a** Endoscopic appearance of a pancreatic rest in the stomach, featuring a pseudopapilla. **b** Endosonographic examination demonstrates a heterogeneous "salt-and-pepper" appearance typical of pancreatic parenchyma within the submucosa, including small anechoic spaces corresponding to ductal structures. **c** Histologic features of an endoscopically resected pancreatic rest

submucosal lobules of pancreatic acinar tissue with associated ducts (Fig. 28.11). These resection techniques may also be employed for treatment of symptomatic pancreatic rests, provided the muscularis propria is not involved based on EUS examination. No specific management other than expectant observation is necessary for asymptomatic, incidentally detected pancreatic rests.

Granular Cell Tumor: What is the Role of Endoscopy in Diagnosis and Management?

Granular cell tumors (GCTs) are rare tumors of Schwann cell origin with a predilection for the upper digestive tract, skin, and soft tissue. They are relatively rare in the gastrointestinal tract, where they are most commonly found the lower third of the esophagus and can be multifocal [100]. These tumors are usually asymptomatic and found incidentally, but rarely can ulcerate, bleed, or obstruct. They are generally considered benign, although rare occurrences of malignant transformation have been reported in large GCTs (>4 cm size) or tumors that exhibit rapid recent growth and/or rapid recurrence after excision [101–103].

Endoscopic and Endosonographic Features

Endoscopically, GCTs appear as a slightly elevated, firm nodule, with a whitish-gray or yellowish hue (Fig. 28.12). On EUS, they appear as hypoechoic lesions with smooth margins, usually confined to the second or third echolayer (deep mucosa or submucosa, respectively) [104, 105].

Diagnosis and Management

In the majority of cases, stacked biopsies using standard forceps will yield the diagnosis [104]. Endoscopic resection using band-ligation EMR or cap-assisted EMR can also be performed for small GCTs to establish the diagnosis and provide definitive treatment. Histologically, they are characterized by sheets or nests of large polygonal cells with granular cytoplasm and small round nuclei. Immunohistochemical stains will be positive for S100, indicative of neural origin.

There is no consensus on the optimal management of small, incidentally detected GCTs of the gastrointestinal tract. Small GCTs (<2 cm) limited to the mucosa and submucosa can be resected via band-ligation EMR or cap-assisted EMR, provided there is available endoscopic expertise [104, 106]. Alternatively, endoscopic/EUS surveillance every 1–2 years may be appropriate, given the low-malignant potential of small gastrointestinal tract GCTs. Patients with large GCTs should be referred for consideration of surgical resection.

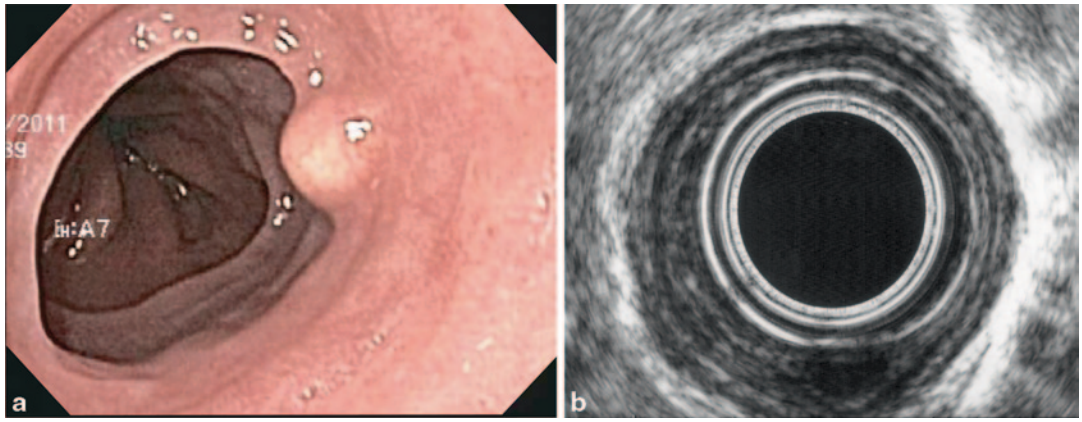

Fig. 28.12 Esophageal granular cell tumor. **a** Endoscopic examination reveals a small, firm nodule with a yellowish hue located in the distal esophagus. **b** Endosonographic appearance of a small esophageal granular cell tumor

Duplication Cysts: What is the Role of EUS/EUS-FNA in Diagnosis?

Duplication cysts arise during embryonic development, possibly related to errors of recanalization and fusion of longitudinal folds. They may occur at any level from oral cavity to rectum, with the small bowel being the most common site. Duplication cysts are usually asymptomatic, but can rarely result in symptoms due to mass effect (dysphagia, gastric outlet or bowel obstruction, pancreatitis), as well as bleeding, intussusception, and even perforation. Instances of malignant transformation (mainly adenocarcinoma arising within gastric duplication cysts) have been reported, although this is a very rare event [107].

Endoscopic and Endosonographic Features

Endoscopically, duplication cysts are rounded or tubular in morphology, with smooth contours. In the esophagus, they may mimic the appearance of esophageal varices, but without the bluish coloration. They are usually compressible and soft in consistency. On EUS imaging, duplication cysts usually appear as anechoic structures within the submucosal layer, or adjacent to the wall of the gastrointestinal tract. A 3- or 5- layer wall may be visible, and fluid levels and internal echogenic foci from mucinous material or debris may be present (Fig. 28.13) [108–111].

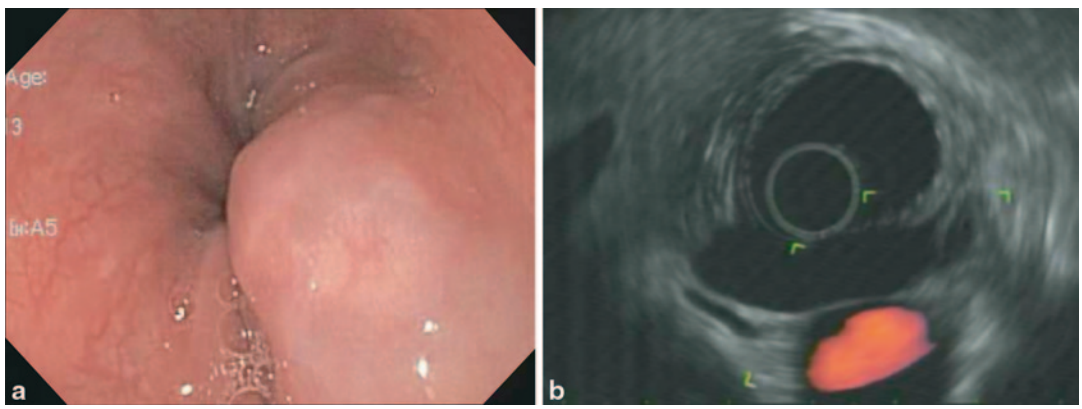

Fig. 28.13 Esophageal duplication cyst. **a** Endoscopic appearance, featuring a shiny, translucent appearance. **b** Endosonographic examination reveals a Doppler-negative anechoic structure

Diagnosis and Management

The diagnosis can be established by EUS-FNA to sample the cyst fluid although this is not always required and the information obtained by FNA must be weighed against the high risk of infection. EUS-FNA is recommended when diagnostic uncertainty remains for atypical-appearing lesions following EUS evaluation. The use of prophylactic antibiotics and smaller gauge needles (22-gauge) is recommended if cyst aspiration is performed [108]. The aspirated fluid may have a thick, gel-like consistency, and cytologic examination may reveal pseudostratified columnar-ciliated epithelium in a background of proteinaceous debris, mucin, and histiocytes [108, 112].

Management of asymptomatic duplication cysts is usually expectant observation, with the option of periodic EUS surveillance. The treatment of symptomatic or enlarging cysts has traditionally been surgical resection or marsupialization. Endoscopic treatments that have been described in case reports include snare resection, endoscopic incision, and marsupialization [113–116].

Inflammatory Fibroid Polyps: What Endoscopic and Histologic Findings are Characteristic?

Inflammatory fibroid polyps (IFPs), also known as Vanek tumors, are rare, benign mesenchymal tumors that can occur throughout the gastrointestinal tract. They are most commonly found in the colon and stomach (although only representing < 0.1 % of all gastric polyps) [117]. The etiology of these lesions is uncertain, but a high frequency of platelet-derived growth factor receptor alpha (PDGFR-A) mutation points to an underlying clonal, neoplastic pathogenesis [118].

The clinical presentation of IFPs largely depends on the location of the lesion. Gastric IFPs may cause abdominal pain, gastric outlet obstruction, or bleeding. Small intestinal lesions frequently present with intussusception [119].

Endoscopic and Endosonographic Features

Endoscopically, IFPs are usually firm, solitary, semi-pedunculated, and often ulcerated or with an erythematous central depression (Fig. 28.14) [120]. Gastric IFPs are usually located in the antrum or pyloric region. On EUS imaging, they appear as hypoechoic, homogenous lesions with indistinct margins, located in the deep mucosa or submucosa, without the involvement of the muscularis propria [121].

Diagnosis and Management

Histologically, IFPs consist of submucosal proliferations of spindle cells, small vessels, and a striking inflammatory infiltrate predominated by eosinophils (Fig. 28.14). Another characteristic finding is the presence of concentric cuffing of vessels by the spindle cells, referred to "onion skinning" [119]. Immunohistochemical staining for CD34 is diffusely and strongly positive in the majority of IFPs, but negative for CD117.

IFPs may be safely resected using standard electrosurgical snare polypectomy, with or without the use of a detachable loop. As most IFPs do not recur after resection, no surveillance is necessary [122].

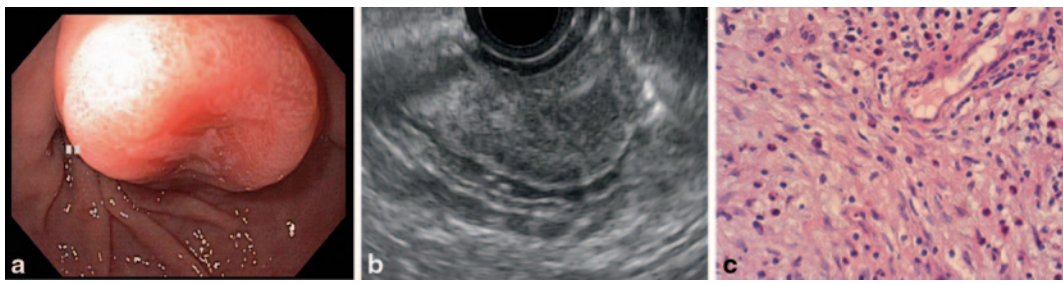

Fig. 28.14 Gastric inflammatory fibroid polyp (Vanek tumor). **a** Endoscopic appearance, characterized by central depression/ulceration and location in the antrum. **b** Endosonographic appearance. **c** Histologic features characterized by prominent eosinophilic infiltrate

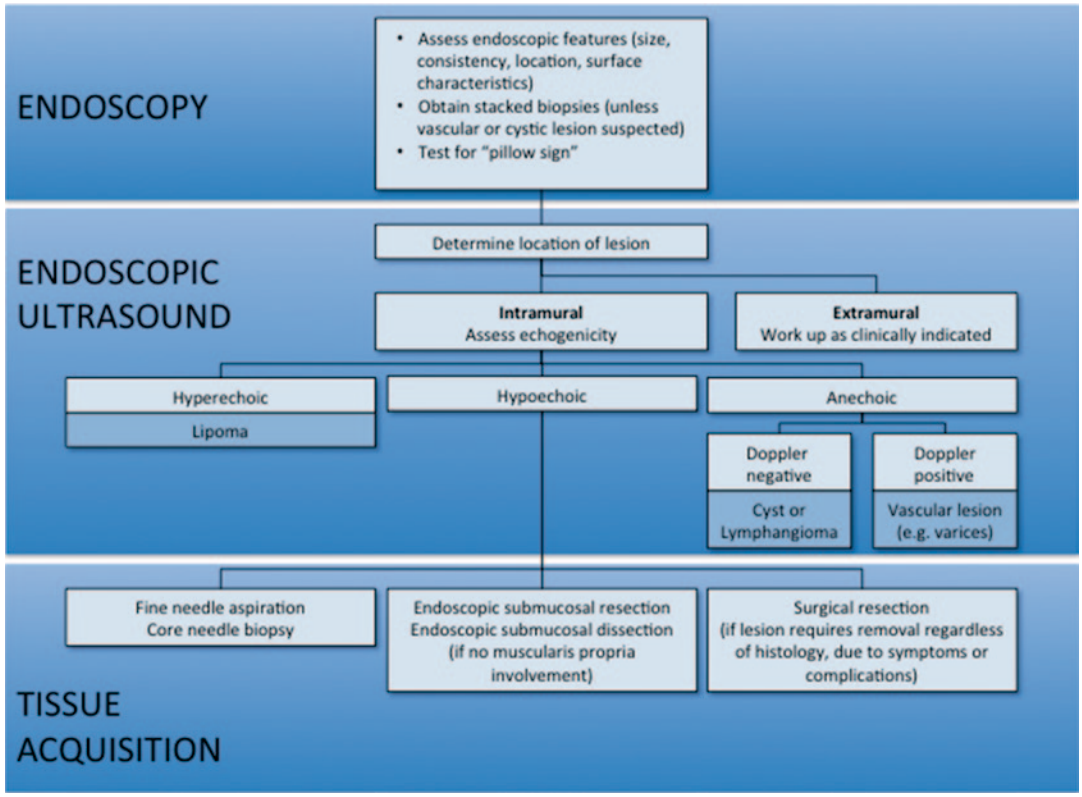

Fig. 28.15 An algorithmic approach to the evaluation of subepithelial lesions of the gastrointestinal tract

Case Continued

The patient underwent laparotomy with low anterior resection of the recurrent tumor. Surgical pathologic examination revealed a 3.5 cm x 3 cm x 2 cm well-to-moderately differentiated mucinous adenocarcinoma located mainly in the muscularis propria, extending to the serosal surface. The patient completed adjuvant chemotherapy and has had no evidence of residual or recurrent disease after 3 years of follow-up since the operation.

Conclusion

Subepithelial lesions of the gastrointestinal tract can represent a wide variety of processes, including congenital abnormalities, extrinsic compression from adjacent structures, and intramural neoplasms. Gastroenterologists should be familiar with the diagnostic features and management of the most commonly encountered subepithelial lesions discussed in this chapter. A stepwise evaluation (Fig. 28.15) including careful endoscopic examination followed by EUS with or without tissue acquisition will lead to the correct diagnosis in the majority of cases.

Key Points

- Subepithelial lesions can occur throughout the gastrointestinal tract, and warrant careful evaluation given the possibility of underlying malignancy or premalignant pathology.
- Routine endoscopic examination and stacked biopsies are useful first steps in evaluation of many subepithelial lesions, but endoscopic ultrasound is the best diagnostic modality and should be performed in the majority of cases.

- Endoscopic ultrasound-guided fine needle aspiration or fine needle biopsy should be performed to achieve a definitive cytologic or histologic diagnosis when there is diagnostic uncertainty or concern for malignancy.
- Tissue acquisition by endoscopic submucosal resection or dissection can be considered for definitive diagnosis and therapy in selected cases, after endosonographic examination excludes involvement of the muscularis propria.

Video Caption

Video 28.1 This video demonstrates the endoscopic and endosonographic appearance of a gastric GIST, as well as two methods for tissue acquisition: stacked biopsies using forceps and fine needle aspiration. In this case, both methods confirmed the diagnosis of GIST

References

1. Landi B, Palazzo L. The role of endosonography in submucosal tumours. Best Pract Res Clin Gastroenterol. 2009;23(5):679–701.
2. Polkowski M. Endoscopic ultrasound and endoscopic ultrasound-guided fine-needle biopsy for the diagnosis of malignant submucosal tumors. Endoscopy. 2005;37(7):635–45.
3. Polkowski M, Butruk E. Submucosal lesions. Gastrointest Endosc Clin N Am. 2005;15(1):33–54.
4. Brullet E, Campo R, Fontanet M, Puig M. False submucosal rectal tumor. Gastrointest Endosc. 2000;52(6):752.
5. Suzuki R, Bhutani MS. Vanishing rectal subepithelial mass. Gastrointest Endosc. 2013;77(4):663.
6. Eckardt AJ, Wassef W. Diagnosis of subepithelial tumors in the GI tract. Endoscopy, EUS, and histology: bronze, silver, and gold standard? Gastrointest Endosc. 2005;62(2):209–12.
7. Hwang JH, Rulyak SD, Kimmey MB. American Gastroenterological Association Institute technical review on the management of gastric subepithelial masses. Gastroenterology. 2006;130(7):2217–28.
8. Hwang JH, Saunders MD, Rulyak SJ, Shaw S, Nietsch H, Kimmey MB. A prospective study comparing endoscopy and EUS in the evaluation of GI subepithelial masses. Gastrointest Endosc. 2005;62(2):202–8.
9. Hoda KM, Rodriguez SA, Faigel DO. EUS-guided sampling of suspected GI stromal tumors. Gastrointest Endosc. 2009;69(7):1218–23.
10. Cantor MJ, Davila RE, Faigel DO. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointest Endosc. 2006;64(1):29–34.
11. Hunt GC, Smith PP, Faigel DO. Yield of tissue sampling for submucosal lesions evaluated by EUS. Gastrointest Endosc. 2003;57(1):68–72.
12. Ji JS, Lee BI, Choi KY, Kim BW, Choi H, Huh M, et al. Diagnostic yield of tissue sampling using a bite-on-bite technique for incidental subepithelial lesions. Korean J Intern Med. 2009;24(2):101–5.
13. Buscaglia JM, Nagula S, Jayaraman V, Robbins DH, Vadada D, Gross SA, et al. Diagnostic yield and safety of jumbo biopsy forceps in patients with subepithelial lesions of the upper and lower GI tract. Gastrointest Endosc. 2012;75(6):1147–52.
14. Keswani RN, Nayar R, Mahajan A, Komanduri S. Touch preparation of jumbo forceps biopsies allows rapid adequacy assessment of subepithelial GI masses. Gastrointest Endosc. 2011;74(2):411–4.
15. Komanduri S, Keefer L, Jakate S. Diagnostic yield of a novel jumbo biopsy "unroofing" technique for tissue acquisition of gastric submucosal masses. Endoscopy. 2011;43(10):849–55.
16. Lee CK, Chung IK, Lee SH, Lee TH, Park SH, Kim HS, et al. Endoscopic partial resection with the unroofing technique for reliable tissue diagnosis of upper GI subepithelial tumors originating from the muscularis propria on EUS (with video). Gastrointest Endosc. 2010;71(1):188–94.
17. Wallace MB, Hoffman BJ, Sahai AS, Inoue H, Van Velse A, Hawes RH. Imaging of esophageal tumors with a water-filled condom and a catheter US probe. Gastrointest Endosc. 2000;51(5):597–600.
18. Motoo Y, Okai T, Ohta H, Satomura Y, Watanabe H, Yamakawa O, et al. Endoscopic ultrasonography in the diagnosis of extraluminal compressions mimicking gastric submucosal tumors. Endoscopy. 1994;26(2):239–42.
19. Karaca C, Turner BG, Cizginer S, Forcione D, Brugge W. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. Gastrointest Endosc. 2010;71(4):722–7.
20. Reddymasu SC, Oropeza-Vail M, Pakseresht K, Moloney B, Esfandyari T, Grisolano S, et al. Are endoscopic ultrasonography imaging characteristics reliable for the diagnosis of small upper gastrointestinal subepithelial lesions? J Clin Gastroenterol. 2012;46(1):42–5.
21. Gress F, Schmitt C, Savides T, Faigel DO, Catalano M, Wassef W, et al. Interobserver agreement for EUS in the evaluation and diagnosis of submucosal masses. Gastrointest Endosc. 2001;53(1):71–6.
22. Chen VK, Eloubeidi MA. Endoscopic ultrasound-guided fine-needle aspiration of intramural and extraintestinal mass lesions: diagnostic accuracy, complication assessment, and impact on management. Endoscopy. 2005;37(10):984–9.

23. Mekky MA, Yamao K, Sawaki A, Mizuno N, Hara K, Nafeh MA, et al. Diagnostic utility of EUS-guided FNA in patients with gastric submucosal tumors. Gastrointest Endosc. 2010;71(6):913–9.
24. Sasaki Y, Niwa Y, Hirooka Y, Ohmiya N, Itoh A, Ando N, et al. The use of endoscopic ultrasound-guided fine-needle aspiration for investigation of submucosal and extrinsic masses of the colon and rectum. Endoscopy. 2005;37(2):154–60.
25. Sepe PS, Moparty B, Pitman MB, Saltzman JR, Brugge WR. EUS-guided FNA for the diagnosis of GI stromal cell tumors: sensitivity and cytologic yield. Gastrointest Endosc. 2009;70(2):254–61.
26. Turhan N, Aydog G, Ozin Y, Cicek B, Kurt M, Oguz D. Endoscopic ultrasonography-guided fine-needle aspiration for diagnosing upper gastrointestinal submucosal lesions: a prospective study of 50 cases. Diagn Cytopathol. 2011;39(11):808–17.
27. Vander Noot MR, 3rd, Eloubeidi MA, Chen VK, Eltoum I, Jhala D, Jhala N, et al. Diagnosis of gastrointestinal tract lesions by endoscopic ultrasound-guided fine-needle aspiration biopsy. Cancer. 2004;102(3):157–63.
28. Ando N, Goto H, Niwa Y, Hirooka Y, Ohmiya N, Nagasaka T, et al. The diagnosis of GI stromal tumors with EUS-guided fine needle aspiration with immunohistochemical analysis. Gastrointest Endosc. 2002;55(1):37–43.
29. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. Gastroenterology. 1997;112(4):1087–95.
30. Akahoshi K, Sumida Y, Matsui N, Oya M, Akinaga R, Kubokawa M, et al. Preoperative diagnosis of gastrointestinal stromal tumor by endoscopic ultrasound-guided fine needle aspiration. World J Gastroenterol. 2007;13(14):2077–82.
31. Watson RR, Binmoeller KF, Hamerski CM, Shergill AK, Shaw RE, Jaffee IM, et al. Yield and performance characteristics of endoscopic ultrasound-guided fine needle aspiration for diagnosing upper GI tract stromal tumors. Dig Dis Sci. 2011;56(6):1757–62.
32. Rong L, Kida M, Yamauchi H, Okuwaki K, Miyazawa S, Iwai T, et al. Factors affecting the diagnostic accuracy of endoscopic ultrasonography-guided fine-needle aspiration (EUS-FNA) for upper gastrointestinal submucosal or extraluminal solid mass lesions. Dig Endosc. 2012;24(5):358–63.
33. Kida M, Araki M, Miyazawa S, Ikeda H, Takezawa M, Kikuchi H, et al. Comparison of diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration with 22- and 25-gauge needles in the same patients. J Interv Gastroenterol. 2011;1(3):102–7.
34. Saftoiu A, Vilmann P, Guldhammer Skov B, Georgescu CV. Endoscopic ultrasound (EUS)-guided Trucut biopsy adds significant information to EUS-guided fine-needle aspiration in selected patients: a prospective study. Scand J Gastroenterol. 2007;42(1):117–25.
35. Storch I, Jorda M, Thurer R, Raez L, Rocha-Lima C, Vernon S, et al. Advantage of EUS Trucut biopsy combined with fine-needle aspiration without immediate on-site cytopathologic examination. Gastrointest Endosc. 2006;64(4):505–11.
36. Bain AJ, Owens DJ, Tang RS, Peterson MR, Savides TJ. Pancreatic rest resection using band ligation snare polypectomy. Dig Dis Sci. 2011;56(6):1884–8.
37. Huang WH, Feng CL, Lai HC, Yu CJ, Chou JW, Peng CY, et al. Endoscopic ligation and resection for the treatment of small EUS-suspected gastric GI stromal tumors. Gastrointest Endosc. 2010;71(6):1076–81.
38. Hwang JC, Kim JH, Shin SJ, Cheong JY, Lee KM, Yoo BM, et al. Endoscopic resection for the treatment of gastric subepithelial tumors originated from the muscularis propria layer. Hepatogastroenterology. 2009;56(94–95):1281–6.
39. Kawamoto K, Yamada Y, Furukawa N, Utsunomiya T, Haraguchi Y, Mizuguchi M, et al. Endoscopic submucosal tumorectomy for gastrointestinal submucosal tumors restricted to the submucosa: a new form of endoscopic minimal surgery. Gastrointest Endosc. 1997;46(4):311–7.
40. Lee IL, Lin PY, Tung SY, Shen CH, Wei KL, Wu CS. Endoscopic submucosal dissection for the treatment of intraluminal gastric subepithelial tumors originating from the muscularis propria layer. Endoscopy. 2006;38(10):1024–8.
41. Park YS, Park SW, Kim TI, Song SY, Choi EH, Chung JB, et al. Endoscopic enucleation of upper-GI submucosal tumors by using an insulated-tip electrosurgical knife. Gastrointest Endosc. 2004;59(3):409–15.
42. Kim HH, Park SJ, Lee SH, Park HU, Song CS, Park MI, et al. Efficacy of endoscopic submucosal resection with a ligation device for removing small rectal carcinoid tumor compared with endoscopic mucosal resection: analysis of 100 cases. Dig Endosc. 2012;24(3):159–63.
43. Lee SH, Park SJ, Kim HH, Ok KS, Kim JH, Jee SR, et al. Endoscopic resection for rectal carcinoid tumors: comparison of polypectomy and endoscopic submucosal resection with band ligation. Clin Endosc. 2012;45(1):89–94.
44. Sun S, Ge N, Wang C, Wang M, Lu Q. Endoscopic band ligation of small gastric stromal tumors and follow-up by endoscopic ultrasonography. Surg Endosc. 2007;21(4):574–8.
45. Sun S, Jin Y, Chang G, Wang C, Li X, Wang Z. Endoscopic band ligation without electrosurgery: a new technique for excision of small upper-GI leiomyoma. Gastrointest Endosc. 2004;60(2):218–22.
46. Sun S, Ge N, Wang S, Liu X, Lu Q. EUS-assisted band ligation of small duodenal stromal tumors and follow-up by EUS. Gastrointest Endosc. 2009;69(3 Pt 1):492–6.
47. Nilsson B, Bumming P, Meis-Kindblom JM, Oden A, Dortok A, Gustavsson B, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib

mesylate era–a population-based study in western Sweden. Cancer. 2005;103(4):821–9.
48. Tryggvason G, Gislason HG, Magnusson MK, Jonasson JG. Gastrointestinal stromal tumors in Iceland, 1990–2003: the icelandic GIST study, a population-based incidence and pathologic risk stratification study. Int J Cancer. 2005;117(2):289–93.
49. Miettinen M, Lasota J. Gastrointestinal stromal tumors–definition, clinical, histological, immunohistochemical, and molecular genetic features and differential diagnosis. Virchows Arch. 2001;438(1):1–12.
50. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol. 2005;29(1):52–68.
51. Miettinen M, Makhlouf H, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the jejunum and ileum: a clinicopathologic, immunohistochemical, and molecular genetic study of 906 cases before imatinib with long-term follow-up. Am J Surg Pathol. 2006;30(4):477–89.
52. Miettinen M, Sarlomo-Rikala M, Sobin LH, Lasota J. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. Am J Surg Pathol. 2000;24(2):211–22.
53. Chak A, Canto MI, Rosch T, Dittler HJ, Hawes RH, Tio TL, et al. Endosonographic differentiation of benign and malignant stromal cell tumors. Gastrointest Endosc. 1997;45(6):468–73.
54. Jeon SW, Park YD, Chung YJ, Cho CM, Tak WY, Kweon YO, et al. Gastrointestinal stromal tumors of the stomach: endosonographic differentiation in relation to histological risk. J Gastroenterol Hepatol. 2007;22(12):2069–75.
55. Sakamoto H, Kitano M, Matsui S, Kamata K, Komaki T, Imai H, et al. Estimation of malignant potential of GI stromal tumors by contrast-enhanced harmonic EUS (with videos). Gastrointest Endosc. 2011;73(2):227–37.
56. Shah P, Gao F, Edmundowicz SA, Azar RR, Early DS. Predicting malignant potential of gastrointestinal stromal tumors using endoscopic ultrasound. Dig Dis Sci. 2009;54(6):1265–9.
57. Palazzo L, Landi B, Cellier C, Cuillerier E, Roseau G, Barbier JP. Endosonographic features predictive of benign and malignant gastrointestinal stromal cell tumours. Gut. 2000;46(1):88–92.
58. Fletcher CD, Berman JJ, Corless C, Gorstein F, Lasota J, Longley BJ, et al. Diagnosis of gastrointestinal stromal tumors: A consensus approach. Hum Pathol. 2002;33(5):459–65.
59. Laurini JA, Carter JE. Gastrointestinal stromal tumors: a review of the literature. Arch Pathol Lab Med. 2010;134(1):134–41.
60. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279(5350):577–80.
61. Kara T, Serinsoz E, Arpaci RB, Gubur O, Orekici G, Ata A, et al. Contribution of DOG1 expression to the diagnosis of gastrointestinal stromal tumors. Pathol Res Pract. 2013;209(7):413–7.
62. Liegl B, Hornick JL, Corless CL, Fletcher CD. Monoclonal antibody DOG1.1 shows higher sensitivity than KIT in the diagnosis of gastrointestinal stromal tumors, including unusual subtypes. Am J Surg Pathol. 2009;33(3):437–46.
63. Novelli M, Rossi S, Rodriguez-Justo M, Taniere P, Seddon B, Toffolatti L, et al. DOG1 and CD117 are the antibodies of choice in the diagnosis of gastrointestinal stromal tumours. Histopathology. 2010;57(2):259–70.
64. Demetri GD, von Mehren M, Antonescu CR, DeMatteo RP, Ganjoo KN, Maki RG, et al. NCCN task force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw. 2010;8(Suppl 2):S1–41.
65. Mullady DK, Tan BR. A multidisciplinary approach to the diagnosis and treatment of gastrointestinal stromal tumor. J Clin Gastroenterol. 2013;47(7):578–85.
66. Casali PG, Jost L, Reichardt P, Schlemmer M, Blay JY. Gastrointestinal stromal tumours: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009;20(Suppl 4):64–7.
67. Bruno M, Carucci P, Repici A, Pellicano R, Mezzabotta L, Goss M, et al. The natural history of gastrointestinal subepithelial tumors arising from muscularis propria: an endoscopic ultrasound survey. J Clin Gastroenterol. 2009;43(9):821–5.
68. Gill KR, Camellini L, Conigliaro R, Sassatelli R, Azzolini F, Messerotti A, et al. The natural history of upper gastrointestinal subepithelial tumors: a multicenter endoscopic ultrasound survey. J Clin Gastroenterol. 2009;43(8):723–6.
69. Kim MY, Jung HY, Choi KD, Song HJ, Lee JH, Kim do H, et al. Natural history of asymptomatic small gastric subepithelial tumors. J Clin Gastroenterol. 2011;45(4):330–6.
70. Lok KH, Lai L, Yiu HL, Szeto ML, Leung SK. Endosonographic surveillance of small gastrointestinal tumors originating from muscularis propria. J Gastrointestin Liver Dis. 2009;18(2):177–80.
71. Melzer E, Fidder H. The natural course of upper gastrointestinal submucosal tumors: an endoscopic ultrasound survey. Isr Med Assoc J. 2000;2(6):430–2.
72. Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol. 2009;6(6):363–71.
73. Zhang Y, Ye LP, Zhou XB, Mao XL, Zhu LH, He BL, et al. Safety and Efficacy of Endoscopic Excavation for Gastric Subepithelial Tumors Originating From the Muscularis Propria Layer: Results From a Large Study in China. J Clin Gastroenterol. 2013;47(8):689–94.
74. Zhang Y, Ye LP, Zhu LH, Zhou XB, Mao XL, Ding JX. Endoscopic muscularis excavation for subepithelial tumors of the esophagogastric junction originating from the muscularis propria layer. Dig Dis Sci. 2013;58(5):1335–40.

75. Seremetis MG, Lyons WS, deGuzman VC, Peabody JW, Jr. Leiomyomata of the esophagus. An analysis of 838 cases. Cancer. 1976;38(5):2166–77.
76. Fei BY, Yang JM, Zhao ZS. Differential clinical and pathological characteristics of esophageal stromal tumors and leiomyomata. Dis Esophagus. 2013;27(1):30–5.
77. Lee LS, Singhal S, Brinster CJ, Marshall B, Kochman ML, Kaiser LR, et al. Current management of esophageal leiomyoma. J Am Coll Surg. [Review]. 2004;198(1):136–46.
78. Kajiyama T, Sakai M, Torii A, Kishimoto H, Kin G, Uose S, et al. Endoscopic aspiration lumpectomy of esophageal leiomyomas derived from the muscularis mucosae. Am J Gastroenterol. 1995;90(3):417–22.
79. Hu B, Mou Y, Yi H, Wang Y, Luo R, Zhang Q, et al. Endoscopic enucleation of large esophageal leiomyomas. Gastrointest Endosc. 2011;74(4):928–31.
80. Sugimoto K, Sato K, Maekawa H, Sakurada M, Orita H, Ito T, et al. Unroofing technique for endoscopic resection of a large colonic lipoma. Case Rep Gastroenterol. 2012;6(2):557–62.
81. Kim CY, Bandres D, Tio TL, Benjamin SB, Al-Kawas FH. Endoscopic removal of large colonic lipomas. Gastrointest Endosc. 2002;55(7):929–31.
82. Aydin HN, Bertin P, Singh K, Arregui M. Safe techniques for endoscopic resection of gastrointestinal lipomas. Surg Laparosc Endosc Percutan Tech. 2011;21(4):218–22.
83. Kaltenbach T, Milkes D, Friedland S, Soetikno R. Safe endoscopic treatment of large colonic lipomas using endoscopic looping technique. Dig Liver Dis. 2008;40(12):958–61.
84. Soares JB, Goncalves R, Rolanda C. Endoscopic resection of a large colonic lipoma by unroofing technique. Endoscopy. 2011;43(Suppl 2 UCTN):E407.
85. Geraci G, Pisello F, Arnone E, Sciuto A, Modica G, Sciume C. Endoscopic resection of a large colonic lipoma: case report and review of literature. Case Rep Gastroenterol. 2010;4(1):6–11.
86. Arnold R. Endocrine tumours of the gastrointestinal tract. Introduction: definition, historical aspects, classification, staging, prognosis and therapeutic options. Best Pract Res Clin Gastroenterol. 2005;19(4):491–505.
87. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut. 2012;61(1):6–32.
88. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–59.
89. Nakamura S, Iida M, Yao T, Fujishima M. Endoscopic features of gastric carcinoids. Gastrointest Endosc. 1991;37(5):535–8.
90. Oberg K, Akerstrom G, Rindi G, Jelic S. Neuroendocrine gastroenteropancreatic tumours: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v223–7.
91. Modlin IM, Latich I, Kidd M, Zikusoka M, Eick G. Therapeutic options for gastrointestinal carcinoids. Clin Gastroenterol Hepatol. 2006;4(5):526–47.
92. Kulke MH, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas. 2010;39(6):735–52.
93. Lawrence B, Kidd M, Svejda B, Modlin I. A clinical perspective on gastric neuroendocrine neoplasia. Curr Gastroenterol Rep. 2011;13(1):101–9.
94. Murray SE, Sippel RS, Lloyd R, Chen H. Surveillance of small rectal carcinoid tumors in the absence of metastatic disease. Ann Surg Oncol. 2012;19(11):3486–90.
95. Choi CW, Kang DH, Kim HW, Park SB, Jo WS, Song GA, et al. Comparison of endoscopic resection therapies for rectal carcinoid tumor: endoscopic submucosal dissection versus endoscopic mucosal resection using band ligation. J Clin Gastroenterol. 2013;47(5):432–6.
96. Rimal D, Thapa SR, Munasinghe N, Chitre VV. Symptomatic gastric heterotopic pancreas: clinical presentation and review of the literature. Int J Surg. 2008;6(6):e52–4.
97. Park SH, Kim GH, Park do Y, Shin NR, Cheong JH, Moon JY, et al. Endosonographic findings of gastric ectopic pancreas: a single center experience. J Gastroenterol Hepatol. 2011;26(9):1441–6.
98. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Gastric aberrant pancreas: EUS analysis in comparison with the histology. Gastrointest Endosc. 1999;49(4 Pt 1):493–7.
99. Khashab MA, Cummings OW, DeWitt JM. Ligation-assisted endoscopic mucosal resection of gastric heterotopic pancreas. World J Gastroenterol. 2009;15(22):2805–8.
100. Voskuil JH, van Dijk MM, Wagenaar SS, van Vliet AC, Timmer R, van Hees PA. Occurrence of esophageal granular cell tumors in The Netherlands between 1988 and 1994. Dig Dis Sci. 2001;46(8):1610–4.
101. Humphris JL, Jones DB. Subepithelial mass lesions in the upper gastrointestinal tract. J Gastroenterol Hepatol. 2008;23(4):556–66.
102. Xu GQ, Chen HT, Xu CF, Teng XD. Esophageal granular cell tumors: report of 9 cases and a literature review. World J Gastroenterol. 2012;18(47):7118–21.
103. Orlowska J, Pachlewski J, Gugulski A, Butruk E. A conservative approach to granular cell tumors of the esophagus: four case reports and literature review. Am J Gastroenterol. 1993;88(2):311–5.
104. Zhong N, Katzka DA, Smyrk TC, Wang KK, Topazian M. Endoscopic diagnosis and resection of esophageal granular cell tumors. Dis Esophagus. 2011;24(8):538–43.
105. Palazzo L, Landi B, Cellier C, Roseau G, Chaussade S, Couturier D, et al. Endosonographic features of esophageal granular cell tumors. Endoscopy. 1997;29(9):850–3.
106. Wehrmann T, Martchenko K, Nakamura M, Riphaus A, Stergiou N. Endoscopic resection of

submucosal esophageal tumors: a prospective case series. Endoscopy. 2004;36(9):802–7.
107. Zheng J, Jing H. Adenocarcinoma arising from a gastric duplication cyst. Surg Oncol. 2012;21(2):e97–101.
108. Fazel A, Moezardalan K, Varadarajulu S, Draganov P, Eloubeidi MA. The utility and the safety of EUS-guided FNA in the evaluation of duplication cysts. Gastrointest Endosc. 2005;62(4):575–80.
109. Van Dam J Rice TW Sivak MV Jr. Endoscopic ultrasonography and endoscopically guided needle aspiration for the diagnosis of upper gastrointestinal tract foregut cysts. Am J Gastroenterol. 1992;87(6):762–5.
110. Bhutani MS, Hoffman BJ, Reed C. Endosonographic diagnosis of an esophageal duplication cyst. Endoscopy. 1996;28(4):396–7.
111. Geller A, Wang KK, DiMagno EP. Diagnosis of foregut duplication cysts by endoscopic ultrasonography. Gastroenterology. 1995;109(3):838–42.
112. Napolitano V, Pezzullo AM, Zeppa P, Schettino P, D'Armiento M, Palazzo A, et al. Foregut duplication of the stomach diagnosed by endoscopic ultrasound guided fine-needle aspiration cytology: case report and literature review. World J Surg Oncol. 2013;11:33.
113. Joyce AM, Zhang PJ, Kochman ML. Complete endoscopic resection of an esophageal duplication cyst (with video). Gastrointest Endosc. 2006;64(2):288–9.
114. Will U, Meyer F, Bosseckert H. Successful endoscopic treatment of an esophageal duplication cyst. Scand J Gastroenterol. 2005;40(8):995–9.
115. Ferrari AP, Jr., Van Dam J, Carr-Locke DL. Endoscopic needle aspiration of a gastric duplication cyst. Endoscopy. 1995;27(3):270–2.
116. Antaki F, Tringali A, Deprez P, Kwan V, Costamagna G, Le Moine O, et al. A case series of symptomatic intraluminal duodenal duplication cysts: presentation, endoscopic therapy, and long-term outcome (with video). Gastrointest Endosc. 2008;67(1):163–8.
117. Carmack SW, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. Am J Gastroenterol. 2009;104(6):1524–32.
118. Daum O, Hatlova J, Mandys V, Grossmann P, Mukensnabl P, Benes Z, et al. Comparison of morphological, immunohistochemical, and molecular genetic features of inflammatory fibroid polyps (Vanek's tumors). Virchows Arch. 2010;456(5):491–7.
119. Liu TC, Lin MT, Montgomery EA, Singhi AD. Inflammatory fibroid polyps of the gastrointestinal tract: spectrum of clinical, morphologic, and immunohistochemistry features. Am J Surg Pathol. 2013;37(4):586–92.
120. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Endoscopic features of gastric inflammatory fibroid polyps. Am J Gastroenterol. 1996;91(8):1595–8.
121. Matsushita M, Hajiro K, Okazaki K, Takakuwa H. Gastric inflammatory fibroid polyps: endoscopic ultrasonographic analysis in comparison with the histology. Gastrointest Endosc. 1997;46(1):53–7.
122. Carmack SW, Genta RM, Graham DY, Lauwers GY. Management of gastric polyps: a pathology-based guide for gastroenterologists. Nat Rev Gastroenterol Hepatol. 2009;6(6):331–41.
123. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39(10):1411–9.

Part VII

Diagnostic EUS in Extraluminal Disorders

Endosonography of the Mediastinum

29

Kondal R. Kyanam Kabir Baig and Michael B. Wallace

Introduction

Endosonography is a highly effective method of evaluating patients with lung cancer, malignant lymphadenopathy, and other mediastinal conditions such as cysts and masses. Due to the central location of the esophagus within the chest, transesophageal EUS offers reliable access to the posterior and inferior mediastinum [1]. Endosonography can be used to assess non-specific generalized lymphadenopathy in the absence of a known primary. Interventional endosonography in the mediastinum with transesophageal drainage of mediastinal fluid collections has also been reported [2–4].

Another complementary tool available for evaluation of mediastinal lymphadenopathy and cancer staging is endobronchial ultrasound (EBUS) which is typically performed during bronchoscopy. The combination of the two modalities allows near-complete access to all mediastinal lymph node stations. Due to the more anterior location of the trachea, EBUS is preferred for evaluating upper anterior pathology, particularly when the air-filled trachea obscures the view from the esophagus.

EUS and its indications within the mediastinum are discussed in this topic review. In addition, the advantages, disadvantages, and complications of EUS are reviewed.

Case

A 62-year-old male smoker with a history of hypertension and diabetes presented with dyspnea, coughing, fatigue, and fevers. He works as a mechanic and denies any history of recent travel. On physical examination, oxygen saturation was 97% on room air, no lymphadenopathy was palpable, and lungs were clear. His chest X-ray was abnormal, showing hilar fullness. A CT chest revealed significant mediastinal lymphadenopathy. Subsequent PET scan revealed mild uptake by the mediastinal lymph nodes. Sputum culture, blood culture, and skin testing for tuberculosis were negative. What is the next step to evaluate the lymphadenopathy?

When Is EUS of the Mediastinum Indicated?

The indications for endosonography of the mediastinum are listed in Table 29.1. Endosonography for Barrett's dysplasia, esophageal cancer and staging, and esophageal mural lesions are addressed elsewhere (Chaps. 25 and 28). In addition to evaluating mediastinal lymphadenopathy, lung cancer staging is the main role of EUS in the mediastinum. When the lesion of interest is paraesophageal, in the posterior or inferior

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Table 29.1 Indications for endosonography/FNA/FNB of mediastinum

Common indications
Lymphadenopathy
Lung cancer nodal staging
Esophageal cancer tumor
Nodal staging
Mediastinal mass
Uncommon indications
Mediastinal vascular abnormalities
Mediastinal cystic lesions
Thyroid mass/lesion
Mediastinal collections

FNA fine-needle aspiration, *FNB* fine-needle biopsy

mediastinum, EUS-guided fine-needle aspiration (FNA) should be the sampling method of choice [1]. EBUS is a complementary modality that is more suitable for lesions in the anterior or superior mediastinum. In support of this concept, our center conducted a prospective blinded study which demonstrated that the combination of EUS and EBUS with FNA was superior to either alone and conventional transbronchial FNA alone and had a high positive and negative predictive value for detecting malignant lymph nodes in lung cancer [5].

What Are the Techniques of Performing EUS and EUS-FNA of the Mediastinum?

As described previously in the textbook, endosonography can be performed with a radial or linear array echoendoscope. The radial echoendoscope provides cross-sectional images perpendicular to the axis of the endoscope (Fig. 29.1 and 29.2). However, tissue or fluid sampling is not possible. The curvilinear array echoendoscope provides images parallel to the echoendoscope. It has an accessory channel for a biopsy needle that can be visualized as a biopsy is being done and can be manipulated with an elevator to target lesions of interest (Figs. 29.3, 29.4 and 29.5). The choice of echoendoscope often depends on the indication and whether biopsy or aspiration is necessary. If biopsy is required, a linear echoendoscope should be used.

Most endosonography for routine indications can be performed safely under moderate or deep sedation. The sonography settings for visualization of the mediastinum differ with the indication, and structures ranging from a few millimeters up to 5–10 cm from the transducer can be visualized depending on the frequency chosen. Typically, moderate frequencies (5–10 megahertz) are used to achieve a balance of high resolution and penetration depth. Examination of the esophageal wall is best performed with higher frequency (10–20 megahertz). The Doppler feature can help not only in identifying vascular and other structures in the path of the needle but also in defining vascular abnormalities and cystic lesions (Fig. 29.6, 29.7 and 29.8). Due to artifacts from air, ultrasound imaging of the lung parenchyma and structures opposite the air-filled trachea/bronchi is limited.

The mediastinal tissue, lymph nodes, pleura, heart, spine, and vascular structures in the mediastinum can be easily identified. The superior mediastinum, above the level of the carina, can be difficult to visualize because of the anterior air containing trachea. The posterior mediastinum in this region can still be visualized effectively. Mediastinal lymph nodes can be seen in the subcarina, the paraesophageal, and aortopulmonary (AP) regions (Fig. 29.1b, 29.2 and 29.3, Videos 29.1 and 29.2). Subcarinal lymph nodes are typically located 27−30 cm from the incisor teeth with the linear echoendoscope facing anterior. With the left atrium visualized on the left side of the screen, and the left pulmonary artery on the right, the subcarinal lymph node is in the center. The AP window lymph nodes are typically located 2 cm proximal to the subcarina with the echoendoscope facing the left chest (90° counterclockwise rotation from subcarina). In this position, the pulmonary artery is on the left screen, aortic arch on the right, and AP window in the center. Paraesophageal lymph nodes are located throughout the lower mediastinum from 30 cm to the gastroesophageal junction. To visualize with a linear echoendoscope, it is necessary to rotate fully 360° at each level, typically every 4−5 cm along the lower esophagus.

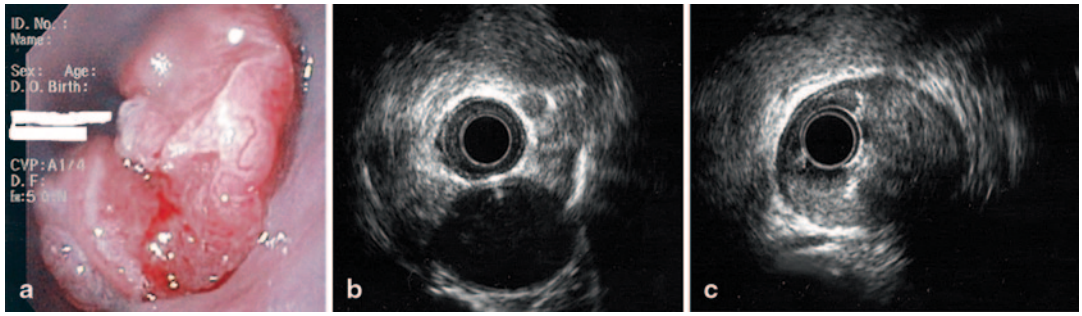

Fig. 29.1 **a** Endoscopic image of circumferential esophageal mass. **b** Peritumoral lymph node in the 2 o'clock position. **c** Radial EUS (endoscopic ultrasound) image of hemicircumferential esophageal mass

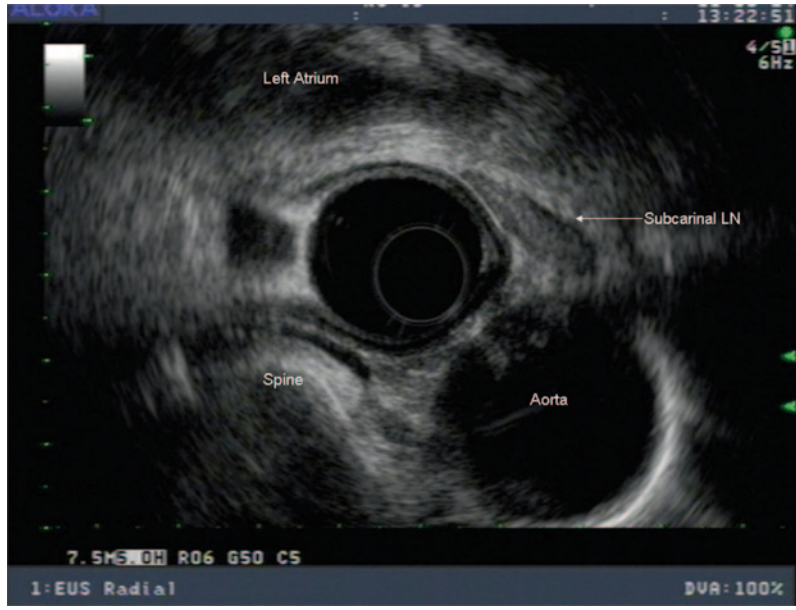

Fig. 29.2 Radial view of subcarinal lymph node

Pretracheal and paratracheal lymph nodes are more challenging to visualize unless these are large or located lateral to the trachea. *However*, the esophagus can sometime be mobilized lateral with the endoscope to allow access even to pretracheal structures. Careful evaluation of the mediastinum may require evaluation with both radial and linear echoendoscopes to better localize the lymph nodes to be targeted for FNA. Lymph nodes lateral to large arteries such as the aorta can be visualized, but FNA through the vessel should generally be avoided, although case reports suggest it can be done safely in specific circumstances [6] (Fig. 29.9).

Fine-needle aspiration—Endosonography with a linear echoendoscope enables FNA under direct visualization and rapid on-site cytological evaluation (Videos 29.3 and 29.4). This ability gives endosonography a unique advantage over other invasive methods such as mediastinoscopy and can provide information that can prevent thoracoscopy and surgery [7–9]. Needles are avail-

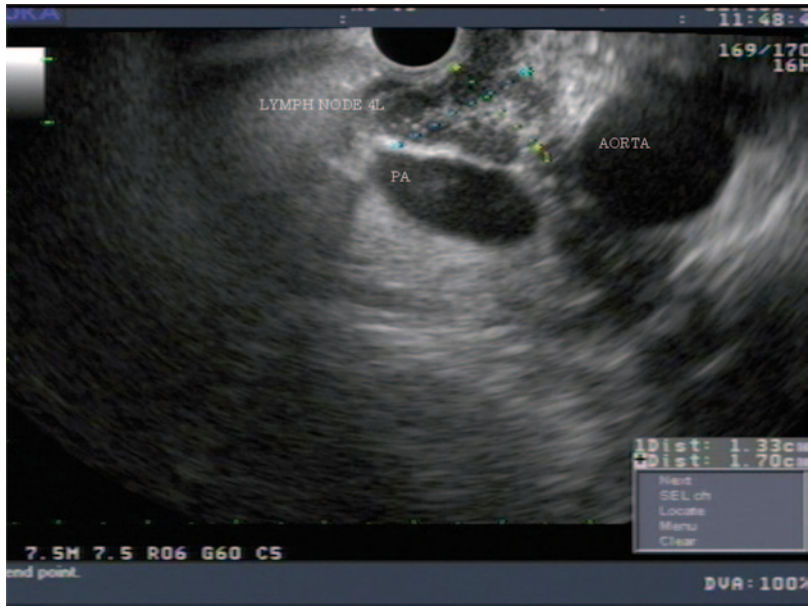

Fig. 29.3 Linear view of aortopulmonary node

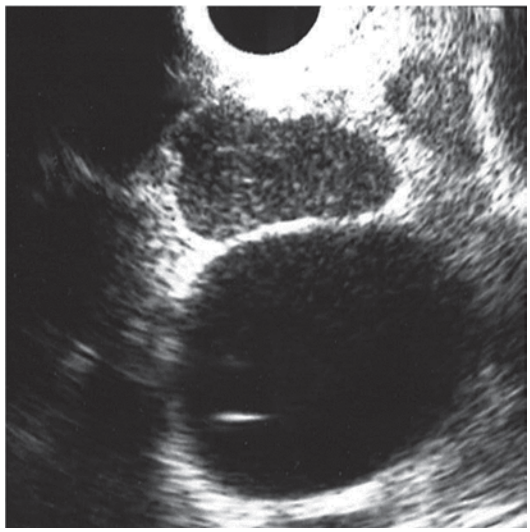

Fig. 29.4 Linear view of periaortic node

able in 25, 22, and 19 gauge sizes. Core biopsy needles are also available that enable histological samples which may be helpful in lymphoma or granulomatous disease [10].

Cytology can be obtained with any size aspiration needle. We typically use 22- or 25-G needles as they are more flexible than a 19G. Core biopsies may be helpful when considering a diagnosis of sarcoidosis or lymphoma, such as in a patient with enlarged lymph nodes in the absence of a primary lung mass. Core samples can typically be obtained with a 19-G aspiration needle or any of the available core biopsy needles. The presence of rapid on-site cytological evaluation (ROSE) by a cytopathologist or cytotechnologist has been shown in studies to increase the diagnostic yield of cytology and is recommended whenever feasible especially when evaluating lymphadenopathy as the cytologist or cytotechnologist will aid in the appropriate triaging of tissue for ancillary testing. If ROSE is unavailable, at least 3 passes should be obtained from the lymph node for both cytology (including flow cytometry if lymphoma is suspected) and microbiology.

Case Continued

Endosonography was performed using a linear echoendoscope to evaluate the mediastinal lymph nodes. Core biopsies were obtained with

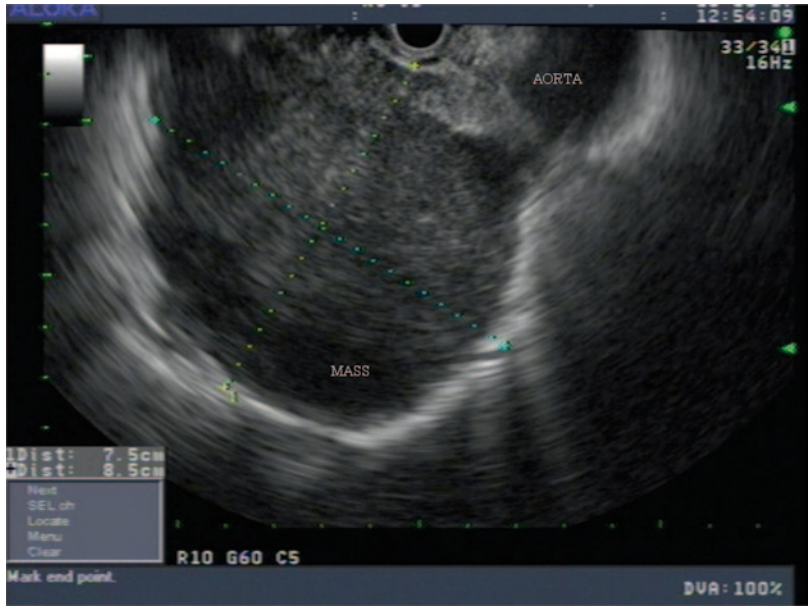

Fig. 29.5 Linear view of lung mass encasing aorta

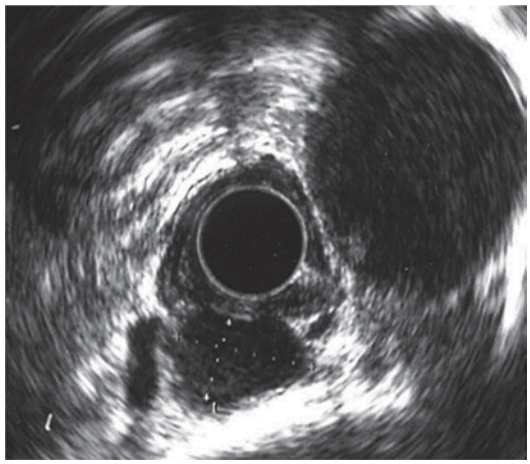

Fig. 29.6 A 1.5-cm vascular aneurysm of a branch from the aorta

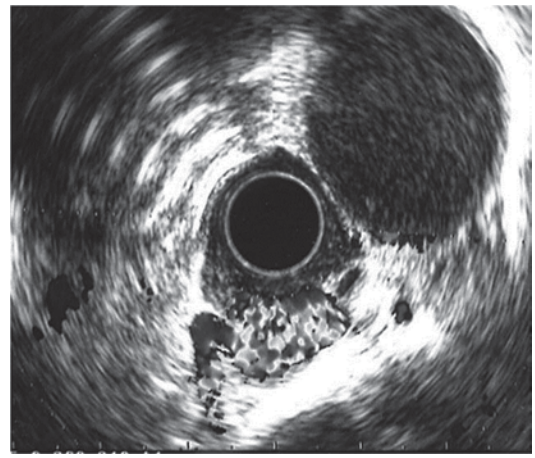

Fig. 29.7 Doppler of aneurysm

a 19-gauge trucut needle (Cook Medical, Bloomington, IN) for histology due to the suspicion for sarcoidosis with lymphadenopathy in the absence of a lung mass. Histology revealed granulomas consistent with sarcoidosis, and cultures were negative for fungi and mycobacterium.

How Accurate Is EUS-FNA for Diagnosing Mediastinal Diseases?

Benign Diseases

Benign lymphadenopathy can be seen in inflammatory conditions such as sarcoidosis and in infections such as tuberculosis and histoplasmosis. EUS-FNA is a safe and minimally invasive

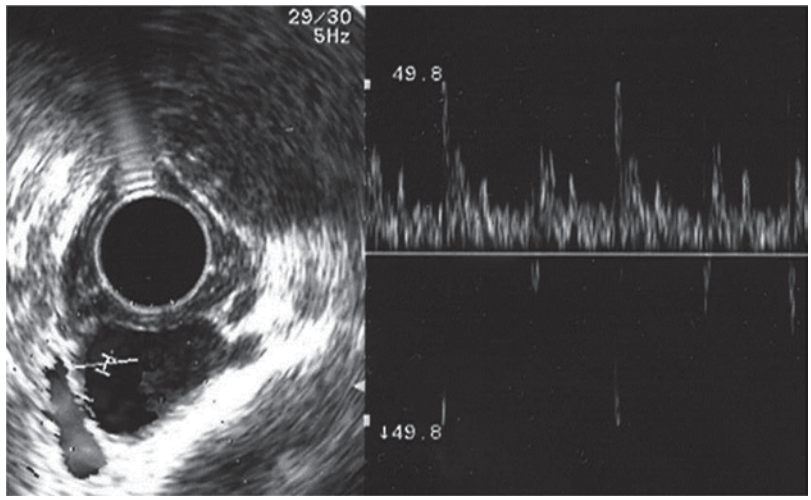

Fig. 29.8 Doppler waveform of aneurysm

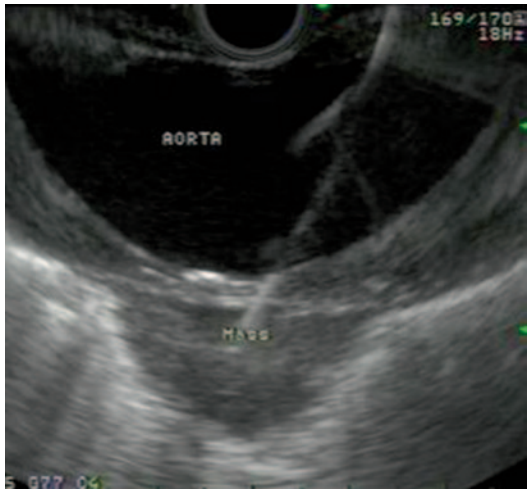

Fig. 29.9 Transaortic FNA (fine-needle aspiration)

method of obtaining tissue and has a robust yield when the index of suspicion is high [11–14]. A recent randomized study of 301 patients suspected of having sarcoidosis compared conventional bronchoscopy with transbronchial and endobronchial mucosal biopsies to EUS or EBUS with FNA [15]. In the EUS/EBUS arm, 22-gauge needles were used, and when a cytologist was not present, 4 passes were performed into the lymph node. Diagnostic yield for detecting granulomas was significantly higher in the ultrasound arm (80 vs. 53%, $p<0.001$) with EUS performing better than EBUS (88 vs. 66%, $p<0.01$). A retrospective study evaluated 124 patients with mediastinal lymphadenopathy of unclear etiology who underwent EUS-FNA using predominantly a 22-gauge needle with 4 passes into the nodes with onsite cytopathology [14]. EUS-FNA was highly accurate for diagnosing sarcoidosis with a sensitivity and specificity of 89 and 96%, respectively. Most of the lymph nodes were located in the subcarinal or the AP window. In another retrospective study of 49 patients who had mediastinal masses without known lung cancer, the overall diagnostic yield of EUS-FNA was 94% [16]. About half these patients had benign diseases which included benign lymph nodes, histoplasmosis, sarcoidosis, and duplication cyst, and FNA was performed with a 22-gauge needle and ROSE. EUS-FNA also accurately distinguishes between mediastinal lymphadenopathy resulting from sarcoidosis and tuberculosis [17]. In this study, patients had undergone an extensive negative evaluation including bronchoscopy and bronchoalveolar lavage before EUS-FNA. A 22-gauge needle was used with 2 passes for cytology and 1 for microbiology. EUS-FNA provided a definite diagnosis in 89% of the cases with 86% sensitivity and 100% specificity for tuberculosis and 100% sensitivity and 93% specificity for sarcoidosis.

Lung Cancer

EUS-FNA is an excellent tool for detecting malignant disease in the mediastinum. Bronchoscopy with or without EBUS is often the first diagnostic test in lung cancer. EUS-FNA is an excellent adjunct tool when a diagnosis has not been made by bronchoscopy, particularly when inferior or posterior lymphadenopathy is present. EUS detected lung cancer in 25/35 patients suspected of having lung cancer despite a negative bronchoscopy and missed the diagnosis in only 1/35 [18]. The other 9 patients had benign disease to yield an overall diagnostic sensitivity and specificity for EUS-FNA of 96 and 100%. EUS-FNA was performed of lymph nodes in the high paratracheal, aortopulmonary, subcarinal, paraesophageal, and hilar regions. The ability of EUS to sample subcentimeter nodes makes it superior to CT and PET [19].

Other Malignancies

In a retrospective study on patients with non–lung cancer malignant mediastinal disease, EUS-FNA detected colon cancer, breast cancer, laryngeal cancer, renal cell cancer, lung cancer, and metastatic disease from an unknown site in 22/49 patients. The accuracy of EUS-FNA for malignant and benign diagnoses was over 90% [16].

A recent retrospective study evaluated the value of EUS and EUS-FNA in diagnosing mediastinal lymphadenopathy as benign, sarcoidosis, lymphoma, or metastatic disease in patients not suspected of having lung cancer [20]. While larger node size was associated with malignancy, a large overlap of size between benign and malignant nodes made this unreliable as the sole criterion for diagnosis. Similarly, the combination of echo features suggestive of malignancy (round, well defined, homogeneous, size > 1 cm) could not reliably differentiate benign from malignant lymph nodes as approximately 20% of sarcoidosis, 40% of lymphoma, and 20% of metastases exhibited these features. Therefore, for mediastinal lymph nodes diagnosed as benign by imaging, further evaluation should occur to rule out malignancy.

What Is the Role of EUS in Lung Cancer Staging?

Lung cancer staging is based on the tumor node metastasis (TNM) system which is also used to inform prognosis and management. EUS can impact each component of TNM staging. Multiple studies have shown that the treatment algorithm for lung cancer is altered in up to 95% of patients when endosonography is utilized in staging [8, 19, 21, 22]. In a prospective cohort study of EUS-FNA of mediastinal lymph nodes, thoracoscopy/mediastinoscopy or surgery was avoided in half the patients [23]. In addition, endosonography was highly cost-effective compared to surgical staging.

T Stage

EUS can define the primary tumor and its relationship to surrounding structures, particularly invasion into vasculature, such as the left atrium and other mediastinal structures (e.g., aorta, azygos vein) to establish T4 disease with 87% sensitivity and 98% specificity [24]. Documentation of T4 disease would preclude surgery.

N Stage

Mediastinal lymph node evaluation is the primary role of EUS and EUS-FNA in lung cancer staging (Fig. 29.10). According to the American Joint Commission on Cancer (AJCC), mediastinal lymph nodes are stage N2 when they are ipsilateral (same side) or midline (subcarina is always considered midline) to the tumor. Contralateral lymph nodes are considered N3 and carry a worse prognosis than N2. Thus, contralateral lymph nodes should be sampled first. If N3 lymph nodes are confirmed by ROSE to be positive, then no further sampling is needed. In most cases, we recommend sampling all suspicious (>1 cm, round, hypoechoic, sharp borders) N3 lymph nodes, then, if necessary, all suspicious N2 lymph nodes. In the absence of a suspicious lymph node, it may still be valuable to sample visible lymph nodes in the common stations.

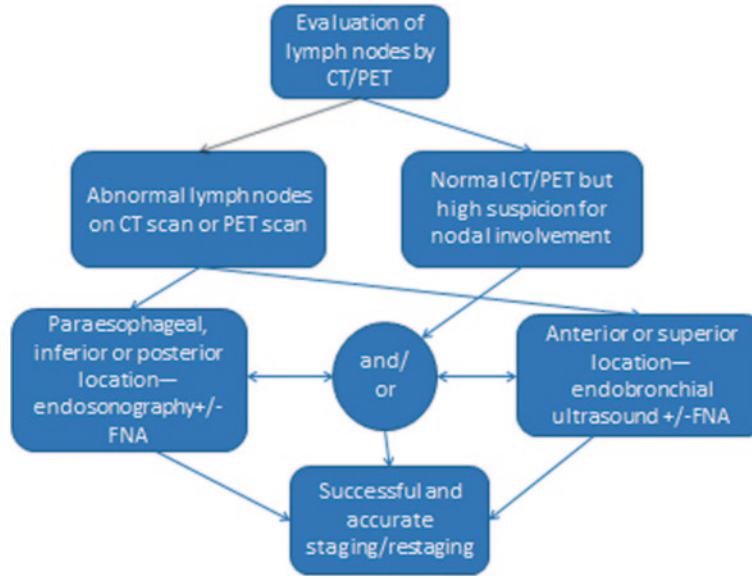

Fig. 29.10 Algorithmic approach to mediastinal lymph nodes in malignancy

Patients with abnormal mediastinal lymph nodes by conventional cross-sectional imaging (CT scan) or PET scan should undergo lymph node sampling [25]. The sensitivity and specificity of diagnosing metastatic disease by imaging alone are inadequate. EUS-FNA is effective at detecting metastatic disease in lymph nodes with an accuracy of 83–97% and a sensitivity of 84–92% [11, 21, 23, 26–31]. A prospective study demonstrated sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 92, 100, 100, 94, and 97%, respectively, in a series of 104 patients with suspected lung cancer who underwent mediastinal lymph node EUS-FNA [27]. As previously described, EUS-FNA and EBUS-TBNA can be used together for incremental benefit. EBUS provides access to anterior and superior mediastinal lymph nodes, while EUS allows access to posterior and inferior mediastinal lymph nodes. When feasible, combined EUS and EBUS in the same setting are most efficient for patient care; however, there are many practical challenges, especially if performed by two separate (GI and pulmonary) physicians. A practical approach is to first do the procedure most likely to confirm nodal metastases (EBUS for anterior lymph nodes or subcarina; EUS for AP window, posterior, and lower paraesophageal), followed by the other procedure if the first is negative.

Endosonography may be uniquely useful in identifying and sampling lymph nodes based on EUS criteria in the absence of lymphadenopathy on cross-sectional imaging [32, 33]. In two studies, EUS was able to detect metastatic disease in 25% of patients with no nodal enlargement by CT scan and also detected advanced local disease in 12% and thus prevented unnecessary surgery. The lesions detected included invasion of mediastinal structures, contralateral and distant lymph node involvement, esophageal involvement, and adrenal metastases [34, 35]. Thus, EUS (or EBUS) should be considered in most patients with suspected lung cancer. An exception is a patient with a peripheral T1 tumor and negative CT/PET of the mediastinum, in whom mediastinal metastases are very rare.

A few small studies have demonstrated a benefit in analyzing the cytology samples for genes that may detect micrometastases in up to 19% of cytologically negative lymph nodes [36–38].

M Stage

While distant metastatic disease is generally detected by cross-sectional imaging, EUS provides a unique opportunity to evaluate and sample abdominal metastatic disease such as celiac lymph nodes and liver and adrenal metastasis at the same time as mediastinal EUS [9, 27, 34]. Endosonography identified celiac lymphadenopathy in 11%

of patients undergoing lung cancer staging and was superior to CT for detecting distant metastases (97 vs. 89%, $p=0.02$) [39]. This was mainly due to the superior diagnostic yield of EUS-FNA over CT for detecting malignant celiac nodes (100 vs. 50%, $p<0.05$). The presence of malignant celiac lymph nodes portends a poor prognosis.

Pleural effusions as small as 2–3 ml can also be routinely and safely aspirated by EUS-FNA although less invasive percutaneous methods are available for large effusions (Video 29.5). The endoscopist should consider aspirating pleural effusions whenever encountered as this confirms metastatic, non-surgical disease. It is important to remember that EUS is typically done in a left lateral decubitus position, and thus, right pleural effusions will be seen layering adjacent to the esophagus. When a right pleural effusion is suspected, the patient position may need to be changed to right lateral decubitus.

Adrenal gland masses occur in 5–15% of lung cancer patients. In a study of 40 patients with known or suspected lung cancer and enlarged left adrenal gland on EUS, EUS-FNA of the adrenal gland changed TNM staging in 70% and altered treatment in 48% [40]. Nearly 93% of patients were downstaged, 5% avoided surgery, while 25% could undergo surgery following EUS-FNA. The right adrenal gland can also be visualized by EUS although less frequently than the left adrenal. No significant complications have been reported following EUS-FNA of adrenal glands [41].

Restaging is often done after neoadjuvant therapy to assess response to therapy and surgical resectability. The persistence of mediastinal lymphadenopathy does not necessarily indicate the presence of malignancy; therefore, tissue sampling is critical. In a prospective study, EUS-FNA was able to diagnose post-treatment lung cancer in mediastinal lymph nodes with a sensitivity and specificity of 75 and 100% [42]. Our study looking at combined EUS and EBUS with FNA in similar patients with a normal CT scan demonstrated a high negative predictive value and changed therapy in 10% of patients [35].

From a patient perspective, EUS-FNA is preferred because it is minimally invasive and can be performed on an outpatient basis under moderate sedation. Technically, EUS-FNA can access posterior mediastinal nodes, which are often a site of metastases from lung cancer and are not easily evaluated by other invasive staging modalities. The real-time evaluation facilitated by endosonography allows the assessment and biopsy of small lesions and decreases the risk of complications associated with other invasive alternatives including mediastinoscopy and thoracoscopy. EUS is also the only modality that allows for concurrent visualization and sampling of extramediastinal regions such as liver, adrenal glands, and abdominal lymph nodes [27, 34, 43, 44].

EUS-FNA does have specific drawbacks. It is not useful in evaluating the mediastinum completely because the air-filled trachea interferes with ultrasound imaging in this region. False-negative biopsies occur due to sampling error; however, this is seen with other methods as well [45]. False-positive results are rare and can occur due to sampling of peritumoral nodes and contamination from intraluminal cancer cells. In addition, the specific expertise required to perform EUS is not available everywhere, but the capability is expanding rapidly.

The few contraindications to EUS-FNA are similar to those for general endoscopy and include difficulty with sedation, serious cardiac or pulmonary comorbidities, and uncorrectable bleeding diathesis.

Other Mediastinal Lesions

Mediastinal cysts can be assessed by endosonography for vascular involvement and the presence of solid or mixed components. The differential includes duplication and bronchogenic cysts. Fluid aspiration of anechoic simple cysts carries a potentially high risk of serious infectious complications including mediastinitis [46–48]. However, one series has demonstrated that aspiration may be safe with broad-spectrum antibiotic prophylaxis and the use of a smaller gauge needle [49]. In practice, FNA of mediastinal cysts should only be considered when there is high suspicion of malignant disease such as a cyst with

solid component or in the setting of other known malignancy. Comparative and randomized trials have not been done to address the concern of mediastinal cyst infection.

Endosonographic assessment of thyroid lesions has been reported in case series for posterior and lateral thyroid lesions. Its utility in documenting the local stage of thyroid cancer and ability to biopsy certain lesions have also been described [50, 51]. EUS-FNA with the scope tip in the cricopharyngeal esophagus has successfully diagnosed thyroid cancer. In addition, EUS was useful in assessing invasion of thyroid cancer into the esophageal wall with 82 % sensitivity and 83 % specificity, which did not differ significantly from MRI.

How Safe Is EUS-FNA in the Mediastinum?

Endosonography is a very safe procedure. A review by American Society for Gastrointestinal Endoscopy states that the perforation rates are comparable to upper endoscopy and less than 0.1 % in two large series [52]. Esophageal strictures, obstructive esophageal malignancy, and multiple attempts at esophageal intubation are independently associated with perforation. The complication rate of EUS-FNA depends on the kind of lesion sampled. EUS-FNA of mediastinal masses or nodes is very safe with 0.5 % complication rate. There is a higher chance (up to 14 %) of infectious complications with EUS-FNA of mediastinal cystic lesions, but this is exceedingly rare with solid lesions. Other rare complications include hemorrhage, drug reaction, bowel wall perforation, and posterior pharyngeal perforation [52]. Though there is a concern for pneumothorax, this has not been reported thus far with EUS-FNA. One case of severe mediastinitis needing thoracotomy following FNA of a mediastinal cyst and one case of esophagomediastinal fistula formation after EUS-FNA of a tuberculous mediastinal lymph node have been reported [47, 53].

Interventional Endoscopy

Endosonography has been utilized and studied extensively for transgastric interventions and drainage of collections, particularly pancreatic collections such as pseudocysts and necroses [54]. Multiple case reports and series have been reported of transesophageal drainage of mediastinal pancreatic collections showing feasibility and safety [2, 4]. However, prospective studies or comparative trials have not been done, and the role of EUS in this setting remains to be defined.

Conclusion

Endosonography is a safe and effective modality for evaluation of mediastinal lesions and tissue acquisition. It provides valuable information in lung cancer staging that alters treatment algorithms, often obviates the need for more invasive and morbid diagnostic procedures, and prevents unnecessary and invasive surgery leading to cost savings. Endosonography is also the most effective and least invasive method in the diagnosis and evaluation of benign mediastinal lymphadenopathy, which includes sarcoidosis and infectious adenopathy.

Key Points

- EUS of the mediastinum is a useful tool for evaluating mediastinal lymphadenopathy and lung cancer staging.
- EUS imaging alone is insufficient for accurate diagnosis of mediastinal lymph nodes, and FNA should be performed, which is highly accurate for sarcoidosis and tuberculosis.
- Ideally, initial cytologic evaluation will be available for FNA of mediastinal lymph nodes. If not present, about 3–4 FNA passes should be performed for cytology (including flow cytometry if lymphoma is suspected) and microbiology.
- The combination of EUS and EBUS with FNA allows near-complete evaluation of mediastinal lymph nodes and is superior to either pro-

cedure alone or conventional bronchoscopy with FNA when evaluating lymph nodes in lung cancer.
- The addition of EUS-FNA in lung cancer staging changes management and allows the avoidance of more invasive and morbid staging procedures including mediastinoscopy and thoracoscopy.
- EUS-FNA of mediastinal cysts should be avoided unless there is suspicion for malignancy, and prophylactic antibiotics must be administered.

Video Captions

Video 29.1 This video demonstrates the various lymph node stations in the mediastinum and the corresponding endosonographic imaging and access for FNA (fine-needle aspiration). These nodes and stations are important in staging esophageal and lung cancer

Video 29.2 This video demonstrates the mediastinal view and anatomy using a linear echoendoscope. The linear echoendoscope is generally advanced carefully through the esophagus, keeping the aorta in view, and then withdrawn proximally from the GE (gastroesophageal) junction

The celiac axis, celiac group of lymph nodes, and celiac ganglion are generally visualized just distal to this location (not shown in the video). The initial view shows the aorta at the level of the gastroesophageal junction. As the endoscope is withdrawn, the aorta is kept in view to maintain orientation. At about 30 cm from the incisors, the aortopulmonary (AP) window is demonstrated between the pulmonary artery and the aortic arch. If this is not readily visible, careful torque at the level will reveal the AP window. This is an important station to inspect for lymph nodes which are accessible to FNA (fine-needle aspiration) with significance in staging malignancies such as lung and esophageal cancers. Further withdrawal by about 3–4 cm reveals the left atrium and the subcarinal window located between the pulmonary artery and left atrium where lymph nodes may be visualized. The carina is shown with its characteristic air shadow. Magnifying the image at this level displays cardiac anatomy. The azygos vein and thoracic duct can be seen at 25 cm from the incisors (approximately T4 level). The final view shows the carotid artery from the proximal esophagus.

Video 29.3 The video demonstrates the standard approach to performing FNA (fine-needle aspiration) in the mediastinum. The lesion of interest is positioned at around 6 to 7 o'clock position using torque and endoscope wheels. The Doppler feature should be used to ensure that vascular structures are not in the needle path (not shown). The needle is then advanced into the lesion with a quick motion maintaining careful control of the distal excursion of the needle tip. The angle of the needle can be further adjusted using the elevator. Different parts of the lesion can be accessed by using the elevator and the up/down wheel as the needle is being advanced, all the while maintaining careful control of the needle location

Video 29.4 The video demonstrates a melanoma mass invading the aorta and located posterolateral to it. It also shows the technique of withdrawal, torque, and echoendoscope manipulation to position the mass directly beneath the tip of the echoendoscope to facilitate FNA. Note the acoustic shadowing arising from the atherosclerotic calcific plaque in the wall of the aorta

Video 29.5 The still image and video demonstrate the radial echoendoscope view of a left-sided pleural effusion relative to the aorta and azygos vein

References

1. Committee ASoP, Jue TL, Sharaf RN, Appalaneni V, Anderson MA, Ben-Menachem T, et al. Role of EUS for the evaluation of mediastinal adenopathy. Gastrointest Endosc. 2011;74(2):239–45.
2. Piraka C, Shah RJ, Fukami N, Chathadi KV, Chen YK. EUS-guided transesophageal, transgastric, and transcolonic drainage of intra-abdominal fluid collections and abscesses. Gastrointest Endosc. 2009;70(4):786–92.
3. Wehrmann T, Stergiou N, Vogel B, Riphaus A, Kockerling F, Frenz MB Endoscopic debridement of paraesophageal, mediastinal abscesses: a prospective case series. Gastrointest Endosc. 2005;62(3):344–9.

4. Gornals JB, Loras C, Mast R, Botargues JM, Busquets J, Castellote J Endoscopic ultrasound-guided transesophageal drainage of a mediastinal pancreatic pseudocyst using a novel lumen-apposing metal stent. Endoscopy. 2012;44 Suppl 2 UCTN:E211–2.
5. Wallace MB, Pascual JM, Raimondo M, Woodward TA, McComb BL, Crook JE, et al. Minimally invasive endoscopic staging of suspected lung cancer. JAMA. 2008;299(5):540–6.
6. Wallace MB, Woodward TA, Raimondo M, Al-Haddad M, Odell JA. Transaortic fine-needle aspiration of centrally located lung cancer under endoscopic ultrasound guidance: the final frontier. Ann Thorac Surg. 2007;84(3):1019–21.
7. Varadarajulu S, Hoffman BJ, Hawes RH, Eloubeidi MA EUS-guided FNA of lung masses adjacent to or abutting the esophagus after unrevealing CT-guided biopsy or bronchoscopy. Gastrointest Endosc. 2004;60(2):293–7.
8. Savides TJ, Perricone A Impact of EUS-guided FNA of enlarged mediastinal lymph nodes on subsequent thoracic surgery rates. Gastrointest Endosc. 2004;60(3):340–6.
9. Kramer H, Groen HJ Diagnosis of mediastinal and left adrenal abnormalities with endoscopic ultrasonography. Resp Med. 2005;99(7):926–8.
10. Varadarajulu S, Fraig M, Schmulewitz N, Roberts S, Wildi S, Hawes RH, et al. Comparison of EUS-guided 19-gauge Trucut needle biopsy with EUS-guided fine-needle aspiration. Endoscopy. 2004;36(5):397–401.
11. Fritscher-Ravens A, Sriram PV, Topalidis T, Hauber HP, Meyer A, Soehendra N, et al. Diagnosing sarcoidosis using endosonography-guided fine-needle aspiration. Chest. 2000;118(4):928–35.
12. Annema JT, Veselic M, Rabe KF Endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of sarcoidosis. Eur Resp J. 2005;25(3):405–9.
13. Tournoy KG, Praet MM, Van Maele G, Van Meerbeeck JP. Esophageal endoscopic ultrasound with fine-needle aspiration with an on-site cytopathologist: high accuracy for the diagnosis of mediastinal lymphadenopathy. Chest. 2005;128(4):3004–9.
14. Wildi SM, Judson MA, Fraig M, Fickling WE, Schmulewitz N, Varadarajulu S, et al. Is endosonography guided fine needle aspiration (EUS-FNA) for sarcoidosis as good as we think? Thorax. 2004;59(9):794–9.
15. von Bartheld MB, Dekkers OM, Szlubowski A, Eberhardt R, Herth FJ, in 't Veen JC, et al. Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. JAMA. 2013;309(23):2457–64.
16. Devereaux BM, Leblanc JK, Yousif E, Kesler K, Brooks J, Mathur P, et al. Clinical utility of EUS-guided fine-needle aspiration of mediastinal masses in the absence of known pulmonary malignancy. Gastrointest Endosc. 2002;56(3):397–401.
17. Fritscher-Ravens A, Ghanbari A, Topalidis T, Pelling M, Kon OM, Patel K, et al. Granulomatous mediastinal adenopathy: can endoscopic ultrasound-guided fine-needle aspiration differentiate between tuberculosis and sarcoidosis? Endoscopy. 2011;43(11):955–61.
18. Fritscher-Ravens A, Soehendra N, Schirrow L, Sriram PV, Meyer A, Hauber HP, et al. Role of transesophageal endosonography-guided fine-needle aspiration in the diagnosis of lung cancer. Chest. 2000;117(2):339–45.
19. Annema JT, Veselic M, Rabe KF EUS-guided FNA of centrally located lung tumours following a non-diagnostic bronchoscopy. Lung cancer. 2005;48(3):357–61; discussion 63–4.
20. Jamil LH, Kashani A, Scimeca D, Ghabril M, Gross SA, Gill KR, Hasan MK, Woodward TA, Wallace MB, Raimondo M. Can Endoscopic ultrasound distinguish between mediastinal benign lymph nodes and those involved by sarcoidosis, lymphoma, or metastasis? Dig Dis Sci. 2014;59:2191–8.
21. Fritscher-Ravens A, Davidson BL, Hauber HP, Bohuslavizki KH, Bobrowski C, Lund C, et al. Endoscopic ultrasound, positron emission tomography, and computerized tomography for lung cancer. Am J Respir Crit Care Med. 2003;168(11):1293–7.
22. Larsen SS, Vilmann P, Krasnik M, Dirksen A, Clementsen P, Maltbaek N, et al. Endoscopic ultrasound guided biopsy performed routinely in lung cancer staging spares futile thoracotomies: preliminary results from a randomised clinical trial. Lung Cancer. 2005;49(3):377–85.
23. Larsen SS, Krasnik M, Vilmann P, Jacobsen GK, Pedersen JH, Faurschou P, et al. Endoscopic ultrasound guided biopsy of mediastinal lesions has a major impact on patient management. Thorax. 2002;57(2):98–103.
24. Varadarajulu S, Schmulewitz N, Wildi SM, Roberts S, Ravenel J, Reed CE, et al. Accuracy of EUS in staging of T4 lung cancer. Gastrointest Endosc. 2004;59(3):345–8.
25. Detterbeck FC, Jantz MA, Wallace M, Vansteenkiste J, Silvestri GA, American College of Chest P. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):202 S–20 S.
26. Wallace MB, Silvestri GA, Sahai AV, Hawes RH, Hoffman BJ, Durkalski V, et al. Endoscopic ultrasound-guided fine needle aspiration for staging patients with carcinoma of the lung. Ann Thorac Surg. 2001;72(6):1861–7.
27. Eloubeidi MA, Cerfolio RJ, Chen VK, Desmond R, Syed S, Ojha B. Endoscopic ultrasound-guided fine needle aspiration of mediastinal lymph node in patients with suspected lung cancer after positron emission tomography and computed tomography scans. Ann Thorac Surg. 2005;79(1):263–8.
28. Giovannini M, Seitz JF, Monges G, Perrier H, Rabbia I. Fine-needle aspiration cytology guided by endoscopic ultrasonography: results in 141 patients. Endoscopy. 1995;27(2):171–7.

29. Wiersema MJ, Vazquez-Sequeiros E, Wiersema LM. Evaluation of mediastinal lymphadenopathy with endoscopic US-guided fine-needle aspiration biopsy. Radiology. 2001;219(1):252–7.
30. Wallace MB, Fritscher-Ravens A, Savides TJ. Endoscopic ultrasound for the staging of non-small-cell lung cancer. Endoscopy. 2003;35(7):606–10.
31. Yasuda I, Kato T, Asano F, Okubo K, Omar S, Kako N, et al. Mediastinal lymph node staging in potentially resectable non-small cell lung cancer: a prospective comparison of CT and EUS/EUS-FNA. Respiration. 2009;78(4):423–31.
32. Kondo D, Imaizumi M, Abe T, Naruke T, Suemasu K. Endoscopic ultrasound examination for mediastinal lymph node metastases of lung cancer. Chest. 1990;98(3):586–93.
33. Arita T, Kuramitsu T, Kawamura M, Matsumoto T, Matsunaga N, Sugi K, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. Thorax. 1995;50(12):1267–9.
34. LeBlanc JK, Devereaux BM, Imperiale TF, Kesler K, DeWitt JM, Cummings O, et al. Endoscopic ultrasound in non-small cell lung cancer and negative mediastinum on computed tomography. Am J Respir Crit Care Med. 2005;171(2):177–82.
35. Wallace MB, Ravenel J, Block MI, Fraig M, Silvestri G, Wildi S, et al. Endoscopic ultrasound in lung cancer patients with a normal mediastinum on computed tomography. Ann Thorac Surg. 2004;77(5):1763–8.
36. Wallace MB, Block MI, Gillanders W, Ravenel J, Hoffman BJ, Reed CE, et al. Accurate molecular detection of non-small cell lung cancer metastases in mediastinal lymph nodes sampled by endoscopic ultrasound-guided needle aspiration. Chest. 2005;127(2):430–7.
37. Pellise M, Castells A, Gines A, Agrelo R, Sole M, Castellvi-Bel S, et al. Detection of lymph node micrometastases by gene promoter hypermethylation in samples obtained by endosonography- guided fine-needle aspiration biopsy. Clin Cancer Res. 2004;10(13):4444–9.
38. Ulivi P, Romagnoli M, Chiadini E, Casoni GL, Capelli L, Gurioli C, et al. Assessment of EGFR and K-ras mutations in fixed and fresh specimens from transesophageal ultrasound-guided fine needle aspiration in non-small cell lung cancer patients. Int J Oncol. 2012;41(1):147–52.
39. Singh P, Camazine B, Jadhav Y, Gupta R, Mukhopadhyay P, Khan A, et al. Endoscopic ultrasound as a first test for diagnosis and staging of lung cancer: a prospective study. Am J Respir Crit Care Med. 2007;175(4):345–54.
40. Bodtger U, Vilmann P, Clementsen P, Galvis E, Bach K, Skov BG. Clinical impact of endoscopic ultrasound-fine needle aspiration of left adrenal masses in established or suspected lung cancer. J Thorac Oncol. 2009;4(12):1485–9.
41. Eloubeidi MA, Black KR, Tamhane A, Eltoum IA, Bryant A, Cerfolio RJ. 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(4):745–53.
42. Annema JT, Veselic M, Versteegh MI, Willems LN, Rabe KF Mediastinal restaging: EUS-FNA offers a new perspective. Lung cancer. 2003;42(3):311–8.
43. Ringbaek TJ, Krasnik M, Clementsen P, Skov BG, Rasmussen EN, Vilmann P Transesophageal endoscopic ultrasound/fine-needle aspiration diagnosis of a malignant adrenal gland in a patient with non-small cell lung cancer and a negative CT scan. Lung cancer. 2005;48(2):247–9.
44. DeWitt J, LeBlanc J, McHenry L, Ciaccia D, Imperiale T, Chappo J, et al. Endoscopic ultrasound-guided fine needle aspiration cytology of solid liver lesions: a large single-center experience. Am J Gastroenterol. 2003;98(9):1976–81.
45. Muehlstaedt M, Bruening R, Diebold J, Mueller A, Helmberger T, Reiser M CT/fluoroscopy-guided transthoracic needle biopsy: sensitivity and complication rate in 98 procedures. J Comput Assist Tomo. 2002;26(2):191–6.
46. Diehl DL, Cheruvattath R, Facktor MA, Go BD Infection after endoscopic ultrasound-guided aspiration of mediastinal cysts. Interact Cardiovasc Thoracic Surg. 2010;10(2):338–40.
47. Wildi SM, Hoda RS, Fickling W, Schmulewitz N, Varadarajulu S, Roberts SS, et al. Diagnosis of benign cysts of the mediastinum: the role and risks of EUS and FNA. Gastrointest Endosc. 2003;58(3):362–8.
48. Ryan AG, Zamvar V, Roberts SA. Iatrogenic candidal infection of a mediastinal foregut cyst following endoscopic ultrasound-guided fine-needle aspiration. Endoscopy. 2002;34(10):838–9.
49. Fazel A, Moezardalan K, Varadarajulu S, Draganov P, Eloubeidi MA The utility and the safety of EUS-guided FNA in the evaluation of duplication cysts. Gastrointest Endosc. 2005;62(4):575–80.
50. Koike E, Yamashita H, Noguchi S, Ohshima A, Watanabe S, Uchino S, et al. Endoscopic ultrasonography in patients with thyroid cancer: its usefulness and limitations for evaluating esophagopharyngeal invasion. Endoscopy. 2002;34(6):457–60.
51. Sawhney MS, Nelson DB, Debol S. The ever-expanding spectrum of GI endoscopy: EUS-guided FNA of thyroid cancer. Gastrointest Endosc. 2007;65(2):319–20; discussion 20.
52. Adler DG, Jacobson BC, Davila RE, Hirota WK, Leighton JA, Qureshi WA, et al. ASGE guideline: complications of EUS. Gastrointest Endosc. 2005;61(1):8–12.
53. von Bartheld MB, van Kralingen KW, Veenendaal RA, Willems LN, Rabe KF, Annema JT. Mediastinal-esophageal fistulae after EUS-FNA of tuberculosis of the mediastinum. Gastrointest Endosc. 2010;71(1):210–2.
54. Puli SR, Graumlich JF, Pamulaparthy SR, Kalva N. Endoscopic transmural necrosectomy for walled-off pancreatic necrosis: a systematic review and meta-analysis. Can J Gastroenterol Hepatol. 2014;28:50–3.

EUS in Pancreatic Tumors

30

Michael Sai Lai Sey, John DeWitt and Mohammad Al-Haddad

Introduction

Examination of the pancreas and other upper abdominal retroperitoneal structures by endoscopic ultrasound (EUS) can be technically challenging to master due to the need to recognize patterns of normal, benign, and pathologic anatomy. However, once these skills are learned, EUS permits the most detailed nonoperative view of the pancreas available. This chapter summarizes the role of EUS for the evaluation of solid pancreatic neoplasms (Table 30.1).

Case

An 81-year-old male with a past history of diabetes, coronary artery disease, congestive heart failure, and end-stage renal disease presented to the hospital with new onset epigastric abdominal pain and unintentional 20-pound weight loss. In the emergency department, he underwent a contrast-enhanced computed tomography (CT) scan of the abdomen, which revealed a 3 cm mass in the body of the pancreas with no obvious vascular invasion or distant metastasis. A staging workup revealed an elevated CA19-9 of 645 U/ml but otherwise normal blood chemistries.

Pancreatic Adenocarcinoma

Detection of Pancreatic Tumors: What Are the Advantages and Limitations of EUS Compared with Radiology?

EUS is the most sensitive nonoperative imaging test for the detection of benign or malignant pancreatic lesions (Table 30.2) [1–8]. Some studies included benign pancreatic disease and ampullary tumors [1, 2, 5], which may have led to a bias of tumor detection in favor of EUS. In studies that compared EUS and CT, the sensitivity of EUS for mass detection was superior to CT [1–8]. EUS is clearly superior to conventional CT [1–3, 6] and transabdominal ultrasound (US) [1–3, 5]. A few comparative studies between EUS and multidetector-row CT (MDCT) for pancreatic tumors have demonstrated the superiority of EUS for tumor detection compared to 4-row CT. Agarwal et al [7] reported an EUS sensitivity of 100% for the diagnosis of cancer compared to 86% for MDCT. Similarly, DeWitt et al [8] reported that the sensitivity of EUS (98%) was statistically superior to MDCT (86%) in a cohort of 80 patients with pancreatic cancer. There are relatively sparse comparative data between EUS and MRI for tumor detection with at least one

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Table 30.1 Exam checklist for evaluation of a suspected pancreatic tumor

Tumor
Note the maximal dimensions, border irregularity, echo-texture, and presence of solid/cystic components in the tumor.
Vascular invasion
Pancreatic head tumor: note the relationship of the tumor with the portal vein, portosplenic confluence, superior mesenteric vessels, hepatic artery, and gastroduodenal artery[a]. Pancreatic body and tail tumor: note the relationship of the tumor with the celiac artery, superior mesenteric artery, portal confluence, hepatic artery, and splenic vessels[a].
EUS-FNA
Start tissue sampling at the most distant metastatic site (e.g., ascites, a distant metastatic lymph node, or a suspicious liver lesion). If these are negative for malignancy, either the suspected tumor or a regional lymph node may be sampled. Note for each biopsy site: numbers of passes, use of suction, whether or not preliminary interpretation of any specimen obtained is available.
Lymph nodes
Examine the following stations for metastatic disease: celiac axis, peripancreatic, porta hepatis, gastrohepatic ligament, aortocaval, and possibly posterior mediastinal stations. Metastatic lymph nodes are usually round, well defined, hypoechoic, and >10 mm in diameter although they may have none of these features. Note the characteristics and distance from the tumor of any suspicious lymph nodes. EUS-FNA should be performed for suspicious distant metastatic lymph nodes.
Liver
Note the presence of any liver metastasis, which are usually hypoechoic, well defined, and possibly multiple. EUS-FNA of any suspicious lesion should be performed when accessible.
Ascites
Examine for a triangular or irregularly shaped anechoic region just outside the duodenal or gastric wall. EUS-guided fluid aspiration for cytology should be performed when accessible.
Staging
All suspected malignant tumors of the pancreas should be assigned a TNM stage based on the most current American Joint Committee on Cancer (AJCC) staging classification.

[a] Notation may be stated as intact hyperechoic tumor/vessel interface, adherent to vessel wall without irregular interface, irregular tumor/vessel interface, tumor invasion, or occlusion of the vessel. For occlusion of the portal or superior mesenteric vein, venous collaterals in the liver hilum, or periduodenal region should be noted. For splenic vein occlusion, collaterals in the splenic hilum, or gastric fundus should be observed

Table 30.2 Sensitivity of EUS compared to other imaging tests for detection of pancreatic masses

Author (yr)	No. patients	EUS	CT	MRI	US
Rosch [1]	102	99	77		67
Rosch [2]	60	98	85		78
Palazzo [3]	49	91	66		64
Muller [4]	33	94	69	83	
Sugiyama [5]	73	96	86		81
Gress [6]	81	100	74		
Agarwal [7]	71	100	86		
Dewitt [8]	80	98	86		

study showing superiority of EUS [4]. Future studies comparing EUS and 3.0 or higher Tesla MRI are needed to define the roles of each for the diagnosis of pancreatic masses.

EUS is particularly useful for the identification of small tumors that have been undetected by other imaging modalities [1, 4, 7, 8]. For tumors ≤30 mm in diameter, EUS was found to have a sensitivity of 93 % compared to 53 % for CT and 67 % for MRI [4]. With thinner slice imaging and precisely timed contrast administration coupled with multiplanar reconstruction (often referred to as pancreas protocol), CT may now be able to identify small pancreatic masses that

previously were undetected by conventional or even single detector dual-phase imaging [8]. We recommend that EUS be performed in all patients with obstructive jaundice or dual pancreatic and bile duct dilations in whom CT or MRI do not definitively identify a pancreatic lesion, both to detect any tumor and to exclude non-neoplastic diseases.

EUS may fail to identify true pancreatic masses in patients with chronic pancreatitis, a diffusely infiltrating carcinoma, a prominent ventral/dorsal split, or a recent episode (<4 weeks) of acute pancreatitis. In a study of 80 patients with clinical suspicion of pancreatic cancer and a normal EUS, Catanzaro et al [9] found that no patient with a normal pancreatic EUS developed cancer during a follow-up period of 24 months. Therefore, a normal pancreas by EUS examination essentially rules out pancreatic cancer although follow-up EUS or other studies should be undertaken in the setting of chronic pancreatitis due to impaired visualization. It is also important to remember that acoustic shadowing caused by an indwelling biliary or pancreatic stent may also impede visualization of a small pancreatic mass.

Due to the ability of EUS to provide high-resolution images, there has been increasing interest in using this technique to screen asymptomatic high-risk cohorts for early cancer detection. Canto et al [10] evaluated an EUS-based screening approach in a prospective cohort of 38 asymptomatic individuals with Peutz–Jeghers syndrome or from kindreds with at least two affected relatives with pancreatic cancer. Five benign and one malignant pancreatic lesions were found by EUS. The diagnostic yield for detecting clinically significant pancreatic neoplasms was 5.3% (2 of 38). Another study found that EUS is superior to MRI among high-risk asymptomatic patients, and may disclose adenocarcinoma and branch duct IPMN during first-time screening in individuals with family history of pancreas cancer or other familial cancer syndromes [11]. A recent consensus statement by the International Cancer of the Pancreas Screening Consortium recommended screening with EUS and/or MRI for the following groups: first-degree relatives (FDRs) of patients with pancreatic cancer from a familial pancreatic cancer kindred with at least two affected FDR, Peutz–Jeghers syndrome, *p16*, or *BRCA2* mutations, and hereditary nonpolyposis colorectal cancer (HNPCC) mutation carriers with ≥1 affected FDR [12]. However, the optimal screening modality, interval, need for FNA, and screening abnormalities of sufficient concern for surgery remain unknown and further studies are required to answer these questions.

Autoimmune pancreatitis (AIP) may mimic pancreatic adenocarcinoma and accurate preoperative detection may avoid unnecessary surgery. The EUS morphology of AIP may include diffuse pancreatic enlargement, a focal mass, focal hypoechoic areas, bile duct wall thickening, or peripancreatic lymphadenopathy (Fig. 30.1) [13]. EUS-FNA may demonstrate a nonspecific plasmacytic predominant chronic inflammatory infiltrate but this finding has variable sensitivity and poor specificity. Diagnosis may be confirmed by EUS-guided core biopsies with staining for IgG4 plasma cells [14, 15].

Imaging-based technologies such as contrast-enhanced ultrasonography (CE-EUS) may be able to differentiate pancreatic adenocarcinoma from pancreatic neuroendocrine tumor (pNET) and inflammatory pseudotumors, which can all present as a hypoechoic mass, whereas ductal adenocarcinomas typically demonstrate hypoenhancement, pNET and inflammatory pseudotumors are hyperenhancing or isoenhancing. A recent meta-analysis of 12 studies involving 1139 patients undergoing CE-EUS reported a pooled sensitivity, specificity, and area under the curve receiver operator characteristic (ROC) of 94%, 89%, and 0.9732, respectively for pancreatic adenocarcinoma [16]. EUS elastography is another emerging technique based on the different stiffness of benign and malignant tissue. In a meta-analysis of 13 studies involving 1044 patients, the pooled sensitivity, specificity, and ROC was 95%, 67%, and 0.90 for elastography differentiating benign from malignant pancreatic masses [17]. However, several limitations to the routine use of these image-based techniques exist and include costs, the lack of both agent availability and expertise with the technique, and need for improved accuracy especially with EUS elastography.

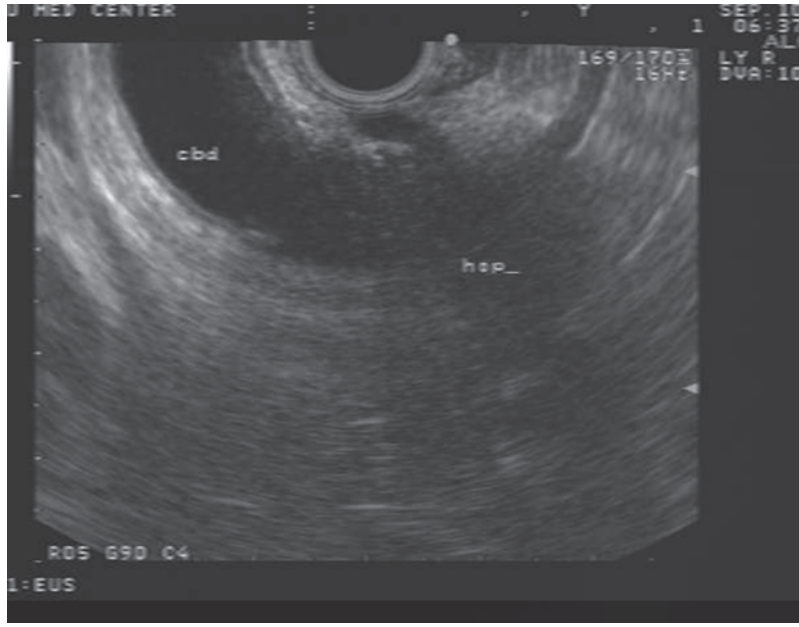

Fig. 30.1 Autoimmune pancreatitis presenting as a poorly defined hypoechoic mass in the head of the pancreas (hop) with marked dilation of the common bile duct up to 1.6 cm

Staging of Pancreatic Adenocarcinoma: What Is the Accuracy and Role of EUS Compared with CT and MRI?

Staging of pancreatic malignancy is done according to the American Joint Committee for Cancer (AJCC) Staging TNM classification, which describes the tumor extension (T), lymph node (N), and distant metastases (M) of tumors, respectively (Table 30.3). Reported accuracies of T staging by EUS range from 62 to 94% (Table 30.4) [2–4, 6, 8, 18–23]. This wide variation may be due to improved detection of distant metastasis or vascular invasion by MDCT, resulting in less operative management for suspected locally advanced or metastatic disease. The exclusion of such patients may have resulted in the decreased T staging accuracy of some recent studies compared to earlier ones. For the last decade, some tertiary referral centers will attempt to achieve negative surgical margins by surgical resection with or without reconstruction of the portal and/or superior mesenteric vein in patients with venous invasion without thrombosis or occlusion. To better reflect this surgical trend, the 2010 staging criteria in the AJCC Manual—7th edition distinguishes potentially resectable (T3) from unresectable (T4) tumors [24]. Currently, only vascular invasion of the celiac or superior mesenteric arteries is classified as T4 cancer.

Despite the changes in T-staging criteria, nodal (N) metastases have uniformly been classified as absent (N0) or present (N1) across all AJCC editions, including the latest 7th edition. The accuracy of EUS for N-staging of pancreatic tumors ranges from 50 to 86% [2–4, 6, 8, 19–21]. Various criteria have been proposed for endosonographic features of metastatic lymph nodes including size greater than 1 cm, hypoechoic echogenicity, distinct margins, and round shape. When all four features are present within a lymph node, there is an 80–100% chance of malignant invasion [25]. However, sensitivity of EUS for malignant lymphadenopathy is often lower, presumably for two reasons. First, most metastatic lymph nodes do not have all four endosonographic features described above. Second, peri-tumoral inflammation and large tumor size may obscure visualization of adenopathy. The specificity of EUS alone for the diagnosis of

Table 30.3 American Joint Committee on Cancer 2010 TNM staging classification for pancreatic cancer [24]

Primary tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis
Distant metastasis (M)
M0: No distant metastasis
M1: Distant metastasis (e.g. distant lymph nodes not peripancreatic and distant organs including liver, lungs, and peritoneum)
AJCC stage groupings
Stage 0: Tis, N0, M0
Stage IA: T1, N0, M0
Stage IB: T2, N0, M0
Stage IIA: T3, N0, M0
Stage IIB: T1, N1, M0 or T2, N1, M0 or T3, N1, M0
Stage III: T4, any N, M0
Stage IV: Any T, any N, M1

Table 30.4 Accuracy of EUS for tumor (T) and nodal (N) staging of pancreatic cancer

Author (yr)	No. enrolled patients	No. patients to surgery with pancreatic cancer	T stage	N stage
Rosch [2]	60	40	–	72
Rosch [20]	46	35	94	80
Palazzo [3]	64	49	82	64
Muller [4]	49	16	82	50
Midwinter [19]	48	23	–	74
Gress [6]	151	75	85	72
Ahmad [18]	NA	89	69	54
Soriano [21]	127	62	62	65
DeWitt [8]	104	53	67	41
Tellez-Avila [22]	50	50	80	–
Shami [23]	127	48	71[a]	

[a] Reported as accuracy for overall stage

metastatic adenopathy in pancreatic cancer is 26–100 % [3, 4, 19, 21], although most report specificities above 70 %. It is presumed that the addition of EUS-FNA of suspicious lymph nodes may increase specificity, although little data support this. For tumors involving the head of the pancreas, malignant lymph nodes are removed en bloc with the surgical specimen and accurate detection of these lymph nodes is not essential. However, since preoperative identification and EUS-FNA of celiac nodes may preclude surgery, meticulous survey of this region is critical during staging of all pancreatic tumors. Mediastinal lymph node metastases occur in a minority of patients, and thus, a brief survey of this region may be helpful during staging of pancreatic lesions.

Although early studies found EUS to be superior to conventional CT for tumor [3, 4] and nodal [2–4] staging of pancreatic cancer, most recent studies have found that the two are equivalent for both tumor [19, 21] and nodal staging [8, 19, 21]. Similarly, early experience reporting on

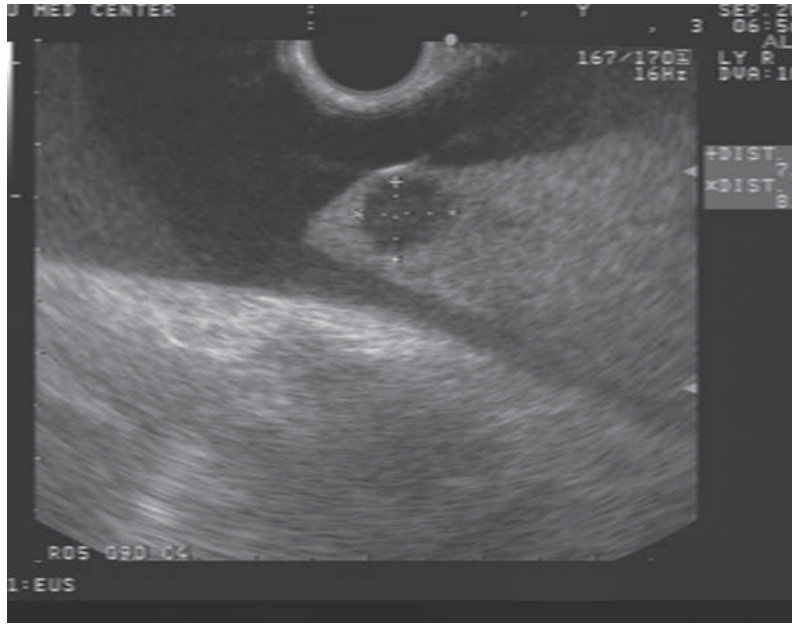

Fig. 30.2 Ascites and a 9-mm oval hypoechoic hepatic nodule in a patient with a large pancreatic mass. FNA of the liver nodule demonstrated metastatic adenocarcinoma of pancreatic origin

the superiority of EUS over MRI [3, 4] has been replaced by more recent data that have found no difference [21, 23, 26]. Clearly, the initial advantage demonstrated by EUS over other imaging modalities for the staging of pancreatic tumors has narrowed considerably. Future studies that compare EUS to MDCT and higher Tesla MRI are needed to confirm these findings and further define the role of EUS for the locoregional staging of pancreatic tumors.

For the detection of non-nodal metastatic cancer, CT and MRI are superior to EUS due to both anatomic limitations of normal upper gastrointestinal anatomy and the limited range of EUS imaging. However, EUS still has an important role in the evaluation of hepatic metastasis in the left or caudate lobe and malignant ascites, both of which may be accessible by EUS-FNA (Fig. 30.2). Identification of liver metastases or malignant ascites by EUS-FNA may preclude surgical resection and is associated with poor survival following diagnosis [27].

Assessment of Vascular Invasion: What Are the Pros and Cons of EUS?

Interpretation of data regarding the accuracy of EUS for vascular invasion is difficult for several reasons. First, there is little histologic correlation with intraoperative findings regarding vascular invasion in most studies. Second, there is no established consensus among endosonographers for the optimal criteria to utilize for the determination of vascular invasion. Consequently, multiple criteria have been proposed by various authors for this indication.

For overall vascular invasion, the accuracy of EUS ranges from 68 to 93% [6, 21, 26, 28]. Sensitivity and specificity of EUS for malignant vascular invasion range from 42 to 91% and 89–100%, respectively [6, 21, 26, 28]. Although some have reported EUS as more accurate [6] than CT for vascular invasion, others report the opposite [21, 26]. Overall accuracy of MRI is reportedly equivalent [21] or superior [26] to EUS.

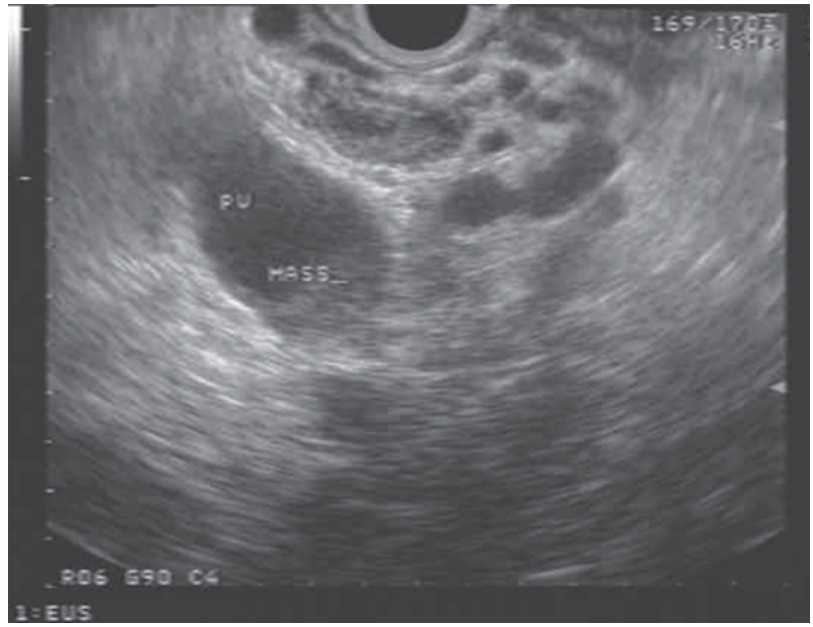

Fig. 30.3 A pancreatic head mass with direct invasion into the portal vein (PV). Multiple vascular collaterals are noted around the duodenal wall due to portal vein obstruction

The sensitivity of EUS for tumor invasion of the portal vein (PV) or PV confluence is 60–100% [2, 5, 19, 20, 29] with most studies demonstrating sensitivities over 80% (Fig. 30.3). The sensitivity of EUS for PV invasion is consistently superior to that of CT [2, 5, 19, 20]. For the superior mesenteric vein (SMV), superior mesenteric artery (SMA), and celiac artery, the sensitivity of EUS is only 17–83% [28], 17% [30], and about 50% [2, 20], respectively. The sensitivity of CT for staging the SMA [19, 30] and celiac artery [2, 20] appears to be better than that of EUS. EUS staging of the superior mesenteric vessels may be difficult due to either the inability to visualize the entire course of the vessel or the obscuring of these vessels by a large tumor in the uncinate or inferior portion of the pancreatic head [29]. This is in contrast to the splenic artery and vein which are generally easily seen and staged well by EUS [20, 29]. Until further conclusive data become available, the assessment of tumor resectability should be done by both EUS and CT (or MRI) rather than by EUS alone.

Several studies have attempted to describe the accuracy of various endosonographic features to assess vascular invasion by malignant pancreatic tumors. Using the criteria 'abnormal contour, loss of hyperechoic interface, and close contact,' Rosch et al [2] found a sensitivity, specificity, and accuracy of 91%, 96%, and 94%, respectively for invasion of the portal vein using these criteria. In blinded videotape review [29], these same authors found that no single criterion (irregular mass–vessel relationship, visualization of tumor in vessel lumen, complete vascular obstruction, collateral vessels) could predict portal venous invasion with a negative predictive value exceeding 35% while positive predictive value was over 80% for only complete vascular obstruction and collateral vessels. The latter two criteria each demonstrated a specificity of 94% for vascular invasion. There exists a tradeoff between various criteria for sensitivity and specificity for vascular invasion. However, criteria with the highest specificity are needed to optimize selection of patients most likely to benefit from surgical exploration. Therefore, the findings of complete vascular obstruction, venous collaterals, and visible tumor within the vessel are the preferred criteria for the assessment of vascular invasion.

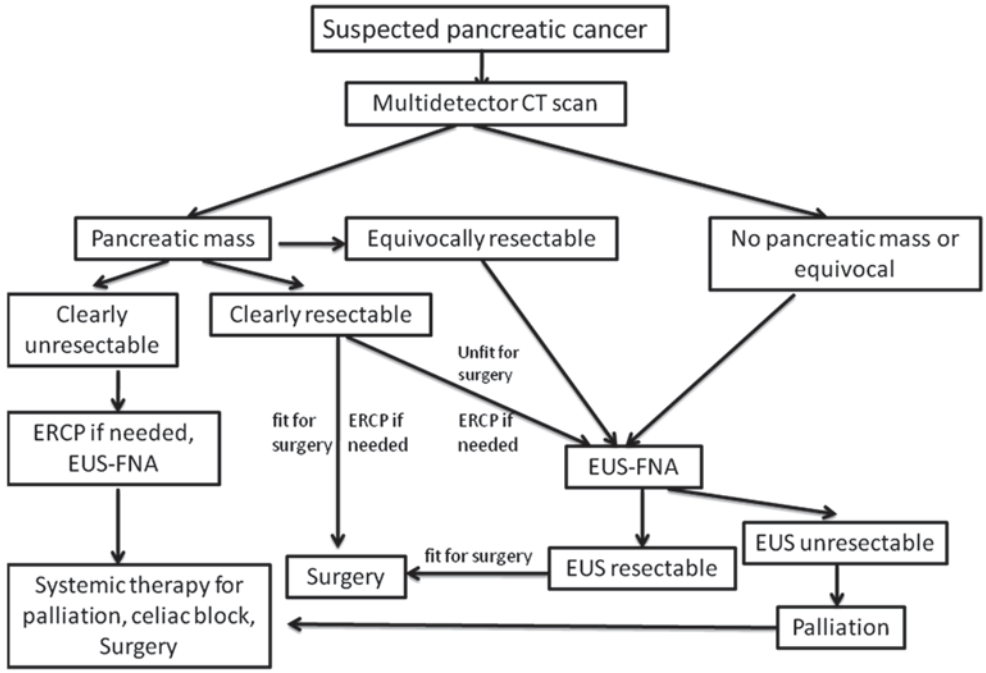

Fig. 30.4 EUS-based management algorithm for suspected pancreatic cancer

Resectability of Pancreatic Tumors: Where Does EUS Fit with MDCT and MRI?

Complete surgical removal of pancreatic cancer with negative histopathologic margins (R0 resection) is the only potentially curative treatment and is an independent predictor of postoperative survival [31]. Therefore, the principle role of preoperative evaluation is to accurately identify patients with resectable disease who may benefit from surgery while avoiding surgery in patients with suspected unresectable disease (Fig. 30.4).

In a pooled analysis of nine studies involving 377 patients, the sensitivity and specificity of EUS for resectability of pancreatic cancer was 69% and 82%, respectively [6, 8, 18, 21, 26, 28, 32–34]. Ranges of reported sensitivities and specificities were 23–91% and 63–100%, respectively. Overall EUS accuracy for tumor resectability was 77%.

Since most studies have reported that EUS is similar to both CT and MRI for the assessment of resectability, some authors have proposed that optimal preoperative imaging of pancreatic cancer requires the use of multiple modalities. Using a decision analysis, Soriano et al [21] found that accuracy for tumor resectability was maximized and costs were minimized when CT or EUS was performed initially followed by the other test in those with potentially resectable neoplasms. Ahmad et al. [18] proposed that although EUS and MRI individually are not sensitive for tumor resectability, their use together may increase positive predictive value of resectability compared to either test alone. When surgery is performed only when MDCT and EUS agree on tumor resectability, DeWitt et al. [8] reported a nonsignificant trend toward improved accuracy of resectability compared to either study alone. However, a study by Bao et al [35] found that MDCT was a better predictor of resectability than EUS, although the performance of EUS improved in patients without biliary stents. From a practical standpoint, the actual role of EUS in staging of pancreatic cancer will depend on its availability, referral patterns, and local expertise.

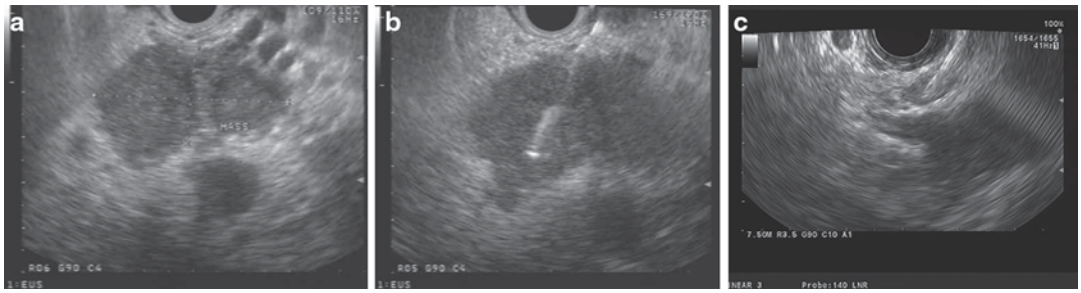

Fig. 30.5 **a** Linear EUS (7.5 MHz) images of a 2.9-cm hypoechoic, irregular pancreatic body mass detected on CT scan. **b** EUS-FNA of a 2.9-cm pancreatic body mass. **c** EUS-guided celiac ganglion neurolysis

Case Continued

The patient was referred for EUS the week following CT. EUS revealed a 2.9-cm hypoechoic heterogenous mass in the body of the pancreas with no evidence of celiac or superior mesenteric artery invasion (Fig. 30.5a–c). Examination of the remainder of the upper gastrointestinal tract was notable for the absence of common bile duct dilation, metastasis in the visualized liver, ascites, or mediastinal adenopathy.

EUS-FNA of Pancreatic Cancer: How Can Diagnostic Yield of EUS-FNA Be Increased?

EUS-guided fine needle aspiration (EUS-FNA) is the currently preferred method to sample pancreatic mass lesions and has largely replaced intraoperative sampling or biopsies under CT or US guidance. EUS-FNA is highly accurate and two recent meta-analyses have reported sensitivity and specificity in the range of 85–89 % and 96–98 %, respectively [36, 37]. However, the diagnostic accuracy of EUS-FNA may be impaired in the setting of chronic pancreatitis. Fritscher-Ravens et al. [38] found that in a series of 207 consecutive patients with focal pancreatic lesions, the sensitivity of EUS-FNA for the diagnosis of malignancy in patients with normal parenchyma (89 %) was superior to those with parenchymal evidence of chronic pancreatitis (54 %). The presence of chronic pancreatitis may impair the visualization of tumors endosonographically or hinder the cytologic interpretation of pancreatic biopsy, thus reducing sensitivity.

At most tertiary referral centers, rapid on-site evaluation (ROSE) with cytopathology review is available to provide immediate feedback to the endosonographer about the quality of EUS-FNA specimens obtained. On-site review was found to correlate highly with the final diagnosis and can improve diagnostic certainty [39]. We recommend that hospital and personnel resources be utilized when feasible to provide ROSE.

Occasionally, ROSE of a suspected pancreatic cancer demonstrates insufficient tissue to confirm malignancy. This may be due to tumor necrosis (particularly with larger tumors), fibrosis, or hypervascularity. Yield may be increased by ‘fanning the lesion’ using different angles of scope deflection in order to sample the peripheral parts of the lesion with more viable tumor [40]. Increasing the number of passes may also overcome this problem, but the additional yield typically plateaus at seven passes and the amount of blood in the aspirate may increase with additional passes [41]. In this situation, avoiding suction and switching to a smaller gauge needle could help limit the amount of blood in the specimen. Finally, EUS-guided core biopsy may be considered in cases when immediate cytology review reveals insufficient material or inconclusive diagnosis although evidence supporting this approach is limited.

The most commonly used commercially available EUS-FNA needles are 19, 22, and 25 gauge needles. Whether the needle gauge affects the diagnostic accuracy of EUS-FNA has been an area of uncertainty until recently. In a meta-analysis of

8 studies involving 1292 patients who underwent EUS-FNA with either a 22- or 25-gauge needle and had surgical histology or at least 6 months follow-up as the reference standard, Madhoun et al [42] reported that the sensitivity of the 25-gauge needle was superior to the 22-gauge needle (93% vs. 85%, $p=0.0003$) although they have comparable specificity (97 and 100%, respectively). In addition, the use of a 25-gauge needle may allow easier access to masses in the uncinate process, which may be difficult to visualize and sample. The echoendoscope should be advanced to the third portion of the duodenum and slowly withdrawn through the duodenum in order to adequately survey the uncinate. When ready to FNA, the scope should be reduced to as straight a position as possible. Part of the uncinate in addition to the head of the pancreas can also be visualized from the antrum occasionally although FNA through this area can be challenging due to the presence of the portal vein and common bile duct.

Major complications following EUS-FNA of solid pancreatic masses occur in 0.5–2.5% of patients [43–45]. Gress et al. [43] reported a 1.2% (2 of 121) risk of pancreatitis and 1% (1/121) risk of severe bleeding following EUS-FNA of solid pancreatic masses. Eloubeidi et al. [44] reported self-limited immediate post-procedure complications in 10/158 (6.3%) patients including hypoxia, abdominal pain, excessive but inconsequential bleeding at the biopsy site, and sore throat. In another prospective study, Al-Haddad et al. reported no delayed complications following EUS-FNA of 127 patients with solid pancreatic masses followed for 30 days [45]. The risk of peritoneal carcinomatosis following EUS-FNA (2.2%) appears to be less than CT-guided FNA (16.3%) [46].

Despite excellent accuracy and a low incidence of major complications, EUS-FNA of pancreatic masses has several limitations. First, an on-site cytopathologist during EUS-FNA is recommended for the assessment of specimen adequacy but is not available at some centers. Second, primary pancreatic lymphomas and well-differentiated ductal adenocarcinomas are often difficult to diagnose by cytology alone. Finally, the low negative predictive value of EUS-FNA does not permit the exclusion of malignancy in negative specimens. To address these limitations, core biopsy devices have been developed to obtain histological tissue samples using a standard linear array echoendoscope. Two such devices include the Quick-Core® and ProCore™ biopsy needles (Cook Medical, Bloomington, Indiana). In a multi-center cohort study of 109 patients with intestinal and extra-intestinal lesions (including 47 pancreatic tumors), the ProCore™ needle provided adequate histology and a correct diagnosis in 96% and 89% of cases, respectively [47]. However, in a recent study comparing the performance of the 22-gauge ProCore™ needle with a standard 22-gauge FNA needle (EchoTip®, Cook Medical, Bloomington, Indiana) in 36 patients with a variety of lesions (17 of pancreatic origin), no difference was found in cytology and cell block parameters, adequacy, and accuracy although the ProCore™ needle was associated with fewer passes (2.94 vs 2.11, $p=0.03$) [48]. Core biopsy needles also have a role in autoimmune pancreatitis [14] and lymphoma [49], where the superiority of core biopsy needles have been confirmed. In addition, core biopsy needles could be used as a rescue technique when on-site FNA results are inconclusive or if this service is not available.

Some investigators have evaluated whether analysis of abnormal genes may increase the diagnostic yield of EUS-FNA of pancreatic masses. A meta-analysis of eight prospective studies involving 931 patients with pancreatic masses undergoing EUS-FNA with k-ras mutation analysis reported a pooled sensitivity and specificity of 77% and 93%, respectively for k-ras [50]. When combined with EUS-FNA alone, the addition of k-ras mutation testing increased sensitivity from 81 to 89% but reduced specificity from 97 to 92%. Among inconclusive EUS-FNA cases, k-ras mutation analysis reduced the false-negative rate by 56% and increased false-positive rate by 11%. Due to the high diagnostic accuracy of standard EUS-FNA, as well as the cost and limited availability of these genetic tests, it appears that the use of genetic testing of EUS-FNA samples should be limited to inconclusive specimens

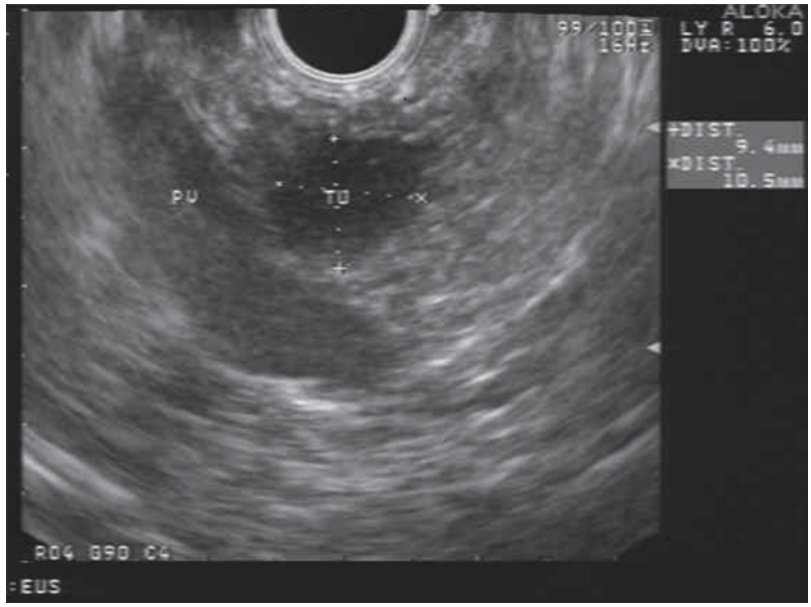

Fig. 30.6 Thick-walled cystic tumor in the head of the pancreas diagnosed on EUS-FNA as a neuroendocrine tumor

and research protocols. Additional assays (such as microRNAs and proteomics) are being evaluated [51]. A recent multicenter prospective study of 228 pancreatic masses sampled by EUS-FNA assessed and validated a 5-microRNA panel to identify pancreatic ductal adenocarcinoma [52]. Diagnosis of malignancy increased from 79% for cytology alone to 91% for cytology combined with microRNA analysis. An additional 22 of 39 samples initially classified by cytology as benign, indeterminate, or nondiagnostic were correctly diagnosed as malignant by microRNA. Further clinical studies are needed to define the role of microRNA in the diagnostic workup of pancreatic tumors.

Case Continued

Fine needle aspiration with a 22 gauge needle of the pancreatic mass was performed (Fig. 30.5b). Preliminary examination by the cytologist revealed an adenocarcinoma, which was confirmed on the final report. The patient was assessed by a pancreatic surgeon and deemed not a surgical candidate due to comorbidities.

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms that represent less than 10% of pancreatic tumors (Fig. 30.6). About one-third of these tumors are classified as functional PNETs (FPNETs) in which excessive hormone secretion produces a distinct clinical syndrome. The two most clinically important FPNETs are gastrinomas and insulinomas. When PNETs do not produce a clinical syndrome, they are classified as nonfunctional (NFPNETs). Due to a lack of characteristic symptoms related to hormone excess, NFPNETs are usually recognized later with larger tumors and nonspecific symptoms such as jaundice, weight loss, abdominal pain, or pancreatitis. Similar to primary ductal adenocarcinoma, surgical resection is the only cure for these tumors. Therefore, a high index of suspicion coupled with a stepwise preoperative evaluation for localization may optimize patient selection for potentially curative surgery.

In a series of studies that compared EUS to other imaging modalities, the sensitivity of EUS for the detection of PNETs was 77–94% [53–56].

EUS appears especially useful for the detection of small PNETs (<2.5 cm) missed by other imaging studies. The sensitivity of transabdominal ultrasound for the detection of PNETs is poor and only between 7 and 29% [53, 54, 56]. Similarly, early studies with CT demonstrated poor sensitivity that was generally less than 30% [53, 54, 56]. However, with ongoing improvements in CT scanners and the development of MDCT, the sensitivity of CT for PNETs has improved. In their study of 217 patients with 231 PNETs, Khashab et al [57] reported an overall sensitivity for MDCT of 84%. Factors associated with reduced sensitivity include small lesions<2 cm in diameter and insulinomas, which had a sensitivity of 54%. Among the 56 patients who had both CT and EUS, the sensitivity of EUS was far greater than CT (91.7% vs. 63.3%, $p=0.0002$). Thus, MDCT is a suitable initial imaging modality for PNET with EUS reserved for cytologic confirmation or the assessment of CT-negative suspected PNET. In addition, EUS is the preferred initial imaging modality for insulinomas due to the low sensitivity of MDCT. Early studies of MRI for PNET had poor sensitivity ranging between 25 and 29% [54, 56]. Newer studies, however, report a sensitivity of 85–100% [58, 59]. Since PNETs are hypervascular tumors, angiography will sometimes demonstrate a 'blush' pattern in the pancreas. Although intuitively promising, the sensitivity of diagnostic angiography for tumor detection is less than 30% [54]. The clinical utility of somatostatin receptor scintigraphy (SRS) for the identification of PNET is variable with sensitivities ranging from 14 to 60% [54, 56, 60].

The use of EUS-FNA permits tissue confirmation of a suspected PNET. In a retrospective study of 30 patients, Ardengh et al. [61] reported a sensitivity, specificity, PPV, NPV, and accuracy for EUS-FNA of 82.6, 85.7, 95, 60, and 83.3%, respectively for tumor diagnosis. In a larger more recent study of 81 patients, EUS-FNA correctly diagnosed a PNET in 73 out of 81 patients with a diagnostic accuracy of 90.1% [62]. For cystic PNET, the use of FNA was studied by Yoon and colleagues in a case series consisting of 19 patients over a 12-year period [63]. The most useful criteria reported was CEA<5 ng/ml, which occurred in all but two patients. The sensitivity of cytology with immunohistochemistry for synaptophysin and/or chromogranin A was 63.2%, which far exceeded most reported sensitivities for mucinous cysts. The authors also suggested that the diagnostic yield of cytology may be improved by aspirating the solid component of the cysts. These studies demonstrate that EUS may not only identify but also accurately sample and diagnose PNETs.

Preoperative EUS-guided injection of India Ink has been demonstrated to aid in intraoperative localization of an insulinoma [64]. This information may aid in appropriate planning of medical or surgical management. Recently, commercial assays allowed genetic markers to be reliably assessed on FNA specimens. A recent study of 29 patients with PNETs followed for an average of 34 months showed that the presence of multiple allelic microsatellite loss was associated with increased PNET recurrence, progression, and mortality although all patients with multiple microsatellite losses had tumors at least 2.5 cm in size [65].

Primary Pancreatic Lymphoma

Primary pancreatic lymphoma (PPL) is rare and accounts for less than 0.5% of pancreatic tumors [66]. They are localized to the pancreas and peripancreatic lymph nodes and by definition do not involve other lymphoid tissue. PPL may present as a large hypoechoic heterogeneous mass with poorly defined borders indistinguishable from pancreatic adenocarcinoma and are typically in the head of the pancreas (Fig. 30.7) [67]. Pancreatic duct dilation and chronic pancreatitis features are usually absent in the pancreas. While EUS and radiographic imaging alone may not confirm the diagnosis, EUS-FNA with flow cytometry is very accurate for PPL. In a case series of 16 patients with PPL, Khashab et al [68] reported a sensitivity and specificity of EUS-FNA with cytology and flow cytometry of 84.6 and 100%, respectively. This contrasts to EUS-FNA with cytology alone, which had sensitivity and specificity less than 30%. This diagnosis should

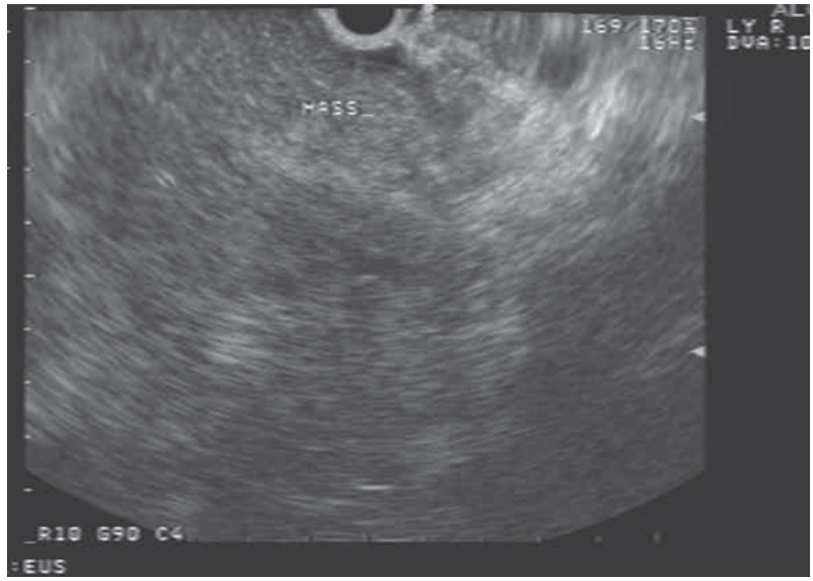

Fig. 30.7 A large, irregular hypoechoic mass in the pancreatic tail diagnosed on FNA as a primary pancreatic lymphoma

be suspected based on clinical appearance, lack of definite malignancy, and abundance of abnormal lymphocytes on ROSE.

Pancreatic Metastases

Isolated pancreatic masses are usually due to focal chronic pancreatitis, benign neoplasms, or primary pancreatic malignancies. Rarely, metastasis to the pancreas from another primary malignancy occurs and has been reported in 2–3 % of pancreatic resections [69]. Accurate identification of isolated pancreatic metastases is clinically important because aggressive surgical resection in selected patients may permit long-term survival. In other patients, however, proper diagnosis may avoid unnecessary surgery and permit triage to more appropriate nonoperative therapy.

EUS features of pancreatic metastases appear different than those observed in cases of primary pancreatic cancer. In seven patients with metastatic pancreatic lesions, Palazzo et al [70] described homogeneous, round well-circumscribed lesions in 15 out of 16 masses observed. Compared to patients with primary cancer ($n=80$), DeWitt et al. [71] found that pancreatic metastases ($n=24$) were more likely to have well-defined rather than irregular margins. In a report of 11 patients with metastatic renal cell carcinoma (RCC) to the pancreas, Bechade et al. [72] found that ten had well-defined borders. Therefore, EUS visualization of a well-defined pancreatic mass in a patient with a history of malignancy should raise suspicion for a metastatic lesion.

EUS-FNA permits an accurate cytologic diagnosis of metastatic lesions to the pancreas. In the largest series to date of 72 masses in 49 patients, El Hajj et al [73] reported metastatic lesions from kidney ($n=21$), lung ($n=8$), skin ($n=6$), colon ($n=4$), breast ($n=3$), small bowel ($n=2$), stomach ($n=2$), liver ($n=1$), ovary ($n=1$), and bladder ($n=1$). All but two of the patients were diagnosed by EUS-FNA. Metastasis to the pancreas may occur many years (especially for RCC) after the diagnosis of the primary tumor. Obtaining a detailed medical history for previous malignancy may raise suspicion for this diagnosis. In patients with a remote history of malignancy, obtaining additional cytological material for cell block and the use of immunocytochemistry may help to confirm the diagnosis of pancreatic metastases and recurrent malignancy.

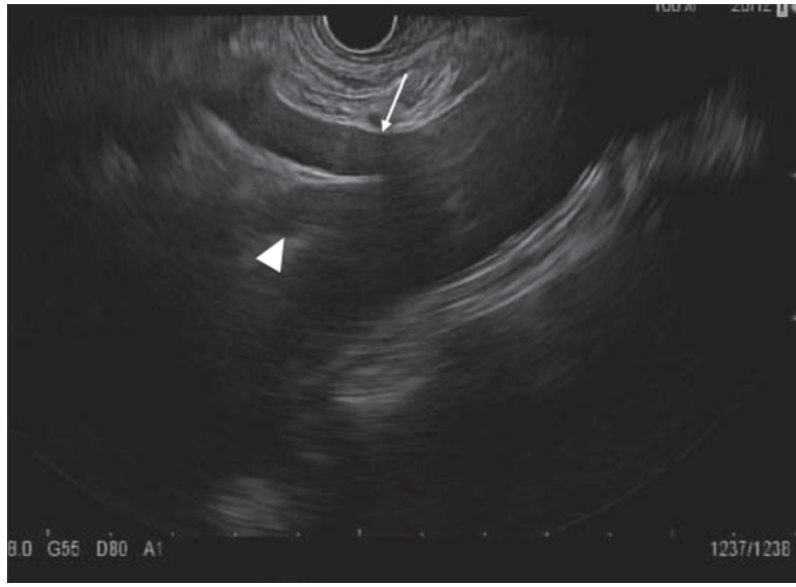

Fig. 30.8 Anatomic landmark for celiac plexus neurolysis demonstrating celiac artery (*arrow*) and superior mesenteric artery (*arrowhead*). (Courtesy of Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

Celiac Plexus Neurolysis (see Chap. 33)

Abdominal pain is a common symptom in patients with pancreatic cancer and may be debilitating. Effective palliation for unresectable cases often require high doses of narcotics which may lead to significant side effects, including sedation, delirium, nausea, and constipation. By disrupting nerve transmission through the celiac axis, celiac plexus neurolysis (CPN) with bupivacaine and alcohol provides an effective adjunct to narcotic analgesia in unresectable pancreatic cancer (Video 30.1). EUS is well suited for the identification of the celiac plexus due to the close approximation of the gastric wall with the celiac takeoff (Fig. 30.8).

In a meta-analysis of randomized controlled trials of EUS-guided CPN for pancreatic cancer in 283 patients, Puli et al [74] reported 80% of patients experienced at least partial pain relief. Although the authors could not determine whether CPN reduced narcotic requirements due to heterogenous reporting in the included studies, an earlier meta-analysis by Yan et al [75] reported a significant reduction in narcotic use with non-EUS guided CPN. Weighted mean difference in morphine-equivalent dose between CPN and the control group was −39.99, −53.69, and −80.45 mg at 2, 4, and 8 weeks, respectively. More importantly, this translated into a reduction in the prevalence of constipation in the CPN group (RR 0.67, 95% CI 0.49–0.91, $p=0.01$). Over the past decade, advancements in echo-endoscope designs have permitted the accurate identification of celiac ganglia and interest has developed in direct ganglia injection to improve the efficacy of CPN. In a recent randomized controlled study, EUS-guided celiac ganglion neurolysis was more effective than EUS-guided celiac plexus neurolysis in relieving pain (73.5% vs 45.5%, respectively; $p=0.026$) [76].

EUS-guided CPN is a safe procedure and complications are uncommon [77]. Diarrhea (4–15%) and orthostasis (1%) due to disruption of the autonomic nervous system are usually mild and transient. A paradoxical increase in pain may occur in up to 9% of cases but generally resolves over several days. Serious complications including paralysis due to anterior spinal cord infarction and death from necrotic gastric perforation or celiac artery thrombosis have been reported but are exceedingly rare [78–80].

Case Concluded

Despite narcotic analgesia, the patient continued to experience abdominal pain and was referred back for EUS-guided celiac plexus neurolysis. This was performed with 20 ml of 0.75 % bupivacaine and 10 ml of 98 % alcohol injected directly into the visualized ganglia (Fig. 30.5c). The patient experienced a reduction in abdominal pain and was referred to medical oncology.

Future EUS-Guided Therapeutics

Image-guided radiotherapy (IGRT) for pancreatic cancer is an emerging technique to deliver highly focused radiation to malignant neoplasms while avoiding normal tissue. Fiducials are inert radiologic markers placed within the neoplasm to guide stereotactic radiotherapy (see Chap. 33). Although traditionally placed intra-operatively or percutaneously under US/CT guidance, EUS provides an alternative that is potentially safer due to direct visualization during insertion [77]. The feasibility and safety of EUS-guided fiducial placement for pancreatic cancer with a 19-gauge needle was recently demonstrated in a cohort of 51 patients with locally advanced or recurrent pancreatic cancer [81]. Successful placement was accomplished in 46/51 patients (90 %), and only one complication occurred (mild pancreatitis after a combined fiducial insertion and CPN procedure).

Instead of placing an inert radiologic marker, brachytherapy involves the insertion of a radioactive seed directly into the pancreatic tumor for local control. In the largest study to date, Jin et al [82] placed a median of 10 iodine-125 seeds in 22 patients with unresectable pancreatic cancer. Dose calculation was based on tumor volume from reconstructed three-dimensional CT images. Although placement under EUS guidance was successful in all patients with no complications, only three achieved partial remission at 4 weeks and no improvement in survival was demonstrated. However, pain was significantly reduced 1 and 4 weeks after the procedure. The same group subsequently used iodine-125 as a neurolytic agent in 23 patients undergoing EUS-guided CPN for unresectable pancreatic cancer [83]. At week 2, 82 % of patients had a reduction in pain score on a visual analog scale, and mean narcotic consumption had decreased. This effect lasted until the study conclusion at 5 months follow-up when only two patients were still alive. The authors postulated that iodine-125 may be a superior neurolytic agent compared to ethanol due to its longer half-life and deeper tissue penetration, although this has yet to be confirmed in a controlled clinical trial.

Recently, interest has developed in the use of interstitial chemotherapy for pancreatic cancer. Through the use of a biological polymer linked to a cytotoxic agent, EUS-guided fine needle injection can deliver potent chemotherapy directly into the pancreas. Initial animal models have already demonstrated the feasibility of this delivery system for paclitaxel, 5-fluorouracil, and irinotecan [84–86]. Although larger human studies are still needed, EUS-guided interstitial chemotherapy promises to be an exciting development in endoscopic treatment of pancreatic cancer.

Key Points

- EUS is the most sensitive imaging modality for the detection of pancreatic masses. It is particularly useful for identification of tumors undetected by other tests such as CT.
- EUS is superior to CT for detecting tumor invasion of the portal vein or confluence. CT appears superior to EUS for determining invasion of the superior mesenteric vessels and major arteries of the upper abdomen.
- Due to anatomical and equipment limitations, CT and MRI are superior to EUS for identifying metastatic cancer. EUS-FNA of liver lesions, ascites, or celiac adenopathy may avert surgical exploration if metastasis is confirmed.
- EUS-FNA of pancreatic tumors has a sensitivity of 85 % with a specificity approaching 100 %. The presence of on-site cytopathology interpretation helps maximize diagnostic yield and avoid repeat examinations for indeterminate cytology results.

- Most studies demonstrate that EUS, CT, and MRI are equivalent for determining surgical resectability of pancreatic cancer. However, EUS is usually used preoperatively to provide histological confirmation of the diagnosis and evaluate for vascular invasion and metastases in combination with CT.
- EUS is the most accurate test for the detection of pancreatic neuroendocrine tumors (PNETs), particularly tumors smaller than 2.0 cm in diameter. Optimal workup of suspected PNETs should incorporate EUS, EUS-FNA with immunohistochemistry, and somatostatin receptor scintigraphy.
- EUS-guided CPN is a safe and effective treatment for pain in unresectable pancreatic cancer.

Video Caption

Video 30.1 This video demonstrates the technique of EUS-guided celiac ganglia neurolysis in a patient with chronic pain from metastatic pancreatic cancer. The EUS shows the celiac artery taking off from the aorta with an oval celiac ganglia appearing hypoechoic and mildly heterogeneous. This is labelled during EUS. Then the 22-gauge needle is advanced into the ganglia followed by aspiration to confirm the lack of blood return and injection of a combination of bupivacaine and alcohol visibly emerging from the tip of the needle

References

1. Rosch T, Lorenz R, Braig C, Feuerbach S, Siewert JR, Schusdziarra V, et al. Endoscopic ultrasound in pancreatic tumor diagnosis. Gastrointest Endosc. 1991;37(3):347–52.
2. Rosch T, Braig C, Gain T, Feuerbach S, Siewert JR, Schusdziarra V, et al. Staging of pancreatic and ampullary carcinoma by endoscopic ultrasonography. Comparison with conventional sonography, computed tomography, and angiography. Gastroenterology. 1992;102(1):188–99.
3. Palazzo L, Roseau G, Gayet B, Vilgrain V, Belghiti J, Fekete F, et al. Endoscopic ultrasonography in the diagnosis and staging of pancreatic adenocarcinoma. Results of a prospective study with comparison to ultrasonography and CT scan. Endoscopy. 1993;25(2):143–50.
4. Muller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. Radiology. 1994;190(3):745–51.
5. Sugiyama M, Hagi H, Atomi Y, Saito M. Diagnosis of portal venous invasion by pancreatobiliary carcinoma: value of endoscopic ultrasonography. Abdom Imaging. 1997;22(4):434–8.
6. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Cummings O, Kopecky K, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. Gastrointest Endosc. 1999;50(6):786–91.
7. Agarwal B, Abu-Hamda E, Molke KL, Correa AM, Ho L. Endoscopic ultrasound-guided fine needle aspiration and multidetector spiral CT in the diagnosis of pancreatic cancer. Am J Gastroenterol. 2004;99(5):844–50.
8. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004;141(10):753–63.
9. Catanzaro A, Richardson S, Veloso H, Isenberg GA, Wong RC, Sivak MV, Jr., et al. Long-term follow-up of patients with clinically indeterminate suspicion of pancreatic cancer and normal EUS. Gastrointest Endosc. 2003;58(6):836–40.
10. Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol. 2004;2(7):606–21.
11. Poley JW, Kluijt I, Gouma DJ, Harinck F, Wagner A, Aalfs C, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. Am J Gastroenterol. 2009;104(9):2175–81.
12. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013 Mar;62(3):339–47.
13. Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. Gastrointest Endosc. 2004;60(6):927–36.
14. Levy MJ, Reddy RP, Wiersema MJ, Smyrk TC, Clain JE, Harewood GC, et al. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. Gastrointest Endosc. 2005;61(3):467–72.
15. Iwashita T, Yasuda I, Doi S, Ando N, Nakashima M, Adachi S, et al. Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. Clin Gastroenterol Hepatol. 2012;10(3):316–22.
16. Gong TT, Hu DM, Zhu Q. Contrast-enhanced EUS for differential diagnosis of pancreatic mass lesions: a meta-analysis. Gastrointest Endosc. 2012;76(2):301–9.
17. Mei M, Ni J, Liu D, Jin P, Sun L. EUS elastography for diagnosis of solid pancreatic masses: a meta-analysis.

Gastrointest Endosc. 2013;77(4):578–89.
18. Ahmad NA, Lewis JD, Siegelman ES, Rosato EF, Ginsberg GG, Kochman ML. Role of endoscopic ultrasound and magnetic resonance imaging in the preoperative staging of pancreatic adenocarcinoma. Am J Gastroenterol. 2000;95(8):1926–31.
19. Midwinter MJ, Beveridge CJ, Wilsdon JB, Bennett MK, Baudouin CJ, Charnley RM. Correlation between spiral computed tomography, endoscopic ultrasonography and findings at operation in pancreatic and ampullary tumours. Br J Surg. 1999;86(2):189–93.
20. Rosch T, Dittler HJ, Lorenz R, Braig C, Gain T, Feuerbach S, et al. [The endosonographic staging of pancreatic carcinoma]. Dtsch Med Wochenschr. 1992;117(15):563–9.
21. Soriano A, Castells A, Ayuso C, Ayuso JR, de Caralt MT, Gines MA, et al. Preoperative staging and tumor resectability assessment of pancreatic cancer: prospective study comparing endoscopic ultrasonography, helical computed tomography, magnetic resonance imaging, and angiography. Am J Gastroenterol. 2004;99(3):492–501.
22. Tellez-Avila FI, Chavez-Tapia NC, Lopez-Arce G, Franco-Guzman AM, Sosa-Lozano LA, Alfaro-Lara R, et al. Vascular invasion in pancreatic cancer: predictive values for endoscopic ultrasound and computed tomography imaging. Pancreas. 2012;41(4):636–8.
23. Shami VM, Mahajan A, Loch MM, Stella AC, Northup PG, White GE, et al. Comparison between endoscopic ultrasound and magnetic resonance imaging for the staging of pancreatic cancer. Pancreas. 2011;40(4):567–70.
24. Edge SB BD, Compton CC, et al. AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 7th edn. New York: Springer; 2010.
25. Catalano MF, Sivak MV, Jr., Rice T, Gragg LA, Van Dam J. Endosonographic features predictive of lymph node metastasis. Gastrointest Endosc. 1994;40(4):442–6.
26. Ramsay D, Marshall M, Song S, Zimmerman M, Edmunds S, Yusoff I, et al. Identification and staging of pancreatic tumours using computed tomography, endoscopic ultrasound and mangafodipir trisodium-enhanced magnetic resonance imaging. Australas Radiol. 2004;48(2):154–61.
27. DeWitt J, Yu M, Al-Haddad MA, Sherman S, McHenry L, Leblanc JK. Survival in patients with pancreatic cancer after the diagnosis of malignant ascites or liver metastases by EUS-FNA. Gastrointest Endosc. 2010;71(2):260–5.
28. Buscail L, Pages P, Berthelemy P, Fourtanier G, Frexinos J, Escourrou J. Role of EUS in the management of pancreatic and ampullary carcinoma: a prospective study assessing resectability and prognosis. Gastrointest Endosc. 1999;50(1):34–40.
29. Rosch T, Dittler HJ, Strobel K, Meining A, Schusdziarra V, Lorenz R, et al. Endoscopic ultrasound criteria for vascular invasion in the staging of cancer of the head of the pancreas: a blind reevaluation of videotapes. Gastrointest Endosc. 2000;52(4):469–77.
30. Mertz HR, Sechopoulos P, Delbeke D, Leach SD. EUS, PET, and CT scanning for evaluation of pancreatic adenocarcinoma. Gastrointest Endosc. 2000;52(3):367–71.
31. Chang DK, Johns AL, Merrett ND, Gill AJ, Colvin EK, Scarlett CJ, et al. Margin clearance and outcome in resected pancreatic cancer. J Clin Oncol. 2009;27(17):2855–62.
32. Howard TJ, Chin AC, Streib EW, Kopecky KK, Wiebke EA. Value of helical computed tomography, angiography, and endoscopic ultrasound in determining resectability of periampullary carcinoma. Am J Surg. 1997;174(3):237–41.
33. Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, et al. Pancreatic tumors: comparison of dual-phase helical CT and endoscopic sonography. AJR Am J Roentgenol. 1998;170(5):1315–22.
34. Tierney WM, Francis IR, Eckhauser F, Elta G, Nostrant TT, Scheiman JM. The accuracy of EUS and helical CT in the assessment of vascular invasion by peripapillary malignancy. Gastrointest Endosc. 2001;53(2):182–8.
35. Bao PQ, Johnson JC, Lindsey EH, Schwartz DA, Arildsen RC, Grzeszczak E, et al. Endoscopic ultrasound and computed tomography predictors of pancreatic cancer resectability. J Gastrointest Surg. 2008;12(1):10–6 (discussion 6).
36. Hewitt MJ, McPhail MJ, Possamai L, Dhar A, Vlavianos P, Monahan KJ. EUS-guided FNA for diagnosis of solid pancreatic neoplasms: a meta-analysis. Gastrointest Endosc. 2012;75(2):319–31.
37. Chen G, Liu S, Zhao Y, Dai M, Zhang T. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for pancreatic cancer: a meta-analysis. Pancreatology (official journal of the International Association of Pancreatology (IAP) [et al]). 2013;13(3):298–304.
38. Fritscher-Ravens A, Brand L, Knofel WT, Bobrowski C, Topalidis T, Thonke F, 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(11):2768–75.
39. Hebert-Magee S, Bae S, Varadarajulu S, Ramesh J, Frost AR, Eloubeidi MA, 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(3):159–71.
40. Bang JY, Magee SH, Ramesh J, Trevino JM, Varadarajulu S. Randomized trial comparing fanning with standard technique for endoscopic ultrasound-guided fine-needle aspiration of solid pancreatic mass lesions. Endoscopy. 2013;45(6):445–50.
41. LeBlanc JK, Ciaccia D, Al-Assi MT, McGrath K, Imperiale T, Tao LC, et al. Optimal number of EUS-guided fine needle passes needed to obtain a correct diagnosis. Gastrointest Endosc. 2004;59(4):475–81.
42. Madhoun MF, Wani SB, Rastogi A, Early D, Gaddam S, Tierney WM, et al. The diagnostic accuracy of

22-gauge and 25-gauge needles in endoscopic ultrasound-guided fine needle aspiration of solid pancreatic lesions: a meta-analysis. Endoscopy. 2013;45(2):86–92.
43. Gress FG, Hawes RH, Savides TJ, Ikenberry SO, Lehman GA. Endoscopic ultrasound-guided fine-needle aspiration biopsy using linear array and radial scanning endosonography. Gastrointest Endosc. 1997;45(3):243–50.
44. Eloubeidi MA, Chen VK, Eltoum IA, Jhala D, Chhieng DC, Jhala N, et al. Endoscopic ultrasound-guided fine needle aspiration biopsy of patients with suspected pancreatic cancer: diagnostic accuracy and acute and 30-day complications. Am J Gastroenterol. 2003;98(12):2663–8.
45. Al-Haddad M, Wallace MB, Woodward TA, Gross SA, Hodgens CM, Toton RD, et al. The safety of fine-needle aspiration guided by endoscopic ultrasound: a prospective study. Endoscopy. 2008;40(3):204–8.
46. Micames C, Jowell PS, White R, Paulson E, Nelson R, Morse M, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc. 2003;58(5):690–5.
47. Iglesias-Garcia J, Poley JW, Larghi A, Giovannini M, Petrone MC, Abdulkader I, et al. Feasibility and yield of a new EUS histology needle: results from a multicenter, pooled, cohort study. Gastrointest Endosc. 2011;73(6):1189–96.
48. Witt BL, Adler DG, Hilden K, Layfield LJ. A comparative needle study: EUS-FNA procedures using the HD ProCore and EchoTip 22-gauge needle types. Diagn Cytopathol. 2013;41(12):1069–74.
49. Eloubeidi MA, Mehra M, Bean SM. EUS-guided 19-gauge trucut needle biopsy for diagnosis of lymphoma missed by EUS-guided FNA. Gastrointest Endosc. 2007;65(6):937–9.
50. Fuccio L, Hassan C, Laterza L, Correale L, Pagano N, Bocus P, et al. The role of K-ras gene mutation analysis in EUS-guided FNA cytology specimens for the differential diagnosis of pancreatic solid masses: a meta-analysis of prospective studies. Gastrointest Endosc. 2013;78(4):596–608.
51. Goggins M. Identifying molecular markers for the early detection of pancreatic neoplasia. Semin Oncol. 2007;34(4):303–10.
52. Brand RE, Adai AT, Centeno BA, Lee LS, Rateb G, Vignesh S, et al. A MicroRNA-based test improves endoscopic ultrasound-guided cytologic diagnosis of pancreatic cancer. Clin Gastroenterol Hepatol. 2014;12(1D):1717–23.
53. Palazzo L, Roseau G, Chaussade S, Salmeron M, Gaudric M, Paolaggi JA. [Pancreatic endocrine tumors: contribution of ultrasound endoscopy in the diagnosis of localization]. Ann Chir. 1993;47(5):419–24.
54. De Angelis C Carucci P Repici A Rizzetto M. Endosonography in decision making and management of gastrointestinal endocrine tumors. Eur J Ultrasound. 1999;10(2–3):139–50.
55. Gouya H, Vignaux O, Augui J, Dousset B, Palazzo L, Louvel A, et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. AJR Am J Roentgenol. 2003;181(4):987–92.
56. Zimmer T, Stolzel U, Bader M, Koppenhagen K, Hamm B, Buhr H, et al. Endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localisation of insulinomas and gastrinomas. Gut. 1996;39(4):562–8.
57. Khashab MA, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, et al. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. Gastrointest Endosc. 2011;73(4):691–6.
58. Semelka RC, Custodio CM, Cem Balci N, Woosley JT. Neuroendocrine tumors of the pancreas: spectrum of appearances on MRI. J Magn Reson Imaging. 2000;11(2):141–8.
59. Van Nieuwenhove Y Vandaele S Op de Beeck B Delvaux G. Neuroendocrine tumors of the pancreas. Surg Endosc. 2003;17(10):1658–62.
60. Proye C, Malvaux P, Pattou F, Filoche B, Godchaux JM, Maunoury V, et al. Noninvasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy. Surgery. 1998;124(6):1134–43 (discussion 43–4).
61. Ardengh JC, de Paulo GA, Ferrari AP. EUS-guided FNA in the diagnosis of pancreatic neuroendocrine tumors before surgery. Gastrointest Endosc. 2004;60(3):378–84.
62. Atiq M, Bhutani MS, Bektas M, Lee JE, Gong Y, Tamm EP, et al. EUS-FNA for pancreatic neuroendocrine tumors: a tertiary cancer center experience. Dig Dis Sci. 2012;57(3):791–800.
63. Yoon WJ, Daglilar ES, Pitman MB, Brugge WR. Cystic pancreatic neuroendocrine tumors: endoscopic ultrasound and fine-needle aspiration characteristics. Endoscopy. 2013;45(3):189–94.
64. Zografos GN, Stathopoulou A, Mitropapas G, Karoubalis J, Kontogeorgos G, Kaltsas G, et al. Preoperative imaging and localization of small sized insulinoma with EUS-guided fine needle tattooing: a case report. Hormones (Athens). 2005;4(2):111–6.
65. Fasanella KE, McGrath KM, Sanders M, Brody D, Domsic R, Khalid A. Pancreatic endocrine tumor EUS-guided FNA DNA microsatellite loss and mortality. Gastrointest Endosc. 2009;69(6):1074–80.
66. Nayer H, Weir EG, Sheth S, Ali SZ. Primary pancreatic lymphomas: a cytopathologic analysis of a rare malignancy. Cancer. 2004;102(5):315–21.
67. Ramesh J, Hebert-Magee S, Kim H, Trevino J, Varadarajulu S. Frequency of occurrence and characteristics of primary pancreatic lymphoma during endoscopic ultrasound guided fine needle aspiration: a retrospective study. Dig Liver Dis. 2014;46(5):470–3.
68. Khashab M, Mokadem M, DeWitt J, Emerson R, Sherman S, LeBlanc J, et al. Endoscopic ultrasound-guided fine-needle aspiration with or without flow cytometry for the diagnosis of primary pancreatic lymphoma - a

case series. Endoscopy. 2010;42(3):228–31.
69. Roland CF, van Heerden JA. Nonpancreatic primary tumors with metastasis to the pancreas. Surg Gynecol Obstet. 1989;168(4):345–7.
70. Palazzo L, Borotto E, Cellier C, Roseau G, Chaussade S, Couturier D, et al. Endosonographic features of pancreatic metastases. Gastrointest Endosc. 1996;44(4):433–6.
71. DeWitt J, Jowell P, Leblanc J, McHenry L, McGreevy K, Cramer H, et al. EUS-guided FNA of pancreatic metastases: a multicenter experience. Gastrointest Endosc. 2005;61(6):689–96.
72. Bechade D, Palazzo L, Fabre M, Algayres JP. EUS-guided FNA of pancreatic metastasis from renal cell carcinoma. Gastrointest Endosc. 2003;58(5):784–8.
73. El H, II, Leblanc JK, Sherman S, Al-Haddad MA, Cote GA, McHenry L, et al. Endoscopic ultrasound-guided biopsy of pancreatic metastases: a large single-center experience. Pancreas. 2013;42(3):524–30.
74. Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. EUS-guided celiac plexus neurolysis for pain due to chronic pancreatitis or pancreatic cancer pain: a meta-analysis and systematic review. Dig Dis Sci. [Meta-Analysis Review]. 2009;54(11):2330–7.
75. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. [Meta-Analysis Research Support, Non-U.S. Gov't Review]. 2007;102(2):430–8.
76. Doi S, Yasuda I, Kawakami H, Hayashi T, Hisai H, Irisawa A, et al. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. Endoscopy. 2013;45(5):362–9.
77. Cho CM, Dewitt J, Al-Haddad M. Echo-endoscopy: new therapeutic frontiers. Minerva gastroenterologica e dietologica. 2011;57(2):139–58.
78. 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(1):151–2.
79. Fujii L, Clain JE, Morris JM, Levy MJ. Anterior spinal cord infarction with permanent paralysis following endoscopic ultrasound celiac plexus neurolysis. Endoscopy. 2012;44(Suppl 2 UCTN):E265–6.
80. Gimeno-Garcia AZ, Elwassief A, Paquin SC, Sahai AV. Fatal complication after endoscopic ultrasound-guided celiac plexus neurolysis. Endoscopy. 2012;44(Suppl 2 UCTN):E267.
81. Sanders MK, Moser AJ, Khalid A, Fasanella KE, Zeh HJ, Burton S, et al. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. Gastrointest Endosc. 2010;71(7):1178–84.
82. Jin Z, Du Y, Li Z, Jiang Y, Chen J, Liu Y. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. Endoscopy. 2008;40(4):314–20.
83. Wang KX, Jin ZD, Du YQ, Zhan XB, Zou DW, Liu Y, et al. EUS-guided celiac ganglion irradiation with iodine-125 seeds for pain control in pancreatic carcinoma: a prospective pilot study. Gastrointest Endosc. 2012;76(5):945–52.
84. 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.
85. Sun S, Wang S, Ge N, Lei T, Lu Q, Zhou Z, et al. Endoscopic ultrasound-guided interstitial chemotherapy in the pancreas: results in a canine model. Endoscopy. 2007;39(6):530–4.
86. Karaca C, Cizginer S, Konuk Y, Kambadakone A, Turner BG, Mino-Kenudson M, et al. Feasibility of EUS-guided injection of irinotecan-loaded microspheres into the swine pancreas. Gastrointest Endosc. 2011;73(3):603–6.

EUS in Pancreatic Cysts

31

Linda S. Lee

Introduction

Pancreatic cysts increasingly challenge the clinician with their frequent detection on imaging, even in up to 20% of magnetic resonance imaging (MRI) studies and 3% of computed tomography (CT) [1, 2]. The key issue with pancreatic cysts, unlike most renal and hepatic cysts, is that a significant proportion of them have malignant potential. Thus, determining which cysts are premalignant or malignant is essential when approaching pancreatic cysts. This malignant potential informs the need to accurately classify pancreatic cysts.

Pancreatic cysts may be broadly categorized into nonneoplastic cysts, cystic neoplasms, and necrotic degeneration of solid tumors. Nonneoplastic epithelial cysts account for 6.3% of all resected cysts and were all incorrectly diagnosed preoperatively by endoscopic ultrasound (EUS) cyst fluid analysis in one study [3]. Cystic neoplasms account for two-thirds of all pancreatic cysts, [4] and include mucinous lesions (mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN)), and nonmucinous cysts (serous cystadenoma (SCA), solid pseudopapillary neoplasm (SPEN); Table 31.1). Mucinous cysts and SPENs have malignant potential. Nearly 90% of cystic neoplasms are MCN, IPMN, or SCA [5].

Diagnosis of pancreatic cysts relies on imaging and analysis of cyst fluid obtained during EUS-guided fine-needle aspiration (FNA). If the cyst is mucinous, then it is important to determine the type of mucinous cyst (MCN, branch duct (BD)-IPMN, mixed or combined type IPMN, or main duct (MD)-IPMN) because the malignant potential, and therefore the management, varies with the different mucinous cysts. Some premalignant lesions may require surgical resection, while others that are benign or indolent can be observed.

Case Study

A 45-year-old female had gallstone pancreatitis and underwent laparoscopic cholecystectomy. A 2.5-cm cyst was visualized in the pancreatic tail, which was presumed to be a pseudocyst. This cyst was followed with serial abdominal CT scan and 4 years later was noted to be larger at 3 cm. What is the differential diagnosis and what diagnostic study should be performed next?

What is the Differential Diagnosis of Pancreatic Cysts?

Pseudocysts

Pseudocysts are sequelae of acute interstitial pancreatitis and require at least 4 weeks to form. A

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Table 31.1 Types of pancreatic cysts

Benign (no malignant potential)	Premalignant or malignant
Serous cystadenoma[a]	Intraductal papillary mucinous neoplasm
Pseudocyst	Mucinous cystic neoplasm
Lymphoepithelial cyst	Solid pseudopapillary neoplasm
Retention cyst	Cystic neuroendocrine tumor
Mucinous nonneoplastic cyst	Cystic degeneration of solid tumors
Lymphangioma	Metastatic cyst
Cavernous hemangioma	

[a] Very rarely malignant

thin capsule of nonepithelialized granulation or fibrotic tissue forms a wall around amylase-rich fluid. Symptoms, when present, typically consist of abdominal pain and early satiety. Gastric outlet and/or biliary obstruction may occur as well. Usually pseudocysts are readily diagnosed by the patient's history of acute or chronic pancreatitis. Without a clear history of acute or chronic pancreatitis, differentiating pseudocysts from MCN and even SCA and BD-IPMN may be difficult by imaging alone. On abdominal CT, pseudocysts typically appear round with a thin or thick wall. Calcifications and communication with the pancreatic duct may be present.

Serous Cystadenoma

Serous cystadenomas are benign pancreatic cystic neoplasms, which very rarely become malignant with a couple of larger studies describing about a 1% rate of malignancy [6, 7]. SCAs account for over 30% of pancreatic cystic neoplasms, typically occur in women over the age of 60, and are defined on pathology by glycogen containing cuboidal epithelial cells (Fig. 31.1) [8]. They arise anywhere throughout the pancreas. When symptomatic, SCAs usually present with nonspecific symptoms, mainly abdominal pain, due to compression of adjacent organs by the cyst. Symptoms occur more commonly in larger cysts > 4 cm (77%) compared to cysts < 4 cm (22%).

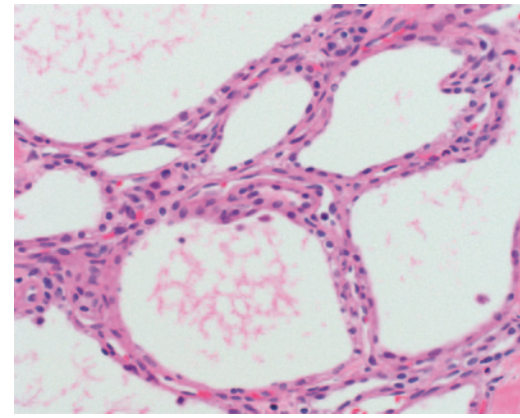

Fig. 31.1 Histology of serous cystadenoma. Cysts are lined by bland cuboidal cells with clear or palely eosinophilic cytoplasm

Radiologically, SCAs may be classified into several subtypes. Over half SCAs are microcystic defined as each cyst compartment less than 1 cm while the rest are macrocystic (composed of cysts larger than 1 cm), mixed, or rarely solid (Fig. 31.2) [6]. A Japanese study of 172 SCA diagnosed by resection and typical imaging findings noted highest diagnostic accuracy for microcystic SCA (85%) with significantly lower diagnostic rates (17–50%) for macrocystic, mixed, and solid types. CT is only approximately 23% accurate for SCA while diffusion-weighted MRI has demonstrated 100% sensitivity and 97% speci-

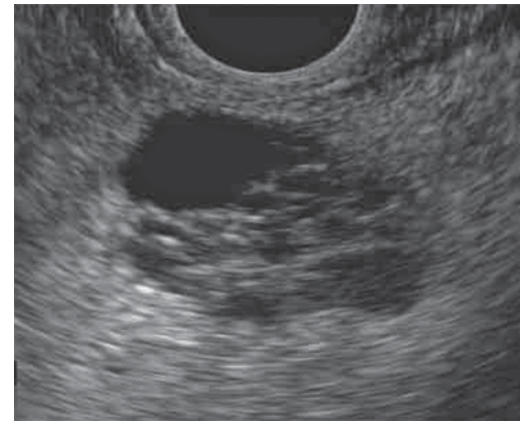

Fig. 31.2 EUS image of serous cystadenoma with microcysts and a macrocyst

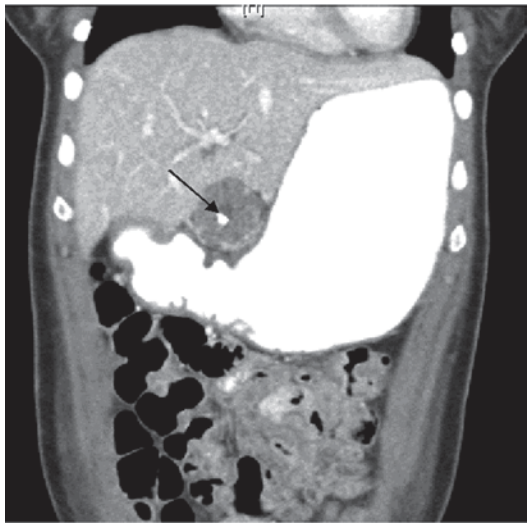

Fig. 31.3 Abdominal CT of central scar (*arrow*) in serous cystadenoma

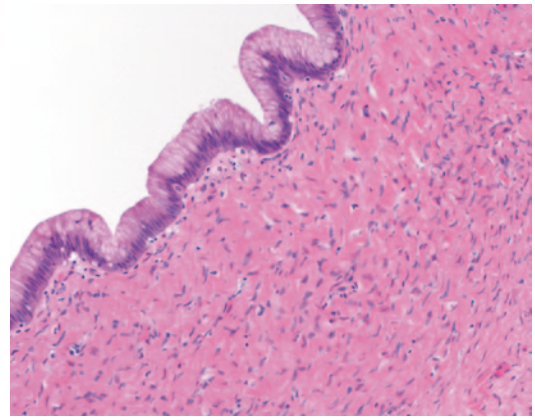

Fig. 31.4 Histology of mucinous cystic neoplasm showing mucinous epithelium and underlying "ovarian-type" stroma

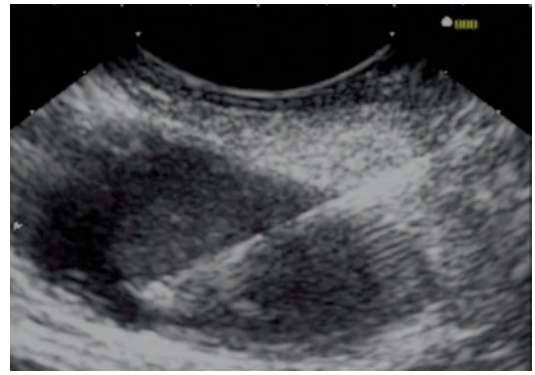

Fig. 31.5 EUS-FNA of mucinous cystic neoplasm appearing round and unilocular

ficity for differentiating mucinous cysts from SCA [9, 10]. The pathognomonic central scar or "sunburst calcification" is present in only about 30% of these cysts (Fig. 31.3) [11].

The natural history of SCAs is not well described; however, they appear to grow over time. Although an older study reported more rapid growth rate in cysts >4 cm, a recent multicenter study failed to confirm these results [12, 13]. A rate of growth of 6.2% per year or a doubling time of 12 years was calculated for the nonresected SCAs while resected SCAs grew faster (17% per year for a doubling time of 4.5 years) [12].

Mucinous Cystic Neoplasm

Mucinous cystic neoplasms are premalignant parenchymal lesions defined by ovarian-like stroma on pathology (Fig. 31.4) and thus almost exclusively occur in women. They arise in the body and tail of the pancreas in approximately 95% of patients. Unlike SCAs, presence of symptoms in mucinous cystic lesions is associated with malignancy. Other features concerning for malignancy in MCN include older age, large size especially >6 cm, and presence of thick cyst wall, mural nodules, or peripheral eggshell calcification [14, 15]. The true incidence of malignancy in MCNs is unknown although recent studies suggest lower rates of invasive cancer (6–27%) with only 5.5% carcinoma in situ [15, 16]. Unlike SCA, MCNs usually appear smooth, well-defined, and unilocular or with a few septations (Fig. 31.5).

IPMN

IPMNs are also mucinous cysts and arise from the pancreatic ductal epithelium of the main duct, side branches, or both. They occur more commonly in men between ages 50 and 60. While IPMNs usually arise in the head of the pancreas,

they can occur anywhere in the pancreas as well as in multiple locations. There are three radiologic subtypes of IPMN: main duct (diffuse or segmental dilation of the main duct > 5 mm), branch duct (dilation of one or more side branches), and mixed-type (both main duct and side branch involvement; Figs. 31.6, 31.7, and 31.8). Typically one relies on MRI/MRCP to distinguish BD-IPMN from mixed-type and MD-IPMN. Rarely can MD-IPMN be diagnosed endoscopically by visualizing the "fish-mouth" papilla, which represents mucus emerging from a widely patulous papilla (Fig. 31.9). Unfortunately, radiology misclassifies 29% of MD-IPMN and 21% of BD-IPMN [17]. Up to 29 % of mixed-type IPMN are misdiagnosed as BD-IPMN [18]. By pathology, IPMN may also be classified as gastric, intestinal, oncocytic, or pancreaticobiliary type. There is increasing appreciation of the histologic subtypes and their relationship with malignancy. In 169 resected IPMNs, 73% were gastric, 25% intestinal, 2% pancreaticobiliary, and 0.6% oncocytic [18]. HGD and cancer occurred more frequently in intestinal (32/42) than gastric type (48/123, $p < 0.0001$). A recent retrospective study of surgically resected IPMNs did note that gastric IPMNs were more likely to be smaller without nodules or masses and higher CEA level [19]. However, the

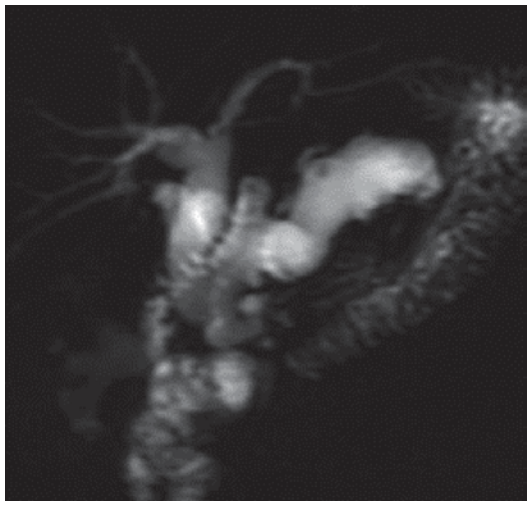

Fig. 31.6 MRCP of MD-IPMN with massively dilated main pancreatic duct

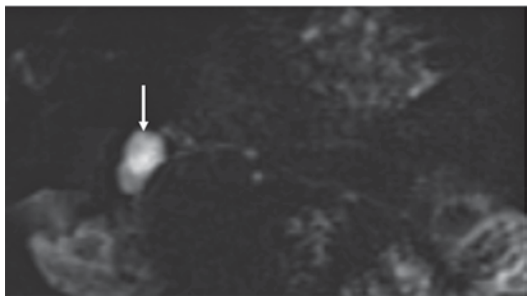

Fig. 31.7 MRCP of BD-IPMN (*arrow*) communicating with nondilated main pancreatic duct

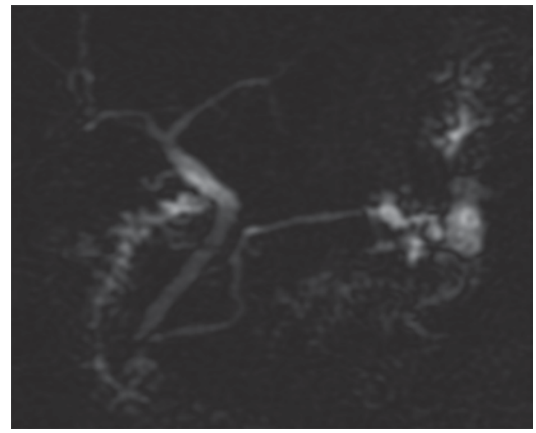

Fig. 31.8 MRCP of mixed-IPMN in tail of pancreas with dilated main pancreatic duct and side branches

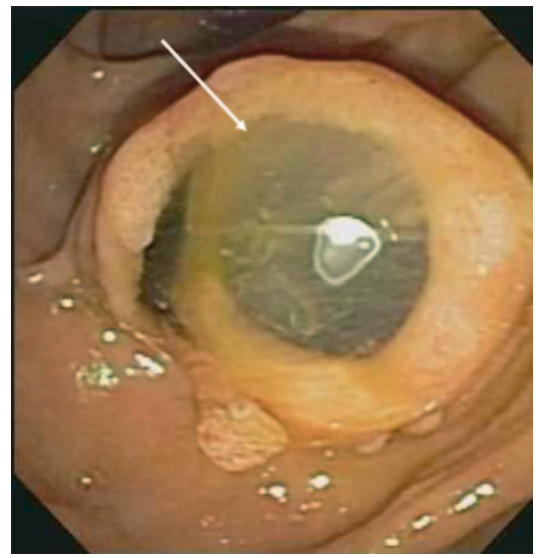

Fig. 31.9 "Fish mouth" papilla on ERCP with mucin at major papilla (*arrow*)

clinical utility of this histological grading remains uncertain as definitive grading is currently available only following surgical resection.

Correctly identifying the radiologic subtypes of IPMN is important because of differences in malignant potential and, therefore, management. MD-IPMN has the greatest malignant potential ranging from 40 to 70 % with nearly comparable risk in mixed-type IPMN. Symptoms do not appear to increase risk of malignancy in MD-IPMN although the passage of time does (1 year following first imaging or symptom onset, 20–42 % malignant; 2 years, 40–54 %; 5 years, 40–66 %) [20, 21]. Not all MD-IPMN and mixed-type IPMN behave the same as certain patients appear to have a more indolent course. MD-IPMN with normal serum CA 19-9 and cyst fluid cytology harbor lower rates of malignancy compared to other MD-IPMN (29 versus 60 %, $p< 0.0001$) [22]. Similarly mixed-type IPMN with noncircumferential involvement of the main duct in one or a few histologic sections and no gross abnormalities other than a dilated pancreatic duct had lower malignancy than mixed-type IPMN not meeting these criteria (17 versus 70%, $p< 0.0001$) [23].

Predictors of malignancy in BD-IPMN include those defined in the 2012 International Association of Pancreatology (IAP) guidelines (presence of a mass, mural nodules, dilated main pancreatic duct ≥ 1 cm, obstructive jaundice with cyst in the head of the pancreas, cytology suspicious or positive for malignancy), cyst size greater than 3 cm, and symptoms [22–28]. Symptoms attributable to IPMN include steatorrhea and diabetes with 15–30 % of IPMNs presenting with acute pancreatitis, which is believed due to obstruction from mucus plugging the ducts. In a small study of BD-IPMN, no asymptomatic patients had cancer while symptomatic patients developed more cancers over time (1 year, 15 %; 2 years, 30 %; 5 years, 37 %) [21].

Regarding the IAP guidelines, the absence of malignant features predicts benign cysts well with nearly 100 % negative predictive value while presence of them less accurately diagnoses malignancy [24]. The 2012 IAP guidelines were revised from the 2006 guidelines, and the former appears to predict malignancy better [29]. A major difference between the 2006 and 2012 guidelines is the removal of cyst size as a definite criterion for resection. Several studies contradict this de-emphasis of size. A metaanalysis of pathologically confirmed IPMNs and predictors of malignancy from the 2006 and 2012 guidelines identified cyst size >3 cm as the strongest predictor of malignancy with odds ratio (OR) 62 followed by nodule (OR 9.3), pancreatic duct >6 mm (OR 7.3), MD-IPMN (OR 4.7), and symptoms (OR 1.6) [30, 31].

Other Pancreatic Cysts

Less common pancreatic cystic neoplasms include solid pseudopapillary neoplasm (SPEN), which occurs almost exclusively in young women. SPENs account for 1–2 % of pancreatic cystic neoplasms. They were first described in 1959 as Frantz or Hamoudi tumors and then renamed SPEN by the World Health Organization in 1996. SPENs are premalignant with reported 2–15 % local invasion or metastatic disease [32]. About 10–15 % of SPENs are malignant, and to date, no predictors of aggressive behavior have been identified [33]. These patients usually present with nonspecific abdominal pain and occasionally with an abdominal mass palpable on examination. SPENs may occur anywhere throughout the entire pancreas. Pathology reveals characteristic pseudopapillae with cystic spaces containing hemorrhage and cholesterol clefts in myxoid stroma alternating with solid tissue.

Neuroendocrine or acinar cell tumors can occasionally undergo cystic degeneration. Cystic neuroendocrine tumors account for only 8–17 % of pancreatic neuroendocrine tumors and are usually nonfunctional [34]. Acinar cystadenocarcinoma is extremely rare with fewer than 10 cases reported in literature and typically presents with abdominal pain and a multilocular cystic lesion [35]. Unlike most other pancreatic cystic lesions, SPEN and cystic neuroendocrine tumors usually have characteristic findings on imaging. SPEN typically presents as a large well-defined encap-

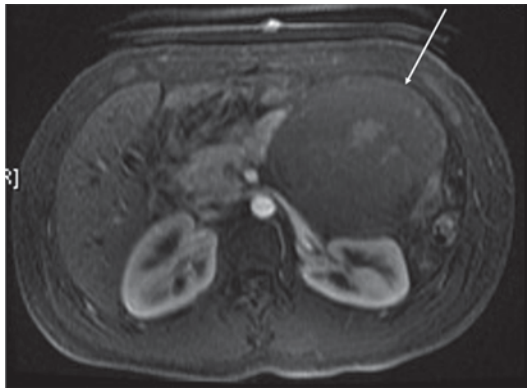

Fig. 31.10 MRI of solid pseudopapillary neoplasm (*arrow*) with thin enhancing rim, internal septations, and hemorrhage

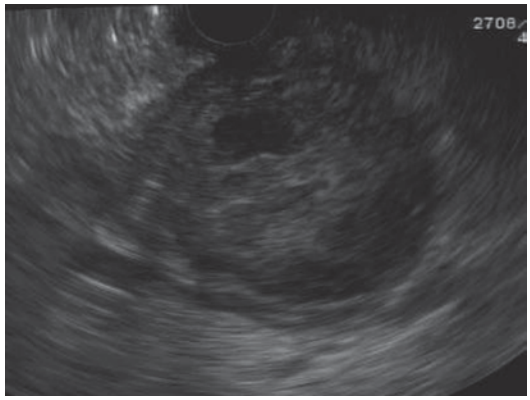

Fig. 31.11 EUS of pancreatic cystic neuroendocrine tumor appearing well-defined, heterogeneous with solid and cystic components

sulated mass with peripheral solid component and cystic degeneration in the center with areas of hemorrhage (Fig. 31.10) [36]. Peripheral calcification occurs rarely. Cystic neuroendocrine tumors are highly vascularized with early enhancement of the rim during early arterial imaging with MRI (Fig. 31.11) [34].

Pancreatic lymphangiomas are endothelium-lined cysts arising from the lymphatic system due to blocked lymphatics from inflammation or congenital anomaly [37]. During embryogenesis, ectopic lymphatic tissue lands in the pancreas and these cysts form from progressive dilation of insufficiently draining lymphatic vessels. Most pancreatic lymphangiomas occur incidentally in women in the body and tail of the pancreas. Complications include abdominal pain, hemorrhage, infection, and hydronephrosis. Lymphangiomas are difficult to distinguish from pancreatic cystic neoplasms on imaging and typically appear multiseptated, well-defined.

Lymphoepithelial cysts are another group of rare nonneoplastic pancreatic cysts accounting for 0.5% of pancreatic cysts [38]. These typically occur in middle-aged men in the body or tail of the pancreas. The cysts are lined by stratified squamous epithelium with subepithelial lymphoid tissue and follicles. The equally rare simple or true cyst is lined by cuboidal epithelial cells and does not communicate with the pancreatic duct. They occur in about 10% of patients with autosomal-dominant polycystic kidney disease. In addition, they are the most common pancreatic lesion seen in von Hippel-Lindau disease (up to 72% of patients) [39].

Retention cysts are actually cystically dilated segments of pancreatic duct resulting from obstruction [38]. The obstruction may result from stones or stricture from chronic pancreatitis or cancer. Viscous mucus in cystic fibrosis may also clog the pancreatic duct.

How Should Pancreatic Cysts Be Evaluated?

An initial diagnostic approach should focus on broadly differentiating mucinous (MCN and IPMN) from nonmucinous (SCA) cysts because these are the most common pancreatic cysts and management differs between them. However, simply distinguishing mucinous from nonmucinous cysts is inadequate for appropriate management because many BD-IPMN qualify for surveillance while current guidelines recommend surgery for MCN and mixed-type and MD-IPMN [22]. Differentiating among the various mucinous cysts, specifically BD-IPMN from MCN and BD-IPMN from mixed-type IPMN is challenging. No available diagnostic studies reliably separate BD-IPMN from MCN.

In addition, efforts should be made to diagnose malignant cysts and cysts at high risk of ma-

lignant degeneration. To define the latter group of cysts, the 2012 IAP guidelines for IPMN and MCN recommend resection for the following: all MCN, MD-IPMN, and BD-IPMN with solid component, main pancreatic duct ≥ 1 cm, obstructive jaundice from the cyst, nodule, and cytology suspicious or positive for cancer [22].

Radiology

Recent consensus by radiologists recommended MRI as the preferred imaging modality to characterize pancreatic cysts with its enhanced ability to detect septa, nodules, ductal communication, main duct involvement, and small branch duct cysts compared to CT [40–42]. MRI images should be obtained at 1.5 or 3 T with T1, T2, and 3-D, fat-saturated, gradient-echo T1 gadolinium-enhanced sequences in pancreatic, portal, and equilibrium phases with magnetic resonance cholangiopancreatography (MRCP). MRI also helps distinguish pseudocysts from cystic neoplasms by identifying internal debris within pseudocysts [43]. MRI is comparable to multidetector (MD) CT for diagnosing the specific type of cyst (40–70% accuracy) and may be superior in identifying mucinous cysts (79–82% accuracy) [44–46]. Both CT and MRI predict the presence of malignancy in pancreatic cysts with high accuracy (73−79%). These accuracy rates are comparable to EUS imaging [47]. MRI and EUS have modest sensitivity (58−67%) for detecting mural nodules, the presence of which are concerning for malignancy.

If MRI cannot be performed due to contraindications or patient intolerance, patients should undergo a "pancreatic protocol" abdominal CT scan. The MDCT should be dual-phase contrast-enhanced with images acquired during the pancreatic and portal venous phases which can be analyzed in 3-D.

Case Continued

The patient underwent MRI pancreas with MRCP showing a 3 cm unilocular cyst in the tail of the pancreas with mild upstream dilation of the main pancreatic duct and possible ductal communication (Fig. 31.12).

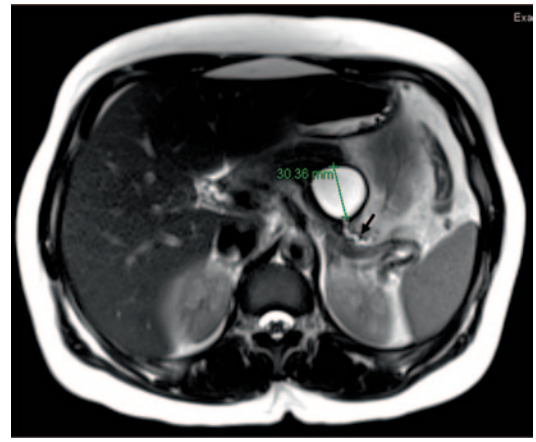

Fig. 31.12 MRI of unilocular cyst (*marked by green tag*) in tail of pancreas with mild upstream main pancreatic duct dilation (*arrow)* and possible communication

EUS and EUS-FNA

Whether EUS and EUS-FNA adds useful information beyond radiology was examined recently. In 154 patients with resected cysts, all underwent EUS, 90% had CT, and 34% had MRI [48]. This study focused on the ability to differentiate neoplastic (MCN, IPMN, SPEN, cystic ductal adenocarcinoma, and cystic neuroendocrine tumor) from nonneoplastic (pseudocyst, simple cyst, benign epithelial cyst, duplication cyst, and SCA) cysts. Sensitivity of EUS with or without cytology, CEA, and amylase was superior to CT and MRI (76 versus 48 and 34%, respectively, $p < 0.0001$). Although this study supports the value of EUS in identifying neoplastic cysts, the low diagnostic accuracy of CT and MRI contradicts other studies. In addition, this study only applies to surgically resected cysts; therefore, it may bias in favor of EUS or EUS-FNA compared to establishing the value of EUS or EUS-FNA among all cysts including the many patients who do not undergo surgery.

Despite this study, not everyone with an incidental pancreatic cyst needs EUS or EUS-FNA. The 2012 IAP guidelines for suspected MCN and IPMN suggest EUS for patients with pancre-

atitis or the following "worrisome features" on imaging: cyst size≥3 cm, thick enhancing cyst wall, nonenhancing nodule, main pancreatic duct (MPD) 5–9 mm, abrupt change in MPD caliber with distal pancreatic atrophy, or lymphadenopathy [22]. Similarly, the American Gastroenterological Association (AGA) guidelines recommend EUS-FNA only for higher risk cysts with at least 2 high risk features (size≥3 cm, dilated main pancreatic duct, solid component) or significant change during surveillance (e.g., increase in pancreatic duct diameter, development of solid component) [87]. Additionally, cysts between 1 and 3 cm could undergo EUS-FNA even without worrisome features to help classify them as mucinous or nonmucinous.

EUS imaging alone is insufficient for diagnosing mucinous cysts with 56% sensitivity, 45% specificity, and 51% accuracy reported in Brugge's seminal paper [49]. In addition, interobserver agreement among expert endosonographers for distinguishing mucinous and nonmucinous cysts by EUS imaging is only fair from an older study while a more recent study found moderate agreement for the actual diagnosis of the cyst [50, 51]. In this Dutch study, agreement among expert endosonographers (performed>1000 pancreas EUS) was better than semi-experts (performed 50–200 pancreas EUS) with experts demonstrating good agreement for nodules, moderate agreement for solid component and communication of the cyst with pancreatic duct, and fair agreement for suspicion of malignancy [50].

During EUS, features to evaluate include cyst size, presence of septations, lobular versus smooth contour, thick cyst wall, solid component to the cyst, nodule within the cyst, evidence of communication between the cyst and pancreatic duct, and size of main pancreatic duct. The following features are predictive of mucus: lesion hypoechoic relative to adjacent tissue, smooth-edge with hyperechoic rim. Nodules are iso- or hyperechoic compared to adjacent tissue without a hyperechoic rim or smooth edge [52]. Rotating the patient during EUS and trying to move the lesion with the FNA needle can help differentiate mucus from a nodule. Diagnostic accuracy of EUS for a nodule is modest (57%) in a pathology-based study of MCN and BD-IPMN. However, after training endosonographers in the above EUS criteria for differentiating a nodule from mucus, accuracy improved to 79%. Sensitivity and specificity of EUS (75 and 83%) were superior to CT (24 and 100%) for nodules [52].

How Can EUS-FNA Aid in Diagnosis?

The potential power of EUS results from the ability to safely perform EUS-FNA of cysts to obtain cyst fluid for analysis [53]. However, cysts need to be at least 1 cm in size in order to obtain sufficient fluid for testing. Cyst fluid cytology has low yield with less than 50% sensitivity for distinguishing mucinous from nonmucinous cysts due to scant cellularity [49, 54, 55]. Diagnostic yield of cytology is higher for SPEN (70–75% accuracy) and cystic neuroendocrine tumors (71% yield) [32, 56, 57]. Similarly, EUS-FNA of pancreatic lymphangiomas may be diagnostic in the presence of chylous-appearing cyst fluid, elevated triglyceride, and numerous benign lymphocytes [58, 59]. The simple technique of passing the needle back and forth through the collapsed cyst wall following fluid aspiration produced a 29% increase in diagnostic yield for mucinous or malignant cysts compared to cyst fluid cytology ($p=0.0001$) [60]. Therefore, rather than sending cyst fluid for cytology (unless cyst fluid is plentiful), tissue obtained from EUS-FNA of the collapsed cyst wall should be evaluated for cytology. In addition, if a nodule or solid component is present, FNA should target these lesions.

Cyst fluid is usually aspirated during EUS-FNA with a single pass using a 22- or 25-gauge needle with the goal of completely collapsing the cyst (Video 31.1). Occasionally, 19-gauge needles can be advanced into larger cysts with thick fluid although these larger needles are difficult to use in the head or uncinate process of the pancreas. Before sending the cyst fluid for analysis, visual inspection of the fluid may offer diagnostic clues. The "string sign," a marker of viscosity, is performed by placing fluid between the thumb and index finger and gently pulling apart. If the fluid stretches out to at least 3.5 mm, this is consistent with a mucinous cyst [61]. SCAs typically have thin, serosanguinous or frankly bloody

Table 31.2 Cyst fluid markers

Cyst fluid marker	Sensitivity (%)	Specificity (%)
CEA < 5 ng/mL (SCA, pseudocyst, neuroendocrine tumor)	54	94
CEA > 192 ng/mL (mucinous lesion)	73	84
Amylase < 250 U/L (excludes pseudocyst)	44	98
k-ras mutation + LOH (malignant lesion)	37	96
k-ras mutation (mucinous lesion)	54	100

fluid. A dose of prophylactic intravenous antibiotics (usually fluoroquinolone) is recommended followed by 3 days of oral antibiotic to prevent infection from cyst aspiration.

Cyst fluid chemistry typically includes carcinoembryonic antigen (CEA) and amylase (Table 31.2). Low amylase less than 250 U/L helps exclude pseudocysts [62]. CEA has been most extensively studied and differentiates mucinous from nonmucinous cysts. Elevated CEA suggests a mucinous lesion although the exact cutoff level is debatable with higher levels producing greater confidence that the cyst is mucinous while missing mucinous cysts with lower CEA values. The classic cutoff is 192 ng/mL, which yields 73% sensitivity and 84% specificity for mucinous cysts and misses about 25% of them [49]. Low CEA less than 5 ng/mL is 95% specific to SCA, pseudocyst, or neuroendocrine tumor [62]. CEA levels do not predict malignancy [63]. An underreported and underappreciated problem with cyst fluid CEA is that currently available assays for tumor markers have been validated in serum but not cyst fluid. This produces up to 85% variation in mean CEA levels among the different assays run on the same specimens [64]. Intraassay variability is low for the Roche Elecsys and Bayer Centaur assays, but interassay values differ by up to 50%.

Commercial DNA analysis of k-ras mutations may improve identification of mucinous cysts with studies demonstrating 90–100% specificity and 42–54% sensitivity (Table 31.2) [65, 66]. Thus, if k-ras mutation is present, this is diagnostic of a mucinous cyst while the absence of k-ras mutation is not helpful. The addition of DNA analysis (k-ras mutation, 2 or more loss of heterozygosity (LOH) mutations and/or DNA quantity greater than 40 ng/μL) to CEA and cytology did not significantly improve accuracy. DNA analysis may be useful in select patients whose CEA, cytology, and imaging results are indeterminate for a mucinous cyst. In addition, if less than 0.5 cc of cyst fluid is available, DNA analysis is likely the only test that can be performed on this small quantity of fluid.

Similarly, a multicenter study suggested high specificity (96%) and low sensitivity (37%) for identifying malignant cysts when k-*ras* mutation was followed by allelic loss [67]. We compared accuracy of the 2006 and 2012 IAP guidelines and commercial DNA analysis (k-ras, LOH mutations, and DNA quantity) for diagnosing malignancy in 257 pancreatic cysts evaluated by EUS-FNA [29]. The 2012 guideline most accurately identified malignant cysts with 88% sensitivity and 90% specificity; DNA analysis did not add significantly useful information beyond this.

Is There a Role for ERCP in Pancreatic Cysts?

Peroral pancreatoscopy and intraductal ultrasound may help characterize IPMNs and diagnose malignancies (Chap. 15). Characteristic findings include papillary tumor and fish-egg-like appearance in 73% [68]. Irrigation cytology (aspiration of saline irrigated into the duct during pancreatoscopy) may diagnose malignancy better than targeted biopsies during pancreatoscopy (100% sensitive and specific versus 25% sensitive) [69]. Mild complications of cholangitis and pancreatitis occurred in 24%. Small Japanese case series of resected IPMN suggest preoperative pancreatoscopy and IDUS are valuable for evaluating the extent of ductal involvement to aid the surgeons in mapping their resection [68, 70, 71]. Which part and how much of the pancreas to resect are important in MD-IPMN because total pancreatectomy may be morbid with brittle diabetes and exocrine insufficiency, and partial resection with

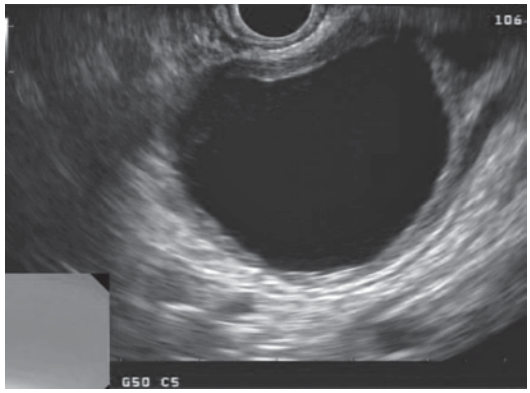

Fig. 31.13 EUS of unilocular cyst with thick wall

the goal of negative margins may be more suitable for older patients with comorbidities.

Case Continued

She was referred for EUS with the following findings: 3-cm-thick-walled unilocular cyst in the tail of the pancreas without a solid component or mural nodule (Fig. 31.13). The main pancreatic duct upstream from the cyst was dilated to 2.4 mm while the rest of the pancreatic duct was normal caliber. FNA using a 22-gauge needle performed with a single pass to drain the cyst completely revealed the following: CEA 304.9 ng/mL, amylase 30630 U/L, cyst wall cytology with no malignant cells. DNA analysis revealed no k-*ras* or loss of heterozygosity mutations. What type of cyst is this and how should it be managed?

Management of Pancreatic Cysts

Patients with pancreatic cysts that should be resected include those with symptoms, evidence of malignancy, a high risk of becoming malignant, and potentially large (> 4 cm) or rapidly growing serous cystadenomas. Specifically, the 2012 IAP guidelines recommend surgical resection for all MCN, MD-IPMN, mixed-type IPMN, and BD-IPMN with solid component, main pancreatic duct≥1 cm, obstructive jaundice from the cyst, nodule, and/or cytology suspicious or positive for cancer [22]. The AGA guidelines also recommend resection for cysts with positive cytology, but suggest the presence of multiple high risk stigmata as an indicator for resection (for example, a 3cm cyst with a nodule and dilated MPD) [87]. Recent papers have suggested a relatively low rate of invasive cancer in MCN with <0.5% rate of cancer or HGD in patients with MCN <3 cm. Therefore, some experts have suggested that surveillance may be reasonable in some of these patients [88, 89].

Following surgical resection for SCA or MCN without invasive cancer, no surveillance is necessary [15, 16]. Patients with invasive cancer regardless of type of cyst should be followed using a protocol similar for pancreatic ductal adenocarcinoma although the AGA guidelines suggest surveillance every 2 years, which may miss cancers that recur early [87]. In addition, patients with IPMNs need ongoing surveillance because of concern for a molecular "field defect" resulting in multifocal disease. With no residual IPMN in the remaining pancreas and a margin of normal or nondysplastic tissue, surveillance MRI is recommended 2 and 5 years after resection. If any dysplasia remains at the margin, MRI should be performed two times a year [22] although the AGA guidelines suggest no surveillance is necessary for low and intermediate grade dysplasia [87].

Unresected pancreatic cysts should be followed unless diagnosed definitively as a non-neoplastic cyst. MRI is preferable to CT for surveillance of pancreatic cysts. Radiation exposure from repeated CT favors MRI [72]. An important issue with MRI involves cost of surveillance. To this end, it may be reasonable to follow pancreatic cysts with nonenhanced MRI, using gadolinium only in select situations, as no malignant cysts were missed with nongadolinium enhanced MRIs in a multicenter study of 301 patients [73].

How often to perform MRI is unclear. The 2012 IAP guidelines recommend an MRI 3–6 months following initial identification of the cyst to ensure stability and then suggest various intervals depending on the cyst size, which have not been validated: < 1 cm, every 2–3 years; 1–2 cm, every year for 2 years and if stable, lengthen interval; 2–3 cm, every 6–12 months; > 3 cm, every 3–6 months [22]. Nonresected SCAs are followed because they could grow although the frequency of imaging is debatable with some advocating

imaging every 12 months while others suggest biennial surveillance [74, 75]. The recent AGA guidelines simplify surveillance recommendations to an MRI 1 year after identification and then every 2 years thereafter [87].

Experts disagree on how long surveillance should continue. The 2012 IAP guidelines support continuing surveillance indefinitely while the American College of Radiology guidelines recommend only a single 1-year follow-up for cysts < 2 cm with no further surveillance in asymptomatic patients [22, 40], and the recent AGA guidelines suggest ceasing surveillance after 5 years of stability without any high risk features detected in the cyst [87]. While the incidence of malignancy in patients who do not meet criteria for resection is low, rare cancers can develop years after initial diagnosis [76]. Recommendations to stop surveillance need further evaluation and should be tailored to the specific patient.

A major issue in managing pancreatic cysts is that often the exact diagnosis remains unclear despite a thorough evaluation with imaging and EUS-FNA [77]. For example, it may be impossible to distinguish MCN from BD-IPMN preoperatively. A Kaiser study stratified 1815 patients with any pancreatic cyst excluding pseudocyst and history of pancreatitis into low (0.3–0.6%), intermediate (1.3–5.1%), and high (9.3–13.6%) risk for malignancy based on a few imaging characteristics (pancreatic duct > 4 mm, size ≥ 3 cm, and cyst growth although this was not defined) [78]. High-risk cysts were ≥ 3 cm without features of SCA (septations with calcification) or 1–3 cm with duct dilation. Although the malignancy rate was low (2.9%) with 74% presenting at cyst diagnosis, the risk of pancreatic cancer was 35 times greater in the cyst cohort compared to noncyst patients. Despite issues with this study, it may help guide management of cysts without a definite diagnosis based on their imaging features.

Case Conclusion

Based on elevated cyst fluid CEA, the cyst is mucinous with the concerning features of thick wall and dilated main pancreatic duct. The lack of DNA mutations is not helpful due to their low sensitivities. Therefore, the diagnostic studies concluded the patient had a mucinous cyst which was either a MCN or mixed-type IPMN. It was impossible to differentiate between these two diagnoses based on available data, and the presence of main pancreatic duct dilation with possible communication raised the concern for mixed-type IPMN. Surgical resection is recommended for both lesions, and this patient was a young, good surgical candidate. Therefore, she underwent distal pancreatectomy without complications, and surgical pathology was consistent with a MCN with low-grade dysplasia (Fig. 31.4). No further follow-up was necessary.

What Does the Future Hold?

Interest has blossomed to discover new biomarkers for pancreatic cysts given the inadequacies of currently available cyst fluid testing. Research has evaluated DNA, micro(mi)RNA, protein (proteomics), and metabolite (metabolomics) changes in many pilot studies. The most promising may be GNAS mutation at codon 201, which has been associated with IPMN in pathology specimens, cyst fluid, and pancreatic juice obtained endoscopically following secretin-stimulation [79–81]. Our own work on pancreatic cyst pathology specimens demonstrated higher prevalence of GNAS mutations in 42% IPMNs compared to 10% SCAs and 0% pancreatic adenocarcinoma and MCN ($p = 0.0003$) [82].

MiRNAs are small, stable, noncoding RNA that have also generated interest as potential biomarkers of pancreatic cysts. Our group published a comprehensive surgical pathology study interrogating 378 miRNAs in 69 specimens (20 SCA, 10 MCN, 20 IPMN, and 19 pancreatic adenocarcinoma), which reported various 4 miRNA panels that accurately differentiated SCAs from MCN and IPMN as well as MCN from BD-IPMN with 85−100% sensitivity and 100% specificity [83]. While exciting, these and results from other studies await large-scale validation in EUS-FNA cyst fluid, ideally in patients with pathologically confirmed diagnoses. In addition to potentially improved diagnostics, the ability to perform analyses on small fluid quan-

tities is attractive especially as more identified cysts are smaller.

Endoscopic advances also attempt to improve diagnosis of pancreatic cysts. Direct endoscopic visualization of the cyst wall using the Spyglass system (Boston Scientific, Marlborough, MA, USA) followed by biopsy of the wall successfully diagnosed MCN in 2 patients [84]. Confocal endomicroscopy allows real-time microscopic imaging. During needle confocal endomicroscopy, a miniprobe advanced through a 19-gauge needle into a cyst analyzes the cyst wall. In a pilot study, sensitivity and specificity of endomicroscopic findings were 69 and 100% for differentiating mucinous cysts from SCA and pseudocysts [85]. Pancreatitis occurred in 3% [86]. The feasibility of performing both needle confocal endomicroscopy and cystoscopy using the SpyGlass fiberoptic probe in pancreatic cysts was demonstrated although the rate of pancreatitis was 7%.

Finally, endoscopy may offer an alternative to surgical resection in the management of pancreatic cysts as well. Recent interest has focused on the technique of EUS-guided fine-needle injection of various agents into lesions including pancreatic cysts (Chap. 33). Alcohol as well as the chemotherapeutic agent paclitaxel has been used to ablate pancreatic cysts with some success and require long-term follow-up data.

Conclusion

Pancreatic cystic lesions challenge clinicians with their increased identification on radiology imaging and the limitations of currently available diagnostics. Following initial identification of a pancreatic cyst, an MRI pancreas with MRCP or pancreatic protocol abdominal CT scan should be performed. A combination of radiologic imaging with EUS-FNA for cyst wall cytology, CEA, amylase, and, in select cases, DNA markers may be used to diagnose pancreatic cystic lesions. Given the inadequacies of imaging and cyst fluid analysis, translational research has flourished to discover better markers of mucinous and malignant cysts. Cyst fluid validation studies are awaited, and similarly endoscopic innovations require further refinement both for improved diagnostics and management of select pancreatic cysts.

Key Points

- The diagnostic approach focuses on differentiating mucinous and nonmucinous cysts and identifying malignant cysts.
- Distinguishing among mucinous cysts (BD-IPMN from MCN and BD-IPMN from mixed-type IPMN) may be difficult or impossible despite the implications for management.
- MCN, MD-IPMN, mixed-type IPMN, BD-IPMN with features concerning for malignancy, and symptomatic cysts should be resected in surgically fit patients.
- MRI of the pancreas with MRCP is the preferred imaging for pancreatic cysts.
- EUS-FNA is recommended in patients with higher risk features including solid component, nodule, dilated main pancreatic duct, and size $\geq$ 3 cm.
- In indeterminate cysts after MRI, EUS-FNA cytology, CEA and amylase, DNA markers may help identify mucinous cysts.
- Revised 2012 International Association of Pancreatology consensus guidelines are superior to the original 2006 guidelines although they still suffer from relatively poor positive predictive value.
- Pancreatic cyst size remains a strong predictor of malignancy.
- Recent AGA guidelines underscore the lack of high quality evidence in pancreatic cyst literature and support decreased surveillance and higher threshold for surgical resection. Better diagnostic and prognostic markers are needed.

Video Caption

Video 31.1 This video demonstrates EUS-FNA of an incidental pancreatic cystic lesion in a 56-year-old female patient with intermittent lower abdominal pain. The cystic lesion is identified in the body of the pancreas, and evaluation includes inspection for nodule, mass, thick wall,

calcification, and communication with the main pancreatic duct, none of which are identified. Following this, a 22-gauge FNA needle is advanced into the larger component of the oligolocular cystic lesion with the goal of completely collapsing the cyst using a single needle pass. After the lesion has been nearly completely aspirated, the needle is advanced back and forth through the collapsed cyst wall a few times to obtain cyst wall tissue for cytology. Prophylactic antibiotics have been administered intravenously and oral ciprofloxacin will be prescribed for 3 days. Cyst fluid will be sent for CEA, amylase, and cytology, and cyst wall tissue will also be evaluated for cytology

References

1. Megibow AJ, Baker ME, Gore RM, Taylor A. The incidental pancreatic cyst. Radiol Clin North Am. 2011;49(2):349–59.
2. Lee KS, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010;105(9):2079–84.
3. Assifi MM, Nguyen PD, Agrawal N, Dedania N, Kennedy EP, Sauter PK, et al. Non-neoplastic epithelial cysts of the pancreas: a rare, benign entity. J Gastrointest Surg. 2014;18(3):523–31.
4. Simeone DM. SSAT/AGA/ASGE state of the art conference on cystic neoplasms of the pancreas. J Gastrointest Surg. 2008;12(8):1475–7.
5. Fasanella KE, McGrath K. Cystic lesions and intraductal neoplasms of the pancreas. Best Pract Res Clin Gastroenterol. 2009;23(1):35–48.
6. Kimura W, Moriya T, Hirai I, Hanada K, Abe H, Yanagisawa A, et al. Multicenter study of serous cystic neoplasm of the Japan pancreas society. Pancreas. 2012;41(3):380–7.
7. Galanis C, Zamani A, Cameron JL, Campbell KA, Lillemoe KD, Caparrelli D, et al. Resected serous cystic neoplasms of the pancreas: a review of 158 patients with recommendations for treatment. J Gastrointest Surg. 2007;11(7):820–6.
8. Sakorafas GH, Smyrniotis V, Reid-Lombardo KM, Sarr MG. Primary pancreatic cystic neoplasms revisited. Part I: serous cystic neoplasms. Surg Oncol. 2011;20(2):e84–92.
9. 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.
10. Schraibman V, Goldman SM, Ardengh JC, Goldenberg A, Lobo E, Linhares MM, et al. New trends in diffusion-weighted magnetic resonance imaging as a tool in differentiation of serous cystadenoma and mucinous cystic tumor: a prospective study. Pancreatology. 2011;11(1):43–51.
11. Shah AA, Sainani NI, Kambadakone AR, Shah ZK, Deshpande V, Hahn PF, et al. Predictive value of multi-detector computed tomography for accurate diagnosis of serous cystadenoma: radiologic-pathologic correlation. World J Gastroenterol. 2009;15(22):2739–47.
12. El-Hayek KM, Brown N, O'Rourke C, Falk G, Morris-Stiff G, Walsh RM. Rate of growth of pancreatic serous cystadenoma as an indication for resection. Surgery. 2013;154(4):794–800; discussion–2.
13. Tseng JF, Warshaw AL, Sahani DV, Lauwers GY, Rattner DW, Fernandez-del Castillo C. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. Ann Surg. 2005;242(3):413–9; discussion 9–21.
14. Sakorafas GH, Smyrniotis V, Reid-Lombardo KM, Sarr MG. Primary pancreatic cystic neoplasms revisited: part II. Mucinous cystic neoplasms. Surg Oncol. 2011;20(2):e93–101.
15. Gil E, Choi SH, Choi DW, Heo JS, Kim MJ. Mucinous cystic neoplasms of the pancreas with ovarian stroma. ANZ J Surg. 2013;83(12):985–90.
16. Crippa S, Salvia R, Warshaw AL, Dominguez I, Bassi C, Falconi M, et al. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 2008;247(4):571–9.
17. Barron MR, Roch AM, Waters JA, Parikh JA, Dewitt JM, Al-Haddad MA, et al. Does preoperative cross-sectional imaging accurately predict main duct involvement in intraductal papillary mucinous neoplasm? J Gastrointest Surg. 2014;18(3):447–56.
18.. Yamada S, Fujii T, Shimoyama Y, Kanda M, Nakayama G, Sugimoto H, et al. Clinical implication of morphological subtypes in management of intraductal papillary mucinous neoplasm. Ann Surg Oncol. 2014;21:2444–52.
19. Yoon WJ, Dagililar ES, Mino-Kenudson M, Morales-Oyarvide V, Pitman MB, Brugge WR. Characterization of epithelial subtypes of intraductal papillary mucinous neoplasm of the pancreas with endoscopic ultrasound and cyst fluid analysis. Endoscopy. 2014;46:1071.
20. Traverso LW, Moriya T, Hashimoto Y. Intraductal papillary mucinous neoplasms of the pancreas: making a disposition using the natural history. Curr Gastroenterol Rep. 2012;14(2):106–11.
21. Moriya T, Hashimoto Y, Traverso LW. The duration of symptoms predicts the presence of malignancy in 210 resected cases of pancreatic intraductal papillary mucinous neoplasms. J Gastrointest Surg. 2011;15(5):762–70; discussion 70–1.
22. Roch AM, DeWitt JM, Al-Haddad MA, Schmidt CM, Ceppa EP, House MG, Zyromski NJ, Nakeeb A, Schmidt CM. Nonoperative management of main pancreatic duct-involved intraductal papillary mucinous neoplasm might be indicated in selected patients. J Am Coll Surg. 2014;219:122-31.

23. Sahora K, Fernandez-del Castillo C, Dong F, Marchegiani G, Thayer SP, Ferrone CR, Sahani DV, Brugge WR, Warshaw AL, Lillemoe KD, Mino-Kenudson M. Not all mixed-type intraductal papillary mucinous neoplasms behave like main-duct lesions: implications of minimal involvement of the main pancreatic duct. Surgery. 2014;156:611-21.
24. Sahora K, Mino-Kenudson M, Brugge W, Thayer SP, Ferrone CR, Sahani D, et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. Ann Surg. 2013;258(3):466–75.
25. Shimizu Y, Yamaue H, Maguchi H, Yamao K, Hirono S, Osanai M, et al. Predictors of malignancy in intraductal papillary mucinous neoplasm of the pancreas: analysis of 310 pancreatic resection patients at multiple high-volume centers. Pancreas. 2013;42(5):883–8.
26. Goh BK, Thng CH, Tan DM, Low AS, Wong JS, Cheow PC, et al. Evaluation of the Sendai and 2012 International consensus guidelines based on cross-sectional imaging findings performed for the initial triage of mucinous cystic lesions of the pancreas: a single institution experience with 114 surgically treated patients. Am J Surg. 2014;208:202–9.
27. Jang JY, Park T, Lee S, Kang MJ, Lee SY, Lee KB, et al. Validation of international consensus guidelines for the resection of branch duct-type intraductal papillary mucinous neoplasms. Br J Surg. 2014;101(6):686–92.
28. Correa-Gallego C, Do R, Lafemina J, Gonen M, D'Angelica MI, DeMatteo RP, et al. Predicting dysplasia and invasive carcinoma in intraductal papillary mucinous neoplasms of the pancreas: development of a preoperative nomogram. Ann Surg Oncol. 2013;20(13):4348–55.
29. Lee LS, Wu BU, Banks PA, Kadiyala V, Mehta S, Saltzman JR, et al. Utility of commercial DNA analysis in detecting malignancy within pancreatic cysts. JOP. 2013;15(2):182–8.
30. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006;6(1–2):17–32.
31. Anand N, Sampath K, Wu BU. Cyst features and risk of malignancy in intraductal papillary mucinous neoplasms of the pancreas: a meta-analysis. Clin Gastroenterol Hepatol. 2013;11(8):913–21; quiz e59–60.
32. Law JK, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, et al. A systematic review of solid-pseudopapillary neoplasms: are these rare lesions? Pancreas. 2014;43(3):331–7.
33. Reddy S, Wolfgang CL. Solid pseudopapillary neoplasms of the pancreas. Adv Surg. 2009;43:269–82.
34. Lee LS. Diagnosis of pancreatic neuroendocrine tumors and the role of endoscopic ultrasound. Gastroenterol Hepatol (N Y). 2010;6(8):520–2.
35. Colombo P, Arizzi C, Roncalli M. Acinar cell cystadenocarcinoma of the pancreas: report of rare case and review of the literature. Hum Pathol. 2004;35(12):1568–71.
36. Frost M, Krige JE, Bornman PC, Panieri E, Beningfield SJ, Wainwright H. Solid pseudopapillary epithelial neoplasm–a rare but curable pancreatic tumour in young women. S Afr J Surg. 2011;49(2):75–6, 8–81.
37. Gures N, Gurluler E, Alim A, Berber I, Gurkan A. Cystic pancreatic lymphangioma. Rare Tumors. 2012;4(2):e27.
38. Molvar C, Kayhan A, Lakadamyali H, Oto A. Non-neoplastic cystic lesions of pancreas: a practical clinical, histologic, and radiologic approach. Curr Probl Diagn Radiol. 2011;40(4):141–8.
39. Charlesworth M, Verbeke CS, Falk GA, Walsh M, Smith AM, Morris-Stiff G. Pancreatic lesions in von Hippel-Lindau disease? A systematic review and meta-synthesis of the literature. J Gastrointest Surg. 2012;16(7):1422–8.
40. Berland LL. The American college of radiology strategy for managing incidental findings on abdominal computed tomography. Radiol Clin North Am. 2011;49(2):237–43.
41. Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, et al. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. J Am Coll Radiol. 2010;7(10):754–73.
42. Waters JA, Schmidt CM, Pinchot JW, White PB, Cummings OW, Pitt HA, et al. CT vs MRCP: optimal classification of IPMN type and extent. J Gastrointest Surg. 2008;12(1):101–9.
43. Macari M, Finn ME, Bennett GL, Cho KC, Newman E, Hajdu CH, et al. Differentiating pancreatic cystic neoplasms from pancreatic pseudocysts at MR imaging: value of perceived internal debris. Radiology. 2009;251(1):77–84.
44. Sahani DV, Kambadakone A, Macari M, Takahashi N, Chari S, Fernandez-del Castillo C. Diagnosis and management of cystic pancreatic lesions. AJR Am J Roentgenol. 2013;200(2):343–54.
45. Sainani NI, Saokar A, Deshpande V, Fernandez-del Castillo C, Hahn P, Sahani DV. Comparative performance of MDCT and MRI with MR cholangiopancreatography in characterizing small pancreatic cysts. AJR Am J Roentgenol. 2009;193(3):722–31.
46. Mohamadnejad M, Eloubeidi MA. Cystsic lesions of the pancreas. Arch Iran Med. 2013;16(4):233–9.
47. Kim YC, Choi JY, Chung YE, Bang S, Kim MJ, Park MS, et al. Comparison of MRI and endoscopic ultrasound in the characterization of pancreatic cystic lesions. AJR Am J Roentgenol. 2010;195(4):947–52.
48. Khashab MA, Kim K, Lennon AM, Shin EJ, Tignor AS, Amateau SK, 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(4):717–21.
49. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, et al. Diagno-

sis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126(5):1330–6.
50. de Jong K, Verlaan T, Dijkgraaf MG, Poley JW, van Dullemen H, Bruno MJ, et al. Interobserver agreement for endosonography in the diagnosis of pancreatic cysts. Endoscopy. 2011;43(7):579–84.
51. Ahmad NA, Kochman ML, Brensinger C, Brugge WR, Faigel DO, Gress FG, et al. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. Gastrointest Endosc. 2003;58(1):59–64.
52. Zhong N, Zhang L, Takahashi N, Shalmiyev V, Canto MI, Clain JE, et al. Histologic and imaging features of mural nodules in mucinous pancreatic cysts. Clin Gastroenterol Hepatol. 2012;10(2):192–8, 8 e1–2.
53. Lee LS, Saltzman JR, Bounds BC, Poneros JM, Brugge WR, Thompson CC. EUS-guided fine needle aspiration of pancreatic cysts: a retrospective analysis of complications and their predictors. Clin Gastroenterol Hepatol. 2005;3(3):231–6.
54. Maker AV, Lee LS, Raut CP, Clancy TE, Swanson RS. Cytology from pancreatic cysts has marginal utility in surgical decision-making. Ann Surg Oncol. 2008;15(11):3187–92.
55. Attasaranya S, Pais S, LeBlanc J, McHenry L, Sherman S, DeWitt JM. Endoscopic ultrasound-guided fine needle aspiration and cyst fluid analysis for pancreatic cysts. JOP. 2007;8(5):553–63.
56. Jani N, Dewitt J, Eloubeidi M, Varadarajulu S, Appalaneni V, Hoffman B, et al. Endoscopic ultrasound-guided fine-needle aspiration for diagnosis of solid pseudopapillary tumors of the pancreas: a multicenter experience. Endoscopy. 2008;40(3):200–3.
57. Morales-Oyarvide V, Yoon WJ, Ingkakul T, Forcione DG, Casey BW, Brugge WR, et al. Cystic pancreatic neuroendocrine tumors: the value of cytology in preoperative diagnosis. Cancer Cytopathol. 2014;122:435–44.
58. Fonseca R, Pitman MB. Lymphangioma of the pancreas: a multimodal approach to pre-operative diagnosis. Cytopathology. 2013 Jun;24(3):172–6.
59. Jathal A, Arsenescu R, Crowe G, Movva R, Shamoun DK. Diagnosis of pancreatic cystic lymphangioma with EUS-guided FNA: report of a case. Gastrointest Endosc. 2005;61(7):920–2.
60. Hong SK, Loren DE, Rogart JN, Siddiqui AA, Sendecki JA, Bibbo M, et al. Targeted cyst wall puncture and aspiration during EUS-FNA increases the diagnostic yield of premalignant and malignant pancreatic cysts. Gastrointest Endosc. 2012;75(4):775–82.
61. Layfield LJ, Ehya H, Filie AC, Hruban RH, Jhala N, Joseph L, et al. Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the papanicolaou society of cytopathology guidelines for pancreatobiliary cytology. Diagn Cytopathol. 2014;42(4):351–62.
62. van der Waaij LA, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. Gastrointest Endosc. 2005;62(3):383–9.
63. Ngamruengphong S, Bartel MJ, Raimondo M. Cyst carcinoembryonic antigen in differentiating pancreatic cysts: a meta-analysis. Dig Liver Dis. 2013;45(11):920–6.
64. Boot C. A review of pancreatic cyst fluid analysis in the differential diagnosis of pancreatic cyst lesions. Ann Clin Biochem. 2014;51(Pt 2):151–66.
65. Nikiforova MN, Khalid A, Fasanella KE, McGrath KM, Brand RE, Chennat JS, et al. Integration of KRAS testing in the diagnosis of pancreatic cystic lesions: a clinical experience of 618 pancreatic cysts. Mod Pathol. 2013;26(11):1478–87.
66. Al-Haddad M, DeWitt J, Sherman S, Schmidt CM, LeBlanc JK, McHenry L, et al. Performance characteristics of molecular (DNA) analysis for the diagnosis of mucinous pancreatic cysts. Gastrointest Endosc. 2014;79(1):79–87.
67. Khalid A, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc. 2009;69(6):1095–102.
68. Yasuda K, Sakata M, Ueda M, Uno K, Nakajima M. The use of pancreatoscopy in the diagnosis of intraductal papillary mucinous tumor lesions of the pancreas. Clin Gastroenterol Hepatol. 2005;3(7 Suppl 1):S53–7.
69. Nagayoshi Y, Aso T, Ohtsuka T, Kono H, Ideno N, Igarashi H, et al. Peroral pancreatoscopy using the SpyGlass system for the assessment of intraductal papillary mucinous neoplasm of the pancreas. J Hepatobiliary Pancreat Sci. 2013;21:410–7.
70. Cheon YK, Cho YD, Jeon SR, Moon JH, Jeong SW, Hur KY, et al. Pancreatic resection guided by preoperative intraductal ultrasonography for intraductal papillary mucinous neoplasm. Am J Gastroenterol. 2010;105(9):1963–9.
71. Itoi T, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, 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.
72. Sodickson A, Baeyens PF, Andriole KP, Prevedello LM, Nawfel RD, Hanson R, et al. Recurrent CT, cumulative radiation exposure, and associated radiation-induced cancer risks from CT of adults. Radiology. 2009;251(1):175–84.
73. Nougaret S, Reinhold C, Chong J, Escal L, Mercier G, Fabre JM, et al. Incidental pancreatic cysts: natural history and diagnostic accuracy of a limited serial pancreatic cyst MRI protocol. Eur Radiol. 2014;24:1020–9.
74. Wargo JA, Fernandez-del-Castillo C, Warshaw AL. Management of pancreatic serous cystadenomas. Adv Surg. 2009;43:23–34.
75. Tseng JF. Management of serous cystadenoma of the pancreas. J Gastrointest Surg. 2008;12(3):408–10.
76. Khannoussi W, Vullierme MP, Rebours V, Maire F, Hentic O, Aubert A, et al. The long term risk of

malignancy in patients with branch duct intraductal papillary mucinous neoplasms of the pancreas. Pancreatology. 2012;12(3):198–202.
77. Correa-Gallego C, Ferrone CR, Thayer SP, Wargo JA, Warshaw AL, Fernandez-Del Castillo C. Incidental pancreatic cysts: do we really know what we are watching? Pancreatology. 2010;10(2–3):144–50.
78. Wu BU, Sampath K, Berberian CE, Kwok KK, Lim BS, Kao KT, et al. Prediction of malignancy in cystic neoplasms of the pancreas: a population-based cohort study. Am J Gastroenterol. 2014;109(1):121-9; quiz 30.
79. Kanda M, Knight S, Topazian M, Syngal S, Farrell J, Lee J, et al. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. Gut. 2013;62(7):1024–33.
80. Siddiqui AA, Kowalski TE, Kedika R, Roy A, Loren DE, Ellsworth E, et al. EUS-guided pancreatic fluid aspiration for DNA analysis of KRAS and GNAS mutations for the evaluation of pancreatic cystic neoplasia: a pilot study. Gastrointest Endosc. 2013;77(4):669–70.
81. Wu J, Matthaei H, Maitra A, Dal Molin M, Wood LD, Eshleman JR, et al. Recurrent GNAS mutations define an unexpected pathway for pancreatic cyst development. Sci Transl Med. 2011;3(92):92ra66.
82. Lee LS, Doyle LA, Houghton J, Sah S, Bellizzi AM, Szafranska-Schwarzbach AE, Conner JR, Kadiyala V, Suleiman SL, Banks PA, Andruss BF, Conwell DL. Differential expression of GNAS and KRAS mutations in pancreatic cysts. JOP. 2014;15:581-6.
83. Lee LS, Szafranska-Schwarzbach AE, Wylie D, Doyle LA, Bellizzi AM, Kadiyala V, et al. Investigating MicroRNA Expression Profiles in Pancreatic Cystic Neoplasms. Clin Transl Gastroenterol. 2014;5:e47.
84. Aparicio JR, Martinez J, Niveiro M, Cabezas A, Ruiz F, De Madaria E, et al. Direct intracystic biopsy and pancreatic cystoscopy through a 19-gauge needle EUS (with videos). Gastrointest Endosc. 2010;72(6):1285–8.
85. Napoleon B, Lemaistre AI, Pujol B, Caillol F, Lucidarme D, Bourdariat R, Morellon-Mialhe B, Fumex F, Lefort C, Lepilliez V, Palazzo L, Monges G, Filoche B, Giovannini M. A novel approach to the diagnosis of pancreatic serous cystadenoma: needle-based confocal laser endomicroscopy. Endoscopy. 2015;47:26-32.
86. Nakai Y, Iwashita T, Park DH, Samarasena J, Lee JG, Chang KJ. Diagnosis of pancreatic cysts: EUS-guided, through-the-needle confocal laser-induced endomicroscopy and cystoscopy trial: DETECT study. Gastrointest Endosc. 2015 Jan 26. Epub ahead of print.
87. Vege SS, Ziring B, Jain R, Moayyedi P. American Gastroenterological Association Institute guidelines for management of asymptomatic neoplastic pancreatic cysts. Gastro 2015.
88. Nguyen D, Dawson DW, Hines J, Reber HA, Donahue TR. Mucinous cystic neoplasms of the pancreas: are we overestimating malignant potential? The American Surgeon 2014;80:915–9.
89. Hart PA and Chari ST. Management of pancreatic mucinous cystic neoplasms: surgery or surveillance? Panceeatology 2015;15:97–8.

EUS in Acute Pancreatitis, Chronic Pancreatitis, and Autoimmune Pancreatitis

32

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Endoscopic Ultrasound in Acute Pancreatitis

Endoscopic ultrasound (EUS) is an important tool for the evaluation of pancreaticobiliary disorders. The proximity of the ultrasound probe from the gastric and duodenal lumen to the pancreas and biliary tree provides very good images of the pancreatic parenchyma and ductal system and also of the gallbladder and common bile duct. In recent years, EUS has emerged as a very useful diagnostic modality for the evaluation of patients with acute pancreatitis (AP). Several studies have shown EUS as a highly accurate method for the diagnosis of common bile duct stones (including microlithiasis) and other causes of AP compared to other imaging methods [1, 2]. In addition, EUS is usually performed as the procedure of choice for the initial management of fluid collections associated with AP (mainly pseudocyst and walled-off necrosis, Chap. 12).

The etiology of AP is not found in up to 10–30 % of patients after the initial examination. Initial workup should include a detailed clinical history with records of recent infectious diseases, abdominal trauma or surgery, ethanol and drug intake, serum calcium, triglyceride levels, liver enzymes, and autoantibodies (ANA, IgG4, rheumatoid factor). In addition, at least one transabdominal ultrasound or abdominal computed tomography (CT) scan is advisable. If this diagnostic workup is normal, these patients are diagnosed with idiopathic acute pancreatitis (IAP) [3].

Case Report

A 74-year-old male with no history of alcohol intake and an ex-smoker was diagnosed 6 months ago with prostate cancer and treated with brachytherapy. He was taking aspirin and nitrates for ischemic cardiac disease and statins for hypercholesterolemia. He was admitted to our department because of severe epigastric abdominal pain and the diagnosis of acute pancreatitis. The blood biochemistry showed normal levels of liver enzymes (AST 11 U/L, ALT 10 U/L, GGT 19 U/L, alkaline phosphatase 102 U/L, bilirubin 0.43 mg/dL) together with markedly high serum lipase (2,250 IU/L). Serum calcium and triglycerides were within normal range. He had a leukocytosis of 12,000 cells/mm^3 and hematocrit 36.8 %. There were no prognostic signs of severe

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pancreatitis. After nothing by mouth, intravenous fluid resuscitation, and analgesia, the patient recovered successfully within 48 h. An abdominal CT scan revealed changes of mild acute pancreatitis (grade C according to Balthazar score) without acute fluid collections or any pancreatic lesion. The gallbladder and common bile duct were reported as normal. After resolution of pain and oral refeeding, the patient was discharged with the diagnosis of IAP on day 5 after admission. He was scheduled for an EUS 6 weeks after discharge and a visit to our outpatient pancreas unit 2 weeks after EUS.

EUS has been widely used to rule out biliary disease (gallbladder and common bile duct microlithiasis) in the setting of IAP, mainly in those cases with an intermediate-high suspicion of biliary origin [4]. However, more interesting is the value of EUS in those cases in whom a biliary cause is not strongly suspected. Despite several publications in this area [1, 2, 5], several questions remain unanswered: What is the real impact of EUS in IAP? Should every patient with IAP be explored by EUS or only those with relapsing pancreatitis? When is the best time to perform EUS after IAP?

What is the Real Impact of EUS in IAP?

The role of EUS in IAP is not limited to the study of biliary disease. EUS is considered one of the most accurate techniques for the diagnosis of chronic pancreatitis, small pancreatic tumors (Chap. 30), and identification and characterization of pancreatic cysts (Chap. 31), mainly tumors such as intraductal papillary mucinous tumor (IPMN) as potential etiologies of AP. During EUS, the ampullary region should be carefully examined for evidence of ampullary lesions and main duct IPMN with mucus filling a gaping ampulla ("fish mouth papilla"). In addition, EUS may also detect anatomical variants including pancreas divisum (Chap. 15) and other pancreaticobiliary junction abnormalities.

Although several studies highlighted the role of EUS in the etiological evaluation of IAP, only a few of them followed these patients to demonstrate that this theoretical advantage is maintained throughout time. Vila et al. [6] performed EUS in 44 patients with IAP who were followed for more than 2 years. EUS identified positive findings in 84 % of the cases (mainly microlithiasis), and the etiological diagnosis was changed after follow-up in only two patients, lowering the diagnostic yield to 79 %. Other trials compared EUS with magnetic resonance cholangiopancreatography (MRCP) in a prospective manner [7, 8]. These studies led to the conclusion that EUS is superior to MRCP for the detection of common bile duct microlithiasis, whereas MRCP is superior to EUS for the diagnosis of pancreatic duct abnormalities. The combination of these two procedures and the clinical course during mean 22-month follow-up reduced the rate of idiopathic acute pancreatitis by 66 % [7].

Should Every Patient with IAP Undergo EUS or Only Those with Recurrent Disease?

The decision to investigate every patient after a single episode of IAP remains controversial. In fact, although some guidelines recommend EUS after the first attack of IAP [9], others do not support this protocol [10]. This topic is well addressed by Yusoff et al. [11], who studied 370 patients after a first episode of idiopathic acute pancreatitis or relapsing disease and proved that the diagnostic yield of EUS does not significantly differ between the two groups. Therefore, in our opinion it is reasonable to perform EUS in every patient after the first attack of IAP, which is shared by other authors [12]. In fact, the ACG guidelines consider it mandatory to rule out a pancreatic tumor in all patients over 40 years old with an episode of IAP [10], and EUS is the best way to identify small pancreatic masses less than 2 cm in size compared to dual-phase CT and contrast-enhanced MRI [13].

When is the Best Time to Perform EUS After IAP?

During acute pancreatitis, edema of the duodenal wall, pancreatic necrosis, and inflammation

or fluid collection around the pancreas can potentially hinder visualization of the pancreas, gallbladder, or bile duct by EUS [14]. While the entire pancreas can be visualized in AP, changes of chronic pancreatitis and small tumors can be missed, and hence, EUS for these indications should be avoided during the acute phase of AP. For all these reasons, we perform EUS no earlier than 4 weeks after hospital discharge for IAP. EUS-FNA can be performed if a solid lesion or a cystic tumor is detected to rule out pancreatic cancer or IPMN.

Case Report Continued

An EUS was performed 6 weeks after the acute attack of AP (Fig. 32.1) showing the presence of a cystic lesion with solid peripheral component measuring 18 × 12 mm in the tail of the pancreas. The cyst clearly communicated with the main pancreatic duct and did not contain mural nodules. The surrounding parenchyma was completely normal, as well as the gallbladder and common bile duct. No enlarged lymph nodes were visualized. With the suspicion of a cystic tumor of the pancreas, an endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) was performed, which revealed low cellularity with no evidence of malignancy on cytology, and cyst fluid CEA level of 271.7 ng/mL (threshold for mucinous cysts is > 192 ng/mL). Because of the suspicion for main duct-IPMN, an MRCP was done (Fig. 32.2), and the patient was discussed with the pancreaticobiliary surgeons. A distal pancreatectomy was performed; the surgical pathology revealed the presence of a main duct-IPMN without cellular atypia, and a concomitant adjacent well-differentiated neuroendocrine tumor of 1.1 cm. The patient is well 2 years after surgery without any further attacks of AP.

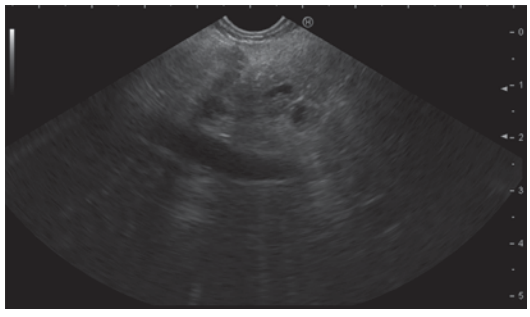

Fig. 32.1 EUS identifies an 18 × 12 mm cystic lesion with solid peripheral component in the tail of the pancreas, which clearly communicates with the main pancreatic duct and did not have mural nodules nor adjacent enlarged lymph nodes

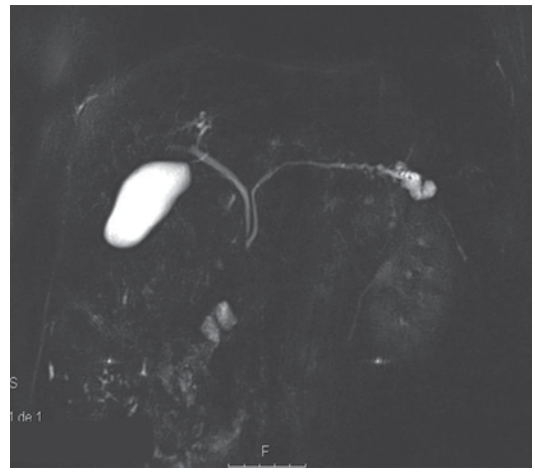

Fig. 32.2 MRCP showing the previously described lesion seen as diffusely dilated main pancreatic duct in the pancreatic tail

Other Indications for EUS in the Context of AP

EUS is widely used in clinical practice for the transgastric drainage of fluid collections after AP, mainly pseudocysts and walled-off necrosis (Chap. 12). EUS-guided puncture of the fluid collection allows avoidance of vessels along the needle tract and makes the appropriate drainage modalities (stenting, necrosectomy) feasible [15].

Endoscopic Ultrasound in Chronic Pancreatitis

Chronic pancreatitis (CP) is a progressive and irreversible disease characterized by chronic inflammation of the pancreatic gland that ultimate-

ly leads to fibrosis and destruction of normal tissue resulting in morphological changes and exocrine as well asendocrine dysfunction. Diagnosis of chronic pancreatitis by imaging techniques is based on the demonstration of morphological changes that develop in the gland as a consequence of pancreatic fibrosis and inflammation. These changes are very evident in advanced stages of the disease but difficult to detect in early phases [16]. The diagnosis is therefore easy to establish in advanced stages of the disease, when the presence of pancreatic calcifications, atrophy of the gland, and pancreatic duct dilation can be visualized by conventional imaging techniques such as abdominal ultrasound and CT. Early CP, on the other hand, remains a major diagnostic challenge today.

Case Report

A 57-year-old male was seen by the gastroenterology department because of epigastric pain lasting for 6 months. The pain did not radiate elsewhere, was not related to meals, and showed poor response to therapy with proton pump inhibitor. The patient did not report weight loss. He was a smoker [15 cigarettes per day) and mild drinker (20 gr of alcohol per day, mainly wine at lunch). In his family history, his mother had died from gastric cancer, and his father was recently diagnosed with type II diabetes mellitus. Abdominal examination was normal. Laboratory data showed no significant abnormality. Because of the patient's age and family history, a gastroscopy was performed, which revealed mild signs of chronic gastritis without mucosal atrophy, acute inflammation, *H. pylori* infection, metaplasia or dysplasia on biopsy. A transabdominal ultrasound was normal. After recommending dietary and life style modification, together with omeprazole 20 mg daily, the patient was scheduled for follow-up 3 months later. During this period, only a minor response to therapy occurred, and the patient maintained his smoking and drinking habit. The patient was then scheduled for additional imaging procedures to exclude extraluminal findings, mainly pancreatic diseases.

Nonendoscopic Imaging Techniques to Evaluate for Chronic Pancreatitis

CT scan, magnetic resonance imaging (MRI), and secretin-stimulated MRCP (s-MRCP) are considered the main imaging techniques for the diagnosis of CP [16].

CT scan is a highly accurate technique for detecting pancreatic calcifications, parenchymal atrophy, and inflammatory masses in the context of chronic pancreatitis. In addition, dilation of the pancreatic duct as shown by CT scan correlates well with endoscopic retrograde pancreatography (ERP) findings [17]. However, the accuracy of CT scan for detecting minimal parenchymal or ductal changes of chronic pancreatitis is limited, and this technique is therefore not indicated for the diagnosis of early stage CP [18].

Compared to CT scan, the combination of MRI and s-MRCP appears to be more sensitive for early changes of chronic pancreatitis [19–21]. The normal high-intensity signal in T1-weighted sequences of the pancreas is lost in chronic pancreatitis. In addition, after intravenous gadolinium administration the signal intensity of the pancreas decreases in the arterial phase and increases in the venous or portal phase, whereas the appearance of the gland becomes heterogeneous in CP [22]. MRCP, mainly after intravenous secretin injection, is able to detect the typical ductal changes of chronic pancreatitis previously described for ERP [19]. Pancreatic duct abnormalities include irregular dilation and a beaded appearance of the main duct, which may contain intraductal calculi, and dilated side branches [21]. Intravenous secretin injection significantly improves visualization of the main pancreatic duct and side branches during MRCP; in addition, it allows the assessment of exocrine pancreatic secretion based on the quantification of duodenal filling [23]. Taken together, the static and dynamic features of the pancreas during gadolinium-enhanced MRI and s-MRCP yield accurate information for the diagnosis of chronic pancreatitis even in early stages of the disease.

Endoscopic Imaging Techniques to Evaluate for Chronic Pancreatitis

Until recent years, ERCP has been considered the gold standard for the diagnosis of CP. However, due to its invasiveness, risk of complications, and the development of new techniques, ERCP can no longer be considered for diagnostic purposes in clinical practice. More recently, EUS has arisen as the most valuable method for establishing the diagnosis of CP.

EUS is presently considered the most sensitive imaging method for the diagnosis of chronic pancreatitis [24, 25]. Using histology as the gold standard, the sensitivity of EUS ranges from 71 to 91 % and specificity from 86 to 100 % [26–28]. The sensitivity and specificity changes based on the threshold number of EUS criteria chosen for the diagnosis of CP. The greater the number of criteria present, the higher the specificity (the less likely that EUS falsely diagnoses CP) at the expense of sensitivity (the more likely that EUS misses a diagnosis of CP). Thus, for patients with at least five EUS criteria, specificity is 91 % with 76 % sensitivity while those with three criteria have 57–81 % specificity and 83–95 % sensitivity [24]. The presence of five or more EUS criteria is generally accepted to support the diagnosis of the disease [26]. Nevertheless, three or four EUS criteria of chronic pancreatitis may be enough for early diagnosis in patients with a clinical picture suggestive of the disease. Moreover, there is an excellent correlation between the number of EUS criteria and the histological severity of chronic pancreatitis [29]. In addition, the following criteria appear associated with severe CP: hyperechoic foci with shadowing, irregular main pancreatic duct, lobularity with honeycombing, dilated side branches, dilated main pancreatic duct, and hyperechoic foci without shadowing [30].

The EUS parenchymal and ductal features of the disease have been properly defined (Table 32.1, Figs. 32.3, 32.4, 32.5) [31–33]. With the assumption that not all criteria are equally important, the Rosemont classification (Tables 32.2 and 32.3) [34] has been proposed, in which the EUS criteria of CP and the various EUS features of CP are strictly defined and given different weights. However, this classification does not seem to improve the diagnostic value of EUS, and further studies are needed to validate it [35]. One weakness of EUS for the diagnosis of CP is the well-known poor interobserver agreement, not only for the final diagnosis of CP but also for isolated criteria. Even the development of the Rosemont classification has not improved this issue [36].

Table 32.1 EUS criteria for the diagnosis of chronic pancreatic and its histological correlation

EUS criteria	Histological correlation
Parenchymal abnormalities	
Hyperechoic foci	Focal fibrosis
Hyperechoic strands	Bridging fibrosis
Lobularity	Interlobular fibrosis
Cysts	Pseudocysts
Hyperechoic foci with shadowing	Calcification
Ductal abnormalities	
Main pancreatic duct dilation	>3 mm head; >2 mm body; >1 mm tail
Main pancreatic duct irregularity	Focal dilation/narrowing
Hyperechoic margin	Periductal fibrosis
Side branches	Dilated side branches
Stones	Calcifications

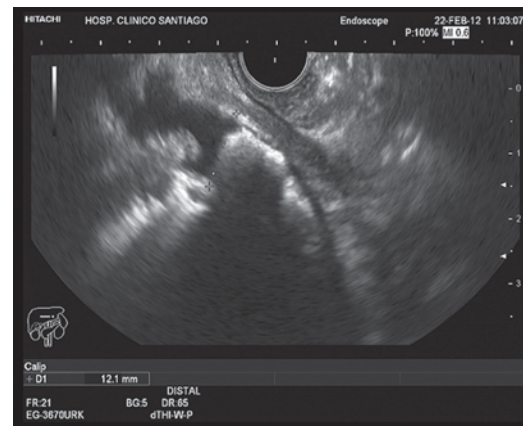

Fig. 32.3 EUS image of dilated main pancreatic duct (marked by *cross marks*) with intraductal stones seen as hyperechoic with shadowing.

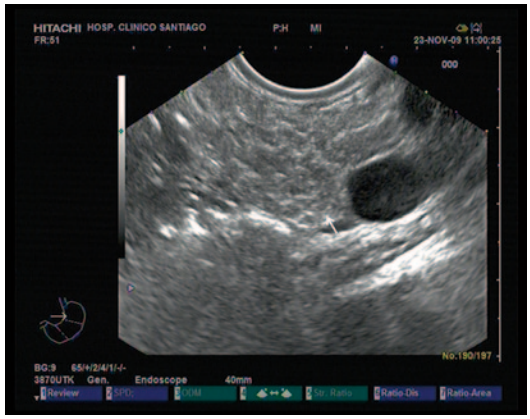

Fig. 32.4 EUS image of lobularity.

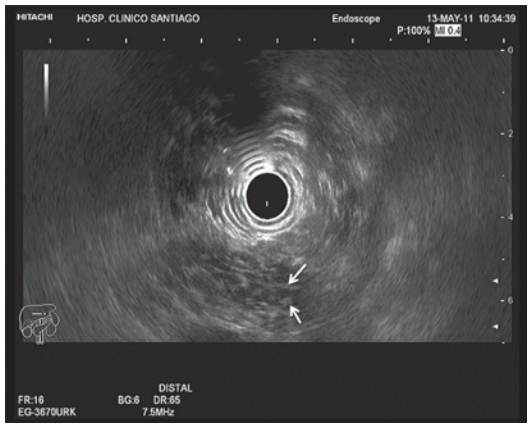

Fig. 32.5 EUS image of hyperechoic strands and hyperechoic foci *(arrows)*.

The accuracy of EUS and MRCP for diagnosing CP was compared in a prospective study of 99 patients with signs or symptoms of CP who underwent both studies, and the gold standards included ERCP, histology, and/or long-term clinical follow-up. Eventually, 40 patients were diagnosed with CP with the other 59 patients serving as normal controls. EUS was more sensitive than MRCP (93 vs. 65%, $p=0.007$) with similar specificity (≥90%) for CP. When either EUS or MRCP was used to diagnose CP, sensitivity was 98% while when both were suggestive of CP, specificity was 100%. Therefore, EUS and MRCP appeared complementary techniques. MRI technology has improved since this study and the addition of secretin increases diagnostic accuracy of MRCP. While EUS may be considered today the best technique to establish the diagnosis of chronic pancreatitis in experienced hands, in reality both s-MRCP and EUS are typically obtained in patients with suspected early CP.

Case Report Continued

The patient underwent EUS, which identified the presence of hyperechoic foci and strands (as parenchymal criteria) and an irregular contour of the main pancreatic duct with a hyperechoic margin (as ductal criteria; Fig. 32.6 and Video 32.1). With these four EUS criteria (two parenchymal and two ductal criteria), he was indeterminate for CP according to the Rosemont classification and was diagnosed with probable early CP.

Does EUS Play Any Role in the Etiological Diagnosis of Chronic Pancreatitis?

Once CP is diagnosed, proper etiological classification becomes important. Major predisposing risk factors for CP have been categorized as toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, or obstructive (TIGAR-O system) [37]. In this context, EUS can detect obstructive causes of CP and provide data supporting an autoimmune origin of the disease (see below).

What Other EUS-associated Techniques May Aid Diagnosis of Early Chronic Pancreatitis?

Some techniques associated with EUS have been attempted to improve the diagnostic accuracy for CP, which mainly include EUS-guided fine needle aspiration (FNA) and biopsy (FNB), elastog-

Table 32.2 Consensus-based parenchymal and ductal features of CP according to Rosemont classification [34]

Feature	Definition	Major criteria	Minor criteria
Hyperechoic foci with shadowing	Echogenic structures ≥2 mm in length and width that shadow	Major A	
Lobularity	Well-circumscribed, ≥ 5 mm structures with enhancing rim and relatively echo-poor center		
A. With honeycombing	Contiguous ≥3 lobules	Major B	
B. Without honeycombing	Noncontiguous lobules		Yes
Hyperechoic foci without shadowing	Echogenic structures ≥2 mm in both length and width with no shadowing		Yes
Cysts	Anechoic, rounded/elliptical structures with or without septations		Yes
Stranding	Hyperechoic lines of ≥3 mm in length in at least 2 different directions with respect to the imaged plane		Yes
MPD calculi	Echogenic structure(s) within MPD with acoustic shadowing	Major A	
Irregular MPD contour	Uneven or irregular outline and ectatic course		Yes
Dilated side branches	3 or more tubular anechoic structures each measuring ≥1 mm in width, budding from the MPD		Yes
MPD dilation	≥ 3.5-mm body or ≥1.5-mm tail		Yes
Hyperechoic MPD margin	Echogenic, distinct structure greater than 50% of entire MPD in the body and tail		Yes

Table 32.3 EUS diagnosis of chronic pancreatitis (CP) based on Rosemont Consensus [34]

I. Consistent with CP	1 major A feature (+) ≥3 minor features
	1 major A feature (+) major B feature
	2 major A features
II. Suggestive of CP	1 major A feature (+) <3 minor features
	1 major B feature (+) ≥3 minor features
	≥ 5 minor features (any)
III. Indeterminate for CP	3 to 4 minor features, no major features
	Major B feature alone or with <3 minor features
IV. Normal	≤2 minor features, no major features

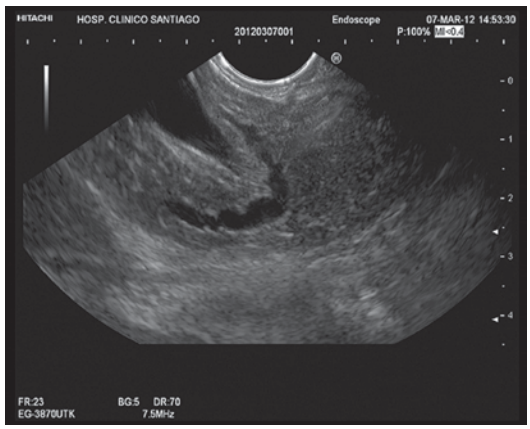

Fig. 32.6 EUS B-mode image demonstrating the presence of hyperechoic strands with an irregular main pancreatic duct with hyperechoic margins.

raphy and contrast enhancement, and pancreatic function testing.

EUS-FNA/FNB has a clear and well investigated role in the differentiation of mass-forming chronic pancreatitis from pancreatic cancer [38], but studies on the use of EUS-guided tissue sampling in distinguishing early CP from normal tissue are scarce. Hollerbach et al. investigated the value of adding a 22-gauge needle FNA to standard EUS evaluation in a series of 37 patients with the clinical suspicion of CP and used ERP as the gold standard. The addition of EUS-FNA improved the negative predictive value of EUS from 75 to 100% with 2 (7%) complications of mild pancreatitis [39]. In another small series

from our group of 14 patients, EUS-FNA using a 22-gauge needle with aspirates placed into formalin for pathology evaluation was able to detect chronic inflammatory cell infiltration in all cases and could also categorize the severity of the disease [40]. The role of EUS-FNB for the diagnosis of early chronic pancreatitis has not been evaluated yet.

Elastography is a noninvasive technique to measure tissue elasticity in real time (Video 32.1). For elastographic evaluation, the probe is placed on the gastrointestinal wall exerting just enough pressure needed for an optimal and stable B-mode image at 7.5 MHz. The region of interest for elastographic evaluation is manually selected to include the whole targeted lesion or area for study. Maximal sensitivity for elastographic registration needs to be used. Different tissue elasticity patterns are qualitatively marked by different colors on the grey-color EUS scale (blue for hard tissue, red for soft tissue, and yellow and green for intermediate stiffness). The stiffness of the tissue can also be quantified as strain ratio (normal<2.2) or hue histogram. Two areas (A and B) from the region of interest are selected for quantitative elastographic strain ratio analysis. Area A represents the target lesion. Area B refers to a soft (red) reference area outside the area of interest, with the gastrointestinal wall being the best option. The strain ratio (B/A) is the measure of the quantitative elastographic evaluation. The hue-histogram is a graphical representation of the distribution of colors (hues) and is based on the qualitative EUS elastographic image obtained. Once the optimal elastographic image is selected, the lesion to be studied by hue-histogram is manually selected. On the x-axis of the histogram, the numeric values of the elasticity are displayed on a scale from 0 (hardest) to 250 (softest). On the y-axis, the height of the spikes displayed indicates the number of pixels of each elasticity level found in the region of interest. Consequently, the mean value of the histogram corresponds to the global hardness or elasticity of the lesion [41].

In our experience, the normal pancreas shows a homogeneous green pattern, whereas a heterogeneous green predominant pattern is frequently seen in patients with chronic pancreatitis [42]. With quantitative EUS elastography, normal pancreas has lower strain ratio levels compared to inflammatory and malignant lesions. Malignant lesions, mainly pancreatic cancer, display a high strain ratio (>6.04) [43]. As a measure of the degree of pancreatic fibrosis in chronic pancreatitis, we recently reported a highly significant direct linear correlation between the number of EUS criteria for chronic pancreatitis and the strain ratio ($r=0.813$; $p<0.0001$). Accuracy of EUS elastography for diagnosing chronic pancreatitis was 91.1% using the gold standards of EUS (≥5 criteria) or equivocal EUS (3–4 criteria) with confirmatory findings on MRI pancreas and s-MRCP. The strain ratio also varied significantly among the different Rosemont classification groups (1.80 normal pancreas, 2.40 indeterminate group, 2.85 suggestive of CP, 3.62 consistent with CP, $p<0.001$) [44]. Thus, EUS elastography may provide interesting objective information supporting the diagnosis of chronic pancreatitis in indeterminate cases.

Intravenous contrast to evaluate the vascularization pattern of solid pancreatic lesions is widely used in clinical practice in Europe. However, data about its use in the setting of CP without an inflammatory mass are anecdotal. We recently conducted a pilot trial administrating 4.8 ml of Sonovue® in patients with EUS findings indeterminate for chronic pancreatitis. Compared to a homogeneous isovascular pattern and slow contrast washout in healthy pancreas, a trabecular contrast enhancement pattern corresponding to the hyperechoic rim of lobules seen on B-mode EUS was observed in all CP patients. In addition, after 90 s there was a complete washout of contrast from the pancreatic parenchyma in all CP cases. Further studies are needed to establish the role of EUS contrast enhancement for the early diagnosis of CP.

Pancreatic function tests (PFT) have been used for the diagnosis of early CP. The PFT with the highest sensitivity for CP is the secretin-cholecystokinin (CCK) stimulation test with aspiration of duodenal content by a triple-lumen probe. The sensitivity and specificity of this test for the diagnosis of CP both exceed 90% [45]. A high agreement between EUS and the secretin-CCK test has

been demonstrated in several studies. Modifications of the secretin-CCK test have been developed in recent years, leading to the emergence of the endoscopic pancreatic function test (ePFT) during which the procedure is shortened to 1 h, and pancreatic juice is collected by a gastroscope placed in the second portion of the duodenum following secretin injection (0.2 mcg/kg) [46]. Peak bicarbonate level (highest value of all the collections) ≥80 mEq/L implies normal exocrine pancreatic function. Practical tips to performing this procedure correctly include completely suctioning gastric contents and clearing the suction channel with duodenal fluid before beginning fluid collection every 15 min, placing the fluid specimens on ice, performing analysis within a few hours of collection, and avoiding performing biopsies until after the collections are finished. The shortened ePFT is a 45-minute test using peak bicarbonate level 75 mEq/L as the cutoff with 94% agreement to the 1-h test [47]. This shortened ePFT should be used to screen patients for CP as its specificity is high (93%). Therefore, if peak bicarbonate is ≥75 mEq/L, the patient does not have exocrine insufficiency. If the test is abnormal, the full 1-h test should be performed to confirm these results. A step forward has been the introduction of a combined test, using both ePFT and EUS to assess both functional and structural changes of CP simultaneously. The method is based on performing a standard EUS for identifying criteria of CP; afterwards, secretin is administered intravenously and duodenal fluid is subsequently collected at 15, 30, and 45 min. Some studies have demonstrated the usefulness of this approach for the diagnosis of early CP [48].

Pancreatic morphology can also be dynamically evaluated by EUS after secretin stimulation. The pancreatic duct dilates after secretin stimulation in the normal pancreas. In a pilot study, dynamic EUS has demonstrated reduced pancreatic duct compliance (defined as percentage change from baseline to peak pancreatic duct diameter after secretin injection) as a consequence of duct fibrosis in CP, most pronounced in the tail of the pancreas [49]. Studies are awaited to evaluate this technique further.

Case Report Concluded

An EUS-ePFT was carried out in the patient to further characterize pancreatic changes. During the procedure, repeat EUS evaluation of the pancreas confirmed the presence of 4 EUS criteria. Elastography was performed, and a mean strain ratio of 7.29 was obtained (normal <2.2; Fig. 32.7). Dynamic dilation of the main pancreatic duct after secretin injection was markedly reduced. In addition, peak bicarbonate level in duodenal juice after secretin injection was 64 mEq/L (normal ≥80 mEq/L for full 1-h test). All these findings helped us to establish the final diagnosis of early chronic pancreatitis.

Role of EUS in Treatment of Chronic Pancreatitis

Various techniques associated with EUS can be helpful in the management of CP patients. The two main procedures are EUS-guided celiac blockade for pain (Chap. 33) and EUS-guided drainage techniques (Chap. 12).

EUS-guided celiac plexus blockade by injecting a combination of corticosteroids (triamcinolone) and anesthetic agents (bupivacaine) around the celiac plexus may help some CP patients to reduce pain and to improve quality of life. Partial alleviation of pain ranges from 50 to 70%, but long-term follow-up studies are lacking [50].

EUS-guided drainage by means of a transgastric or transduodenal stent can be considered as the therapy of choice for symptomatic pseudocysts in the context of chronic pancreatitis. Several series have been reported, and randomized trials have shown a significantly better success rate for EUS-guided drainage than for conventional endoscopic drainage or even surgical cystgastrostomy [51].

Finally EUS has also been used to guide access to the main pancreatic duct in order to provide minimally invasive drainage in patients. This can be performed either through the gastric or the duodenal wall. Success rates of 77−92% have been reported. However, complications related to the technique are frequent, including pain, bleed-

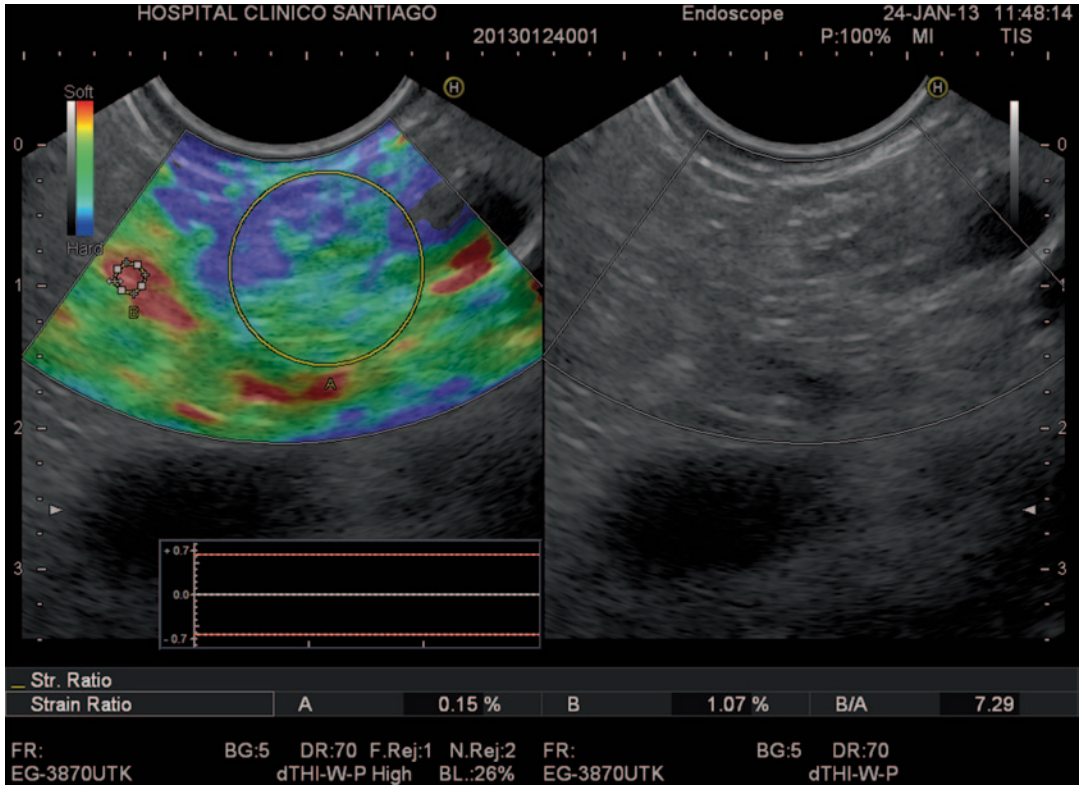

Fig. 32.7 EUS-guided elastography of the patient with findings suggestive of early chronic pancreatitis, and a strain ratio of 7.3

ing, perforation, and hematoma. Therefore, EUS-guided access of the main pancreatic duct is a technically challenging procedure and should always be performed by experts under fluoroscopic guidance [52].

EUS in Autoimmune Pancreatitis

Autoimmune pancreatitis (AIP) has historically been considered a rare disorder, but it is increasingly recognized due to an improved understanding of its diverse nature and proper means of diagnosis. The current international consensus diagnostic criteria (ICDC) for the diagnosis of AIP incorporate 5 cardinal features: imaging characteristics of the pancreas (parenchyma and duct), serology, other organ involvement, pancreatic histology, and response to steroids (Table 32.4) [53]. However, even when the diagnosis of AIP is strongly considered, the diagnosis often remains elusive [54]. In fact, AIP has been demonstrated in 3–5 % of specimens from patients undergoing surgical resection for suspected pancreatic cancer [55]. Imaging techniques recommended in the guidelines include CT scan, MRI/MRCP, ERCP, and more recently EUS.

Case Report

A 47-year old woman who drinks occasional wine and smokes 10 cigarettes per day was admitted to the Emergency Department because of epigastric pain over the last 3 months, together with weight loss of about 5 kg and jaundice. The patient did not report any relevant family history. Physical examination was normal, except for jaundice. Laboratory data revealed normal hemogram, and serum biochemistry showed bilirubin of 7 mg/dL, AST 120 U/L, ALT 240 U/L, and alkaline phosphatase 680 U/L. A dilated common

Table 32.4 International criteria for the diagnosis of autoimmune pancreatitis

	Criterion	Level 1	Level 2
P	Parenchymal imaging	Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Indeterminate (including atypical): Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (endoscopic retrograde pancreatography)	Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size <5 mm)
S	Serology	IgG4, >2 x upper limit of normal value	IgG4, 1–2 x upper limit of normal value
OOI	Other organ involvement	a or b *a. Histology of extrapancreatic organs* *Any three of the following*: Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration Storiform fibrosis Obliterative phlebitis Abundant (10 cells/HPF) IgG4-positive cells *b. Typical radiological evidence* *At least one of the following:* Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture Retroperitoneal fibrosis	a or b *a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct* *Both of the following:* Marked lymphoplasmacytic infiltration without granulocytic infiltration Abundant (10 cells/HPF) IgG4-positive cells *b. Physical or radiological evidence* *At least one of the following:* Symmetrically enlarged salivary/lacrimal glands Radiological evidence of renal involvement described in association with AIP
H	Histology	*LPSP (core biopsy/resection)* At least 3 of the following: Periductal lymphoplasmacytic infiltrate without granulocytic infiltration Obliterative phlebitis Storiform fibrosis Abundant (10 cells/HPF) IgG4-positive cells	*LPSP (core biopsy)* Any 2 of the following: Periductal lymphoplasmacytic infiltrate without granulocytic infiltration Obliterative phlebitis Storiform fibrosis Abundant (10 cells/HPF) IgG4-positive cells
Response to steroids		Diagnostic steroid trial Rapid (≤2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

HPF high power field; *LPSP* lymphoplasmacytic sclerosing pancreatitis

bile duct and peripancreatic lymph nodes were observed on transabdominal ultrasound. At this point, the patient was scheduled for a CT scan.

How Do Different Imaging Studies Differentiate Mass-form Chronic Pancreatitis, Pancreatic Cancer, and AIP?

Findings on CT scan or MRI often offer the first clues raising the suspicion of pancreatic cancer or AIP. Nevertheless, differentiating between mass-forming chronic pancreatitis, AIP, and pancreatic cancer based on CT scan can be challenging [38, 56]. CT findings suggestive of AIP include focal or diffusely enlarged pancreas without dilatation of the main pancreatic duct, a capsule-like rim around the pancreas and the absence of calcifications and pseudocysts. On the contrary, a low density mass on contrast-enhanced CT with pancreatic ductal dilatation or stricture supports the diagnosis of pancreatic cancer [38]. MRI and MRCP may provide additional information to help diagnose AIP [57]. In fact, main pancreatic duct narrowing for ≥1/3 of the pancreatic duct length, multiple segmental lesions of the duct, the presence of side branches at the narrowed

main pancreatic duct, and smooth and straight intrapancreatic common bile duct stenosis are findings suggestive of AIP. Overall, an important point is that the diagnostic workup in unclear cases with solid pancreatic masses should primarily be directed at excluding pancreatic cancer [53].

Case Report Continued

CT scan showed a focal pancreatic mass located at the head of the pancreas with an otherwise diffusely enlarged pancreas. There was no dilatation of the main pancreatic duct. A capsule-like rim around the pancreas was observed. Enlarged lymph nodes were also identified, mainly located around the pancreatic head and liver hilum. CT scan also confirmed the presence of a dilated common bile duct. Regarding vessel evaluation, the superior mesenteric vein, confluence, and portal vein were not infiltrated, but they were very close to the pancreatic solid lesion; the superior mesenteric artery was clearly free from invasion. Serum Ig4 level was slightly elevated. The solid pancreatic mass was suggestive of AIP, but since pancreatic cancer could not be excluded, the patient underwent an EUS of the pancreas.

What is the Role of EUS and Its Associated Techniques in the Diagnosis of AIP?

There are emerging data suggesting the potential utility of EUS in the diagnosis of AIP [58–60]. EUS not only has the ability to provide high-definition imaging of the pancreas, but also to acquire tissue through either FNA or FNB. There are additional techniques associated with EUS as discussed previously that can greatly aid in establishing the diagnosis of AIP, especially in those cases that present as a solid pancreatic mass. Therefore, EUS has the potential to play an important role in the diagnosis of AIP and the exclusion of other pancreatic diseases.

There are no pathognomonic EUS findings of AIP, but some characteristics are commonly seen in this disease. These include a diffusely enlarged gland (called "sausage-shaped") with hypoechoic, patchy heterogeneous-appearing parenchyma (Fig. 32.8). However, patients do not often present with all these features, thereby limiting the diagnostic accuracy of EUS for AIP. Other EUS features seen in AIP are similar to those in patients with chronic pancreatitis of any other etiology, which include hyperechoic foci, hyperechoic strands, and lobularity.

With mass-forming AIP, the lesion typically appears hypoechoic and occurs in the head of the pancreas leading to obstructive jaundice. The bile duct and main pancreatic duct may be narrowed with duct wall thickening (Fig. 32.9). The mass may appear to invade adjacent vessels, cause upstream dilation of the main pancreatic duct, and even be associated with enlarged peripancreatic lymph nodes, making differentiation from pancreatic cancer very difficult [58, 61]. Hoki et al. reported that diffuse hypoechoic areas, diffuse enlargement of the pancreas, bile duct wall thickening, and peripancreatic hypoechoic margins were more commonly seen in AIP than pancreatic cancer. On the other hand, focal hypoechoic areas and focal enlargement were more commonly seen in pancreatic cancer [62]. Finally, common bile duct and gallbladder wall thickening are

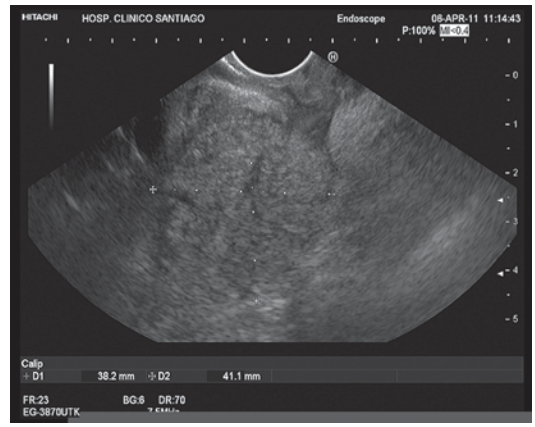

Fig. 32.8 EUS image of autoimmune pancreatitis with hypoechoic, mildly heterogeneous, diffusely enlarged pancreatic parenchyma with hypoechoic margin in the tail of the pancreas. Because of concern for pancreatic malignancy despite negative EUS-FNA, distal pancreatectomy was performed and confirmed diagnosis of autoimmune pancreatitis.

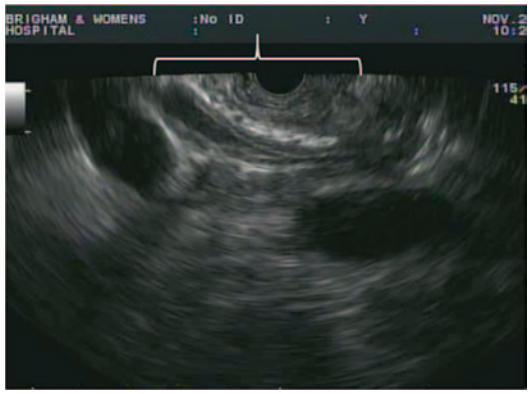

Fig. 32.9 EUS image of patient with autoimmune pancreatitis and distal biliary stricture with diffusely and symmetrically thickened bile duct wall (*white bracket*). (Courtesy of Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

frequently seen in patients with AIP and not in those with pancreatic cancer [63].

EUS elastography could help differentiate AIP from pancreatic cancer. In fact, consistent data demonstrate the usefulness of elastography in differentiating malignant from benign solid pancreatic masses, with an overall accuracy ranging from 80 to 95 % [41]. However, there are scarce data on the role of elastography in the diagnosis of AIP. In the study from Dietrich et al. [64], 5 patients with focal AIP were found to have a homogenous stiff (blue) pattern throughout the entire pancreas including the mass, which differed from pancreatic cancer or normal pancreas in which the pancreatic parenchyma (apart from the cancer) was predominately intermediate stiffness (green).

Contrast-enhanced EUS could also be used, since AIP is associated with hypervascularity within the mass and the surrounding pancreatic parenchyma compared to pancreatic cancer where the mass is hypovascular compared with surrounding pancreatic tissue [65]. In patients with focal AIP, contrast uptake and distribution are iso-enhanced and homogenous, whereas this is rarely seen in pancreatic cancer. The majority of patients with pancreatic cancer have a hypo-enhanced uptake in a heterogeneous pattern [66].

Is EUS-FNA/FNB a Good Option for the Diagnosis of AIP?

EUS-FNA/FNB has proven very accurate for the differential diagnosis of solid pancreatic masses, mainly for establishing the diagnosis of pancreatic cancer [67]. However, the role of EUS-guided tissue acquisition has not been extensively studied in the context of AIP. Cytology from EUS-FNA does not enable the diagnosis of AIP [68, 69]. Even EUS-FNA using a 19-gauge needle for histological review only achieved a diagnosis of AIP in 43 % of patients [70]. Due to the inability to obtain adequate core specimens using standard FNA needles, some advocate using less rigorous or incomplete pathology criteria for the cytologic diagnosis of AIP (mainly the presence of a lymphoplasmacytic infiltrate alone without evaluating the location of the inflammatory infiltrate or the degree of preservation of ductules, venules or arterioles within the specimen). However this approach may lead to low specificity for the diagnosis of AIP. In this setting, the hypothetical benefit of EUS-FNA is its ability to exclude pancreatic cancer rather than to diagnose AIP [60, 71]. However, we need to recognize that the false-negative rate of EUS-FNA for cancer is as high as 10–40 % in patients with features of CP [38].

The current ICDC guidelines recommend a pancreatic core biopsy in patients presenting with a focal mass and/or obstructive jaundice if cancer has been excluded and the diagnosis remains elusive [53]. The needle used for EUS-FNB may be important. Core tissue samples can be safely obtained with the 19-gauge Quick-Core® needle (Cook Medical, Bloomington, IN) [72]. This device has been shown to be useful for diagnosing neoplasms that are often difficult to diagnose by cytology. Furthermore, with the larger specimen size and the ability to preserve tissue architecture, the Quick-Core® needle can help differentiate among AIP, chronic pancreatitis, and pancreatic cancer [73]. EUS-FNB with this needle may provide sufficient material to aid in the diagnosis of AIP, thereby guiding treatment and avoiding surgical intervention [74]. However, sampling

lesions located in the head of the pancreas with this needle is strongly limited due to mechanical friction of the needle firing mechanism resulting from the bended position of the scope. The more recent Procore™ biopsy needle available in 19, 22, 25 G (Cook Medical, Bloomington, IN) seems to have solved this problem and enables obtaining a core tissue sample from solid pancreatic lesions in the majority of cases [75, 76]. However, data are lacking regarding the usefulness of the Procore™ needle in the evaluation of AIP.

Case Report Concluded

An EUS was performed in our patient, which visualized the solid hypoechoic, well-defined lesion located in the head of the pancreas without vascular infiltration, but involving the common bile duct. The rest of the pancreatic parenchyma was patchy, hypoechoic, and diffusely enlarged. The main pancreatic duct was narrowed with duct wall thickening. An EUS elastography was also performed, which revealed a heterogeneous blue predominant pattern with a strain ratio of 152 (Fig. 32.10). At this point, 4.8 mL of Sonovue® was intravenously administered in order to perform contrast-enhanced harmonic EUS, which showed an isovascular pattern. In order to confirm the diagnosis, an EUS-FNB was performed using a 19-gauge Procore™ biopsy needle. A core sample from the pancreatic lesion was obtained, and the pathological analysis reported the presence of fibrosis and a pronounced infiltration of inflammatory cells, mainly lymphocytes and plasma cells. With all these findings, the patient was diagnosed with focal AIP and treated with steroids (40 mg a day of prednisolone orally). He demonstrated significant clinical and biochemical improvement. A repeat CT scan performed 4 weeks later revealed marked improvement of the pancreatic morphology.

Key Points

- Endoscopic ultrasound (EUS) is indicated in patients after an episode of acute idiopathic pancreatitis in order to exclude microlithiasis and pancreatic tumors in patients over the age of 40.
- EUS guidance makes drainage of pseudocysts and wall-off necrosis feasible and safe.
- Diagnosis of chronic pancreatitis can be established in patients with 5 or more EUS criteria of the disease. However, the presence of 3 or 4 criteria may be enough to diagnose chronic pancreatitis in patients with clinical suspicion of the disease.
- The combination of elastography and endoscopic pancreatic function test during EUS may help support the diagnosis of chronic pancreatitis in patients with mild EUS changes.
- Diagnosis of autoimmune pancreatitis (AIP) is a challenge. The presence of a diffusely enlarged pancreas together with high serum IgG4 levels strongly supports the diagnosis.
- Differentiating between AIP and pancreatic cancer is difficult in cases with solid pancreatic masses. EUS may show some findings to support the diagnosis of AIP, but EUS-guided fine needle biopsy is usually required to exclude pancreatic malignancy and potentially provide a proper diagnosis.

Video Caption

Video 32.1 EUS B-mode video demonstrating the presence of multiple hyperechoic strands and nondilated pancreatic duct with hyperechoic margins. Elastography demonstrates heterogeneous green pattern to pancreatic parenchyma with area A selected in large circle to represent the target lesion and area B selected with a small circle around red tissue as the reference point to calculate the strain ratio

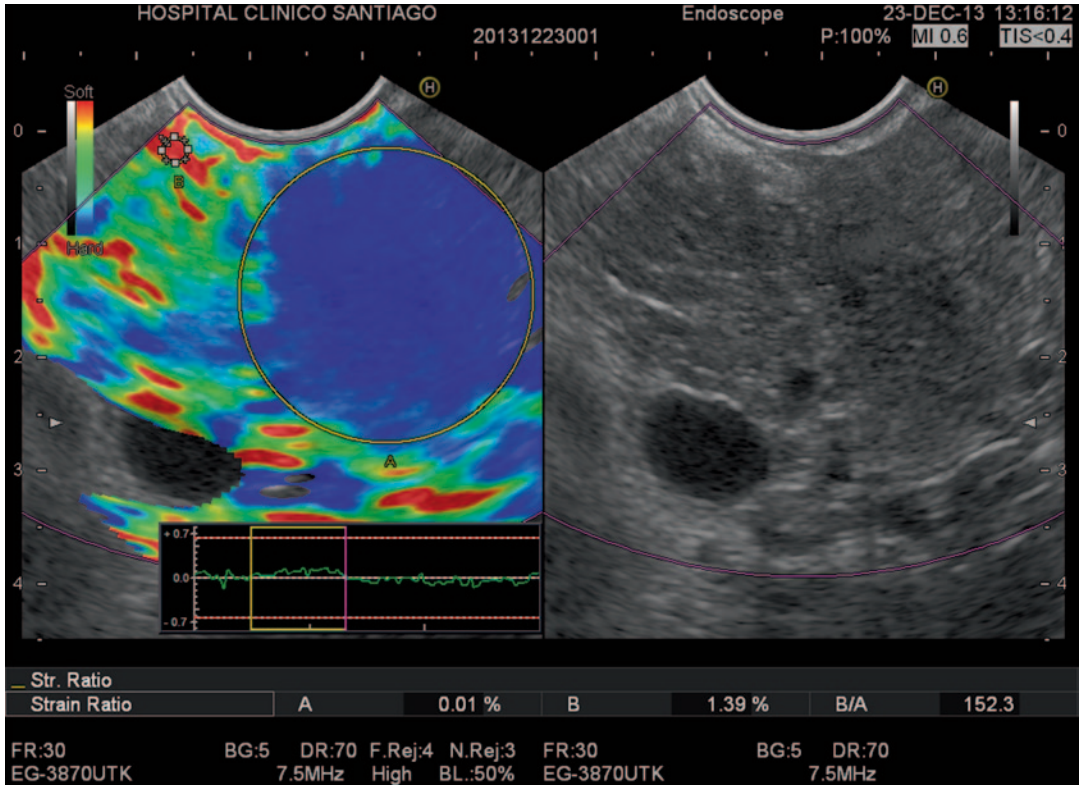

Fig. 32.10 EUS-guided elastographic image of a solid pancreatic mass located in the pancreatic head with a heterogeneous blue predominant pattern and a very high strain ratio consistent with autoimmune pancreatitis

References

1. Norton SA, Alderson D. Endoscopic ultrasonography in the evaluation of idiopathic acute pancreatitis. Br J Surg. 2000;87(12):1650–5. PubMed PMID: 11122178.
2. Tandon M, Topazian M. Endoscopic ultrasound in idiopathic acute pancreatitis. Am J Gastroenterol. 2001;96(3):705–9. PubMed PMID: 11280538.
3. Vila JJ. Endoscopic ultrasonography and idiopathic acute pancreatitis. World J Gastrointest Endosc. 2010;2(4):107–11. PubMed PMID: 21160725. Pubmed Central PMCID: 2999169.
4. Petrov MS, Savides TJ. Systematic review of endoscopic ultrasonography versus endoscopic retrograde cholangiopancreatography for suspected choledocholithiasis. Br J Surg. 2009;96(9):967–74. PubMed PMID: 19644975.
5. Repiso Ortega A Gomez-Rodriguez R Gonzalez de Frutos C de la Cruz Perez G Navajas J Perez Grueso MJ et al. Utility of endoscopic ultrasonography in the etiological diagnosis of patients with acute idiopathic pancreatitis. Gastroenterol Hepatol. 2008;31(4):207–12. PubMed PMID: 18405484.
6. Vila JJ, Vicuna M, Irisarri R, de la Higuera BG, Ruiz-Clavijo D, Rodriguez-Gutierrez C, et al. Diagnostic yield and reliability of endoscopic ultrasonography in patients with idiopathic acute pancreatitis. Scand J Gastroenterol. 2010;45(3):375–81. PubMed PMID: 20034361.
7. Thevenot A, Bournet B, Otal P, Canevet G, Moreau J, Buscail L. Endoscopic ultrasound and magnetic resonance cholangiopancreatography in patients with idiopathic acute pancreatitis. Dig Dis Sci. 2013;58(8):2361–8. PubMed PMID: 23508982.
8. Ortega AR, Gomez-Rodriguez R, Romero M, Fernandez-Zapardiel S, Cespedes Mdel M, Carrobles JM. Prospective comparison of endoscopic ultrasonography and magnetic resonance cholangiopancreatography in the etiological diagnosis of "idiopathic" acute pancreatitis. Pancreas. 2011;40(2):289–94. PubMed PMID: 21206330.
9. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. 2013;13(4 Suppl 2):e1–15. PubMed PMID: 24054878.
10. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400–15; 16. PubMed PMID: 23896955.

11. Yusoff IF, Raymond G, Sahai AV. A prospective comparison of the yield of EUS in primary vs. recurrent idiopathic acute pancreatitis. Gastrointest Endosc. 2004;60(5):673–8. PubMed PMID: 15557941.
12. Al-Haddad M, Wallace MB. Diagnostic approach to patients with acute idiopathic and recurrent pancreatitis, what should be done? World J Gastroenterol. 2008;14(7):1007–10. PubMed PMID: 18286679. PubMed Central PMCID: 2689400.
13. DeWitt J, Devereaux B, Chriswell M, McGreevy K, Howard T, Imperiale TF, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med. 2004;141(10):753–63. PubMed PMID: 15545675.
14. Kotwal V, Talukdar R, Levy M, Vege SS. Role of endoscopic ultrasound during hospitalization for acute pancreatitis. World J Gastroenterol. 2010;16(39):4888–91. PubMed PMID: 20954274. PubMed Central PMCID: 2957596.
15. Varadarajulu S, Phadnis MA, Christein JD, Wilcox CM. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic walled-off pancreatic necrosis. Gastrointest Endosc. 2011;74(1):74–80. PubMed PMID: 21612778.
16. Kinney TP, Freeman ML. Pancreatic imaging: current state of the art. Gastroenterology. 2009;136(3):776–9. PubMed PMID: 19168064.
17. Malfertheiner P, Buchler M. Correlation of imaging and function in chronic pancreatitis. Radiol Clin North Am. 1989;27(1):51–64. PubMed PMID: 2642276.
18. Choueiri NE, Balci NC, Alkaade S, Burton FR. Advanced imaging of chronic pancreatitis. Curr Gastroenterol Rep. 2010;12(2):114–20. PubMed PMID: 20424983.
19. Schlaudraff E, Wagner HJ, Klose KJ, Heverhagen JT. Prospective evaluation of the diagnostic accuracy of secretin-enhanced magnetic resonance cholangiopancreaticography in suspected chronic pancreatitis. Magn Reson Imaging. 2008;26(10):1367–73. PubMed PMID: 18583078.
20. Balci C. MRI assessment of chronic pancreatitis. Diagn Interv Radiol. 2011;17(3):249–54. PubMed PMID: 20945291.
21. Miller FH, Keppke AL, Wadhwa A, Ly JN, Dalal K, Kamler VA. MRI of pancreatitis and its complications: part 2, chronic pancreatitis. AJR. 2004;183(6):1645–52. PubMed PMID: 15547204.
22. Balci NC, Alkaade S, Magas L, Momtahen AJ, Burton FR. Suspected chronic pancreatitis with normal MRCP: findings on MRI in correlation with secretin MRCP. J Magn Reson Imaging. 2008;27(1):125–31. PubMed PMID: 18058927.
23. Akisik MF, Aisen AM, Sandrasegaran K, Jennings SG, Lin C, Sherman S, et al. Assessment of chronic pancreatitis: utility of diffusion-weighted MR imaging with secretin enhancement. Radiology. 2009;250(1):103–9. PubMed PMID: 19001148.
24. Seicean A. Endoscopic ultrasound in chronic pancreatitis: where are we now? World J Gastroenterol. 2010;16(34):4253–63. PubMed PMID: 20818808.
25. Kahl S, Glasbrenner B, Leodolter A, Pross M, Schulz HU, Malfertheiner P. EUS in the diagnosis of early chronic pancreatitis: A prospective follow-up study. Gastrointest Endosc. 2002;55(4):507–11. PubMed PMID: 11923762.
26. Stevens T. Role of endoscopic ultrasonography in the diagnosis of acute and chronic pancreatitis. Gastrointest Endosc Clin N Am. 2013;23(4):735–47. PubMed PMID: 24079787.
27. Chong AK, Hawes RH, Hoffman BJ, Adams DB, Lewin DN, Romagnuolo J. Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. Gastrointest Endosc. 2007;65(6):808–14. PubMed PMID: 17466199.
28. Varadarajulu S, Eltoum I, Tamhane A, Eloubeidi MA. Histopathologic correlates of noncalcific chronic pancreatitis by EUS: a prospective tissue characterization study. Gastrointest Endosc. 2007;66(3):501–9. PubMed PMID: 17640639.
29. Albashir S, Bronner MP, Parsi MA, Walsh RM, Stevens T. Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis. Am J Gastroenterol. 2010;105(11):2498–503. PubMed PMID: 20606675.
30. LeBlanc JK, Chen JH, Al-Haddad M, Juan M, Okumu W, McHenry L, et al. Endoscopic ultrasound and histology in chronic pancreatitis: how are they associated? Pancreas. 2014;43(3):440–4. PubMed PMID: 24622076.
31. Wiersema MJ, Hawes RH, Lehman GA, Kochman ML, Sherman S, Kopecky KK. Prospective evaluation of endoscopic ultrasonography and endoscopic retrograde cholangiopancreatography in patients with chronic abdominal pain of suspected pancreatic origin. Endoscopy. 1993;25(9):555–64. PubMed PMID: 8119204.
32. Sahai AV, Zimmerman M, Aabakken L, Tarnasky PR, Cunningham JT, van Velse A, et al. Prospective assessment of the ability of endoscopic ultrasound to diagnose, exclude, or establish the severity of chronic pancreatitis found by endoscopic retrograde cholangiopancreatography. Gastrointest Endosc. 1998;48(1):18–25. PubMed PMID: 9684659.
33. Catalano MF, Lahoti S, Geenen JE, Hogan WJ. Prospective evaluation of endoscopic ultrasonography, endoscopic retrograde pancreatography, and secretin test in the diagnosis of chronic pancreatitis. Gastrointest Endosc. 1998;48(1):11–7. PubMed PMID: 9684658.
34. Catalano MF, Sahai A, Levy M, Romagnuolo J, Wiersema M, Brugge W, et al. EUS-based criteria for the diagnosis of chronic pancreatitis: the Rosemont classification. Gastrointest Endosc. 2009;69(7):1251–61. PubMed PMID: 19243769.
35. Stevens T, Lopez R, Adler DG, Al-Haddad MA, Conway J, Dewitt JM, et al. Multicenter comparison of the interobserver agreement of standard EUS

scoring and Rosemont classification scoring for diagnosis of chronic pancreatitis. Gastrointest Endosc. 2010;71(3):519–26. PubMed PMID: 20189510.
36. Del Pozo D, Poves E, Tabernero S, Beceiro I, Moral I, Villafruela M, et al. Conventional versus Rosemont endoscopic ultrasound criteria for chronic pancreatitis: interobserver agreement in same day back-to-back procedures. Pancreatology. 2012;12(3):284–7. PubMed PMID: 22687386.
37. Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology. 2001;120(3):682–707. PubMed PMID: 11179244.
38. Iglesias-Garcia J, Lindkvist B, Larino-Noia J, Dominguez-Munoz JE. The role of EUS in relation to other imaging modalities in the differential diagnosis between mass forming chronic pancreatitis, autoimmune pancreatitis and ductal pancreatic adenocarcinoma. Rev Esp Enferm Dig. 2012;104(6):315–21. PubMed PMID: 22738702.
39. Hollerbach S, Klamann A, Topalidis T, Schmiegel WH. Endoscopic ultrasonography (EUS) and fine-needle aspiration (FNA) cytology for diagnosis of chronic pancreatitis. Endoscopy. 2001;33(10):824–31. PubMed PMID: 11571676.
40. Iglesias-Garcia J, Abdulkader I, Larino-Noia J, Forteza J, Dominguez-Munoz JE. Histological evaluation of chronic pancreatitis by endoscopic ultrasound-guided fine needle biopsy. Gut. 2006;55(11):1661–2. PubMed PMID: 17047112. PubMed Central PMCID: 1860137.
41. Iglesias-Garcia J, Dominguez-Munoz JE. Endoscopic ultrasound image enhancement elastography. Gastrointest Endosc Clin N Am. 2012;22(2):333–48, x–xi. PubMed PMID: 22632955.
42. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. EUS elastography for the characterization of solid pancreatic masses. Gastrointest Endosc. 2009;70(6):1101–8. PubMed PMID: 19647248.
43. Iglesias-Garcia J, Larino-Noia J, Abdulkader I, Forteza J, Dominguez-Munoz JE. Quantitative endoscopic ultrasound elastography: an accurate method for the differentiation of solid pancreatic masses. Gastroenterology. 2010;139(4):1172–80. PubMed PMID: f20600020.
44. Iglesias-Garcia J, Dominguez-Munoz JE, Castineira-Alvarino M, Luaces-Regueira M, Larino-Noia J. Quantitative elastography associated with endoscopic ultrasound for the diagnosis of chronic pancreatitis. Endoscopy. 2013;45(10):781–8. PubMed PMID: 24019131.
45. Dominguez Munoz JE. Diagnosis of chronic pancreatitis: functional testing. Best Pract Res Clin Gastroenterol. 2010;24(3):233–41. PubMed PMID: 20510825.
46. Stevens T, Conwell DL, Zuccaro G, Jr., Van Lente F, Lopez R, Purich E, et al. A prospective crossover study comparing secretin-stimulated endoscopic and Dreiling tube pancreatic function testing in patients evaluated for chronic pancreatitis. Gastrointest Endosc. 2008;67(3):458–66. PubMed PMID: 18294508.
47. Stevens T, Conwell DL, Zuccaro G, Jr., Lewis SA, Love TE. The efficiency of endoscopic pancreatic function testing is optimized using duodenal aspirates at 30 and 45 min after intravenous secretin. Am J Gastroenterol. 2007;102(2):297–301. PubMed PMID: 17100964.
48. Stevens T, Dumot JA, Parsi MA, Zuccaro G, Vargo JJ. Combined endoscopic ultrasound and secretin endoscopic pancreatic function test in patients evaluated for chronic pancreatitis. Dig Dis Sci. 2010;55(9):2681–7. PubMed PMID: 20101462.
49. Gardner TB, Purich ED, Gordon SR. Pancreatic duct compliance after secretin stimulation: a novel endoscopic ultrasound diagnostic tool for chronic pancreatitis. Pancreas. 2012;41(2):290–4. PubMed PMID: 21926934. PubMed Central PMCID: 3244551.
50. Puli SR, Reddy JB, Bechtold ML, Antillon MR, Brugge WR. 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(11):2330–7. PubMed PMID: 19137428.
51. Aghdassi A, Mayerle J, Kraft M, Sielenkamper AW, Heidecke CD, Lerch MM. Diagnosis and treatment of pancreatic pseudocysts in chronic pancreatitis. Pancreas. 2008;36(2):105–12. PubMed PMID: 18376299.
52. Tessier G, Bories E, Arvanitakis M, Hittelet A, Pesenti C, Le Moine O, et al. EUS-guided pancreatogastrostomy and pancreatobulbostomy for the treatment of pain in patients with pancreatic ductal dilatation inaccessible for transpapillary endoscopic therapy. Gastrointest Endosc. 2007;65(2):233–41. PubMed PMID: 17258981.
53. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: Guidelines of the International Association of Pancreatology. Pancreas. 2011;40(3):352–8. PubMed PMID: 21412117.
54. Kamisawa T, Egawa N, Nakajima H, Tsuruta K, Okamoto A, Kamata N. Clinical difficulties in the differentiation of autoimmune pancreatitis and pancreatic carcinoma. Am J Gastroenterol. 2003;98(12):2694–9. PubMed PMID: 14687819.
55. Wolfson D, Barkin JS, Chari ST, Clain JE, Bell RH, Jr., Alexakis N, et al. Management of pancreatic masses. Pancreas. 2005;31(3):203–17. PubMed PMID: 16163050.
56. Taylor B. Carcinoma of the head of the pancreas versus chronic pancreatitis: diagnostic dilemma with significant consequences. World J Surg. 2003;27(11):1249–57. PubMed PMID: 14502404.
57. Hakime A, Giraud M, Vullierme MP, Vilgrain V. MR imaging of the pancreas. J Radiol. 2007;88(1 Pt 1):11–25. PubMed PMID: 17299363.

58. Farrell JJ, Garber J, Sahani D, Brugge WR. EUS findings in patients with autoimmune pancreatitis. Gastrointest Endosc. 2004;60(6):927–36. PubMed PMID: 15605008.
59. Finkelberg DL, Sahani D, Deshpande V, Brugge WR. Autoimmune pancreatitis. N Engl J Med. 2006;355(25):2670–6. PubMed PMID: 17182992.
60. Moon SH, Kim MH. The role of endoscopy in the diagnosis of autoimmune pancreatitis. Gastrointest Endosc. 2012;76(3):645–56. PubMed PMID: 22898422.
61. Buscarini E, Lisi SD, Arcidiacono PG, Petrone MC, Fuini A, Conigliaro R, et al. Endoscopic ultrasonography findings in autoimmune pancreatitis. World J Gastroenterol. 2011;17(16):2080–5. PubMed PMID: 21547126. Pubmed Central PMCID: 3084392.
62. Hoki N, Mizuno N, Sawaki A, Tajika M, Takayama R, Shimizu Y, et al. Diagnosis of autoimmune pancreatitis using endoscopic ultrasonography. J Gastroenterol. 2009;44(2):154–9. PubMed PMID: 19214678.
63. De Lisi S, Buscarini E, Arcidiacono PG, Petrone M, Menozzi F, Testoni PA, et al. Endoscopic ultrasonography findings in autoimmune pancreatitis: be aware of the ambiguous features and look for the pivotal ones. JOP. 2010;11(1):78–84. PubMed PMID: 20065561.
64. Dietrich CF, Hirche TO, Ott M, Ignee A. Real-time tissue elastography in the diagnosis of autoimmune pancreatitis. Endoscopy. 2009;41(8):718–20. PubMed PMID: 19618344.
65. Hocke M, Ignee A, Dietrich CF. Contrast-enhanced endoscopic ultrasound in the diagnosis of autoimmune pancreatitis. Endoscopy. 2011;43(2):163–5. PubMed PMID: 21165827.
66. Imazu H, Kanazawa K, Mori N, Ikeda K, Kakutani H, Sumiyama K, et al. Novel quantitative perfusion analysis with contrast-enhanced harmonic EUS for differentiation of autoimmune pancreatitis from pancreatic carcinoma. Scand J Gastroenterol. 2012;47(7):853–60. PubMed PMID: 22507131.
67. Iglesias Garcia J Larino Noia J Dominguez Munoz JE. Endoscopic ultrasound in the diagnosis and staging of pancreatic cancer. Rev Esp Enferm Dig. 2009;101(9):631–8. PubMed PMID: 19803666.
68. Kanno A, Ishida K, Hamada S, Fujishima F, Unno J, Kume K, 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(3):594–602. PubMed PMID: 22898417.
69. Deshpande V, Mino-Kenudson M, Brugge WR, Pitman MB, Fernandez-del Castillo C, Warshaw AL, et al. Endoscopic ultrasound guided fine needle aspiration biopsy of autoimmune pancreatitis: diagnostic criteria and pitfalls. Am J Surg Pathol. 2005;29(11):1464–71. PubMed PMID: 16224213.
70. Iwashita T, Yasuda I, Doi S, Ando N, Nakashima M, Adachi S, et al. Use of samples from endoscopic ultrasound-guided 19-gauge fine-needle aspiration in diagnosis of autoimmune pancreatitis. Clin Gastroenterol Hepatol. 2012;10(3):316–22. PubMed PMID: 22019795.
71. Takuma K, Kamisawa T, Gopalakrishna R, Hara S, Tabata T, Inaba Y, et al. Strategy to differentiate autoimmune pancreatitis from pancreas cancer. World J Gastroenterol. 2012;18(10):1015–20. PubMed PMID: 22416175. PubMed Central PMCID: 3296974.
72. Levy MJ, Wiersema MJ. EUS-guided Trucut biopsy. Gastrointest Endosc. 2005;62(3):417–26. PubMed PMID: 16111962.
73. Suda K, Takase M, Fukumura Y, Ogura K, Ueda A, Matsuda T, et al. Histopathologic characteristics of autoimmune pancreatitis based on comparison with chronic pancreatitis. Pancreas. 2005;30(4):355–8. PubMed PMID: 15841047.
74. Levy MJ, Reddy RP, Wiersema MJ, Smyrk TC, Clain JE, Harewood GC, et al. EUS-guided trucut biopsy in establishing autoimmune pancreatitis as the cause of obstructive jaundice. Gastrointest Endosc. 2005;61(3):467–72. PubMed PMID: 15758927.
75. Iglesias-Garcia J, Poley JW, Larghi A, Giovannini M, Petrone MC, Abdulkader I, et al. Feasibility and yield of a new EUS histology needle: results from a multicenter, pooled, cohort study. Gastrointest Endosc. 2011;73(6):1189–96. PubMed PMID: 21420083.
76. Larghi A, Iglesias-Garcia J, Poley JW, Monges G, Petrone MC, Rindi G, et al. Feasibility and yield of a novel 22-gauge histology EUS needle in patients with pancreatic masses: a multicenter prospective cohort study. Surg Endosc. 2013;27(10):3733–8. PubMed PMID: 23644834.

Part VIII
EUS in Therapeutics

Endoscopic Ultrasound-Guided Fine-Needle Injection

33

Jason B. Samarasena, Jason Yan-Lin Huang, Muhammad F. Dawwas and Kenneth J. Chang

Introduction

The advent of linear endoscopic ultrasound (EUS) in the 1990s has transformed EUS from a purely diagnostic modality to a platform for advanced diagnostic and therapeutic applications. The capability of EUS-guided fine-needle aspiration (EUS-FNA) has brought us the ability to access countless anatomic sites to sample tumors and lymph nodes as well as drain cysts and fluid collections. The development of EUS-guided celiac plexus neurolysis started a new era in EUS-guided techniques where the fine needle has become the vehicle for delivery of various ablative agents, chemotherapeutic agents, radiopaque markers, and miniature devices. The following is a case-based overview of some of the mainstream and upcoming applications of endoscopic ultrasound-guided fine-needle injection.

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Endoscopic Ultrasound-Guided Celiac Plexus and Ganglia Interventions

Case 1

Mr. H is a 57-year-old Caucasian male with pancreatic cancer and metastatic disease to the liver and lung diagnosed 2 months ago. His last CT scan showed a primary tumor in the pancreas body measuring 38 × 30 mm in size demonstrating invasion of the celiac axis. He is having worsening epigastric pain which is constant and radiates to the mid-back, ranging in intensity between 7 and 9 out of 10. He is on high-dose oral narcotics and complains that his pain is suboptimally controlled. He is struggling with opiate-induced constipation and feels he is getting more detached from his family because he is in a constant "fog."

Chronic abdominal pain is a common and debilitating symptom for patients with chronic pancreatitis (CP) and pancreatic cancer. The etiology of pancreatic pain is multifactorial and can be attributed to multiple causes such as increased intrapancreatic pressure, pancreatic ischemia, fibrosis, pseudocysts, neurogenic inflammation, as well as invasion of pancreatic perineural space by cancer cells [1]. The current pharmacologic management for pancreatic pain involves starting with non-opioid analgesics such as non-steroidal anti-inflammatory drugs and progressing to increasing

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doses of opioid analgesics [2]. However, opioids often provide suboptimal pain relief and their use is limited by side effects such as constipation, nausea, confusion, somnolence, addiction, and impaired immune function[3, 4]. Sympathetic nerves innervating the pancreas pass through the celiac plexus, and celiac plexus neurolysis (CPN) can be performed with the goal of improving pain control, increasing quality of life (QOL), and reducing the risk of drug-induced side effects.

Relevant Anatomy

The celiac plexus is comprised of a dense network of ganglia and interconnecting fibers and is located caudal to the diaphragm (in an antecrural position) and surrounds the origin of the celiac trunk. Celiac ganglia vary in number (usually 1–5), size (0.5–4.5 cm), and location (T12-L2) [5]. The celiac plexus transmits pain sensation from the pancreas and most of the abdominal viscera except the left colon, rectum, and pelvic organs [6]. The neurons that innervate the pancreas can receive nociceptive stimulation and then transmit this pain information to the celiac plexus [3].

How Effective are Non-EUS Methods for Celiac Plexus Neurolysis (CPN) and Block (CPB)?

CPN and CPB can be performed percutaneously, surgically or under EUS guidance. The retrocrural approach involves injecting the solution, which diffuses over the splanchnic nerves. The anterocrural approach or "true" CPN involves injection anterior to the diaphragm, thereby causing the solution to diffuse over the celiac ganglia.

Efficacy studies on percutaneous guided celiac plexus neurolysis (PQ CPN) for patients with pancreatic cancer have shown mixed results but overall have demonstrated some benefit with fairly low risk. A recent Cochrane meta-analysis evaluated six randomized trials with 358 patients undergoing PQ CPN for pancreatic cancer pain [7]. At four weeks and eight weeks, patients in the treatment arm had significant improvement in pain compared with the control arm. Furthermore, opioid consumption was significantly lower in the treatment arm. In another meta-analysis by Eisenberg and colleagues of 24 studies with 1145 patients treated with PQ CPN for palliation of cancer pain (of which 63 % were pancreatic cancer patients), good-to-excellent pain relief was noted in 70–90 % of patients up to 3 months after the procedure regardless of which type of percutaneous technique was used [8].

EUS-Guided Celiac Plexus Neurolysis and Block: How Should the Patient Be Prepared?

Linear array echoendoscopic imaging from the proximal posterior stomach was shown early to demonstrate superb visualization of the aorta and the takeoff of the celiac artery and in fact is often regarded as "home base" for novice endosonographers given its reproducibility as a landmark in nearly all patients. As a result, development of an EUS-guided technique for celiac neurolysis became a logical next step.

EUS-guided celiac plexus neurolysis/block is usually performed in the outpatient setting and sometimes during the index examination conducted for the purpose of pancreatic cancer diagnosis and staging. Contraindications to CPB/CPN in our practice include uncorrectable coagulopathy (INR > 1.5), thrombocytopenia (platelets < 50,000 /L), inadequate hydration, and altered anatomy prohibiting visualization or access to the celiac plexus/ganglia. Patients are initially hydrated with 500–1000 ml of normal saline to minimize risk of hypotension. The procedure is performed with the patient in the left lateral decubitus position under moderate sedation or anesthesia. Continuous monitoring is necessary during and for 2 h after the procedure. Before discharge, the blood pressure is rechecked in a supine and erect position to assess for orthostasis [3]. Although there are reports of retroperitoneal abscess following EUS-CPB, there is little evidence to support prophylactic antibiotics; thus, we do not routinely administer post-procedure antibiotics in our practice.

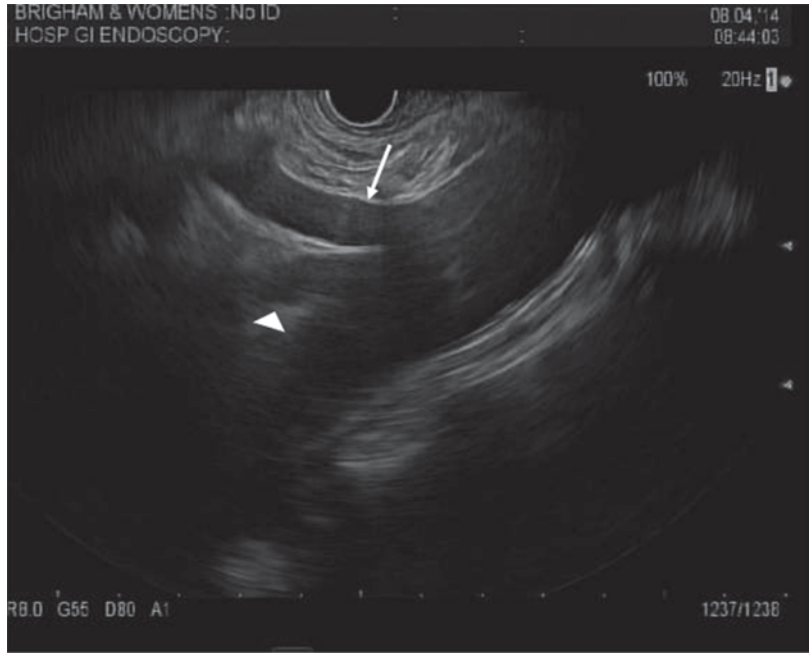

Fig. 33.1 EUS image of celiac artery (*arrow*) and SMA (*arrowhead*) taking off from the aorta. (Courtesy Dr. Linda Lee, Brigham and Women's Hospital, Boston, MA)

What is the Technique of EUS-Guided Celiac Plexus Neurolysis and Block?

The most widely performed approach to EUS-guided CPN/CPB involves diffuse injection into the region of the celiac plexus [9]. Linear array endosonographic imaging from the posterior lesser curve of the gastric fundus allows identification of the aorta, which appears in a longitudinal plane. The aorta is traced distally to the celiac trunk, which is the first major branch below the diaphragm (Fig. 33.1). Targeting with CPN is based on the expected location of the celiac plexus relative to the celiac trunk, and Doppler should be used to clearly delineate vascular structures. In our practice, a standard 22-gauge needle without stylet is primed with the injectant and advanced through the scope working channel and affixed at the inlet. The needle is inserted under EUS guidance immediately adjacent and anterior to the lateral aspect of the aorta at the level of the celiac trunk. An aspiration test is performed to rule out vascular penetration prior to each injection. For pancreatic cancer patients, we typically inject a premixed 20 ml solution of 98% dehydrated alcohol and 0.25 or 0.75% bupivacaine in a 70:30 ratio. For chronic pancreatitis patients, a solution of 0.25 or 0.75% bupivacaine mixed with 80 mg triamcinolone can be injected. Following injection, the needle should be cleared with a few cc of normal saline.

When performing celiac plexus neurolysis/block, we inject bilaterally using a modified technique, with half the volume on the left side of the celiac takeoff and the remainder at the midline at the takeoff. Our rationale for the modified technique is that the right side of the celiac artery is not as accessible, given the slight tilt of the artery relative to the scope position. Therefore, left and midline are the preferred areas for injection. Some prefer to inject at a single site, usually midline. The practice of bilateral injection has been supported by several studies including a recent meta-analysis which showed the proportion of patients with initial pain relief was 84.5% with bilateral compared to 45.9% for unilateral (midline) injection [10, 11]. However, a randomized study including 50 patients with pancreatic cancer found no difference in pain relief between unilateral and bilateral injections (74 and 81%,

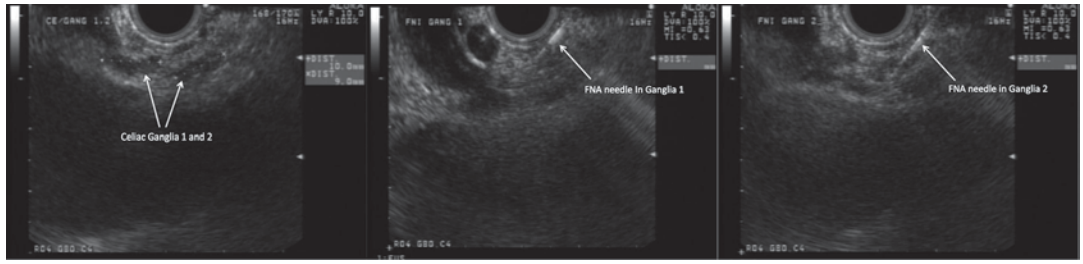

Fig. 33.2 EUS-guided direct injection of alcohol and bupivacaine solution into two celiac ganglia in a patient with pancreatic cancer

p = 0.351) with median pain relief lasting for 11–14 weeks [12]. The same group performed a similar randomized study of chronic pancreatitis patients undergoing EUS-CPB and found similar results (unilateral 57% versus bilateral 54% pain relief, p = 0.8) [13]. Another study of 53 patients with unresectable pancreatic cancer showed no difference in efficacy with bilateral versus unilateral injection [14].

An alternative approach that has been described that may be more applicable to advanced abdominal cancer is EUS-guided broad plexus neurolysis (BPN). In this technique, the injection is performed at the level of the superior mesenteric artery resulting in a broader distribution of neurolysis. A study by Sakamoto and colleagues of 67 patients showed that BPN had significantly better 7- and 30-day pain relief scores as compared to conventional EUS-CPN [15].

EUS-Guided Direct Celiac Ganglion Neurolysis

Recently, it has been recognized that the individual celiac ganglia can be visualized and accessed by EUS allowing for direct injection into the individual celiac ganglia to perform celiac ganglion neurolysis (CGN). The celiac ganglia are typically oval or almond shaped ranging in size between 2–20 mm and most readily detected to the left of the celiac artery, anterior to the aorta. Compared to the surrounding retroperitoneal fat, the ganglia are echo poor and often display similar echogenicity to the left adrenal gland. Within the ganglia, often central echo-rich strands and foci are present and the margins of the ganglia are irregular. Color Doppler demonstrates little to no flow within these structures. Ganglia are detected by EUS in between 81 and 89% of patients [16]. Our approach is to perform CGN rather than CPN if ganglia are visualized although further data are needed on this approach.

What is the Technique for EUS-Guided CGN?

All aspects of the procedure including patient candidacy, sedation, antibiotic use, and follow-up are the same as standard CPN/CPB. The technique for CGN and volume of solution injected has not been standardized. Our approach is to target as many ganglia as possible by injecting a total of 10–20 ml of premixed alcohol and bupivacaine (mixture as outlined above) among all the ganglia in amounts relative to their size (Fig. 33.2, see Video 30.1). For example, if three ganglia are visualized (small, medium, and large), we would typically inject 5 ml in the largest ganglion, 3 ml in the medium sized ganglion, and 2 ml in the small ganglion. For larger ganglia, we typically advance the needle tip into the deepest point within the ganglia and then inject while slowly withdrawing the needle, creating an even distribution of injectate throughout the ganglion. For smaller ganglia, we usually target the ganglia's center. During injection, a clear "ballooning" of the ganglia should be visualized; otherwise, needle placement is considered suboptimal.

Clinical Trial Data

The clinical trial data for CGN and CPN for patients with pancreatic cancer are summarized in Table 33.1. Within the literature, there is great variability among the studies in terms of injection technique, type of injectate and volume, definition of pain relief, and follow-up. Most studies are small retrospective studies with short follow-up.

For celiac plexus neurolysis, partial pain relief has been reported between 50 and 78% within the first 4 weeks [11, 15, 17–19]. A meta-analysis including 119 patients found that EUS-CPN alleviated abdominal pain in 73% of patients. [20] In a randomized trial, 96 patients with inoperable pancreatic cancer were randomized into conventional pain management or EUS-CPN. At 3 months, patients treated with CPN had greater pain relief with a trend toward lower morphine consumption, although no difference was observed in quality of life [21].

Results of celiac plexus block are less successful than CPN with two meta-analyses reporting 51 and 60% pain relief [10, 20]. Of those who respond, duration of relief is short-lived at about 4 weeks [13]. A randomized study comparing percutaneous fluoroscopy directed CPB to EUS-CPB in chronic pancreatitis found that significantly more patients reported improvement in pain scores in the EUS group (70 versus 30%, $p=0.04$) [22]. Unfortunately, by 24 weeks following CPB, nearly all patients had returned to their baseline pre-procedure pain score. Another prospective non-randomized study confirmed this lack of durability of pain relief with only 10% reporting some pain relief at 24 weeks [23].

For celiac ganglion neurolysis, partial pain relief has been reported between 65 and 94% [24–26]. In the only prospective trial to date comparing CGN to CPN, 68 patients with upper abdominal cancer (over 85% were pancreatic cancer) were randomly assigned to treatment using either EUS-CGN or EUS-CPN with one midline injection. The positive response rate was significantly higher in the EUS-CGN group (73.5%) than in the EUS-CPN group (45.5%). The complete response rate was also significantly higher in the EUS-CGN group (50%) than in the EUS-CPN group (18.2%) although the response rate for EUS-CPN was much lower than reported in other studies. There was no difference in adverse events or duration of pain relief between the groups [24]. Follow-up was only 7 days, and much longer term follow-up studies are needed as well as comparison with bilateral EUS-CPN injections.

What Common and Serious Complications Can Occur?

Most complications related to CPN/CPB and CGN are transient, and serious complications are rare. A large series of 220 patients undergoing EUS-CPN/CPB had an overall complication rate of 1.8% with complications defined as any side effect requiring management beyond standard post-procedure observation [27]. The most common side effects reported are transient hypotension (up to 35%), diarrhea (up to 20%), and transient exacerbation of pain following procedure which are consistent with rates seen with the PQ approach [8]. Hypotension and diarrhea are related to sympathetic blockade and the relative unopposed visceral parasympathetic activity. Hypotension generally responds to intravenous fluid administration. The diarrhea related to this procedure is usually self-limited and resolves in less than 48 h. CPN via a PQ approach has been associated with a 2% rate of serious complications including neurologic complications (lower extremity weakness, paresthesia, paralysis), pain (pleuritic chest, shoulder), pneumothorax, and hiccupping [8]. A very small number of serious complications ($\leq 0.6\%$) including fatalities and paralysis mainly with alcohol injection have been reported with the EUS approach in case report and abstract form [28, 29]. Serious infections including retroperitoneal abscess and empyema have occurred as well as severe ischemic damage to abdominal organs.

Table 33.1 Clinical trial data for EUS-guided celiac plexus neurolysis

Study	Design	*n*	Injection site	Injectate	Pain relief (% of patients)	Complications
Doi et al. 2013 [24]	Prospective	68	Ganglia vs. plexus	1–2 ml bupivacaine 0.25–0.5 % 10–20 ml alcohol	73.5 vs. 45.5 % partial 50 vs. 18.2 % Complete	Hypotension 2.9 % vs. 6.0 UGI bleed 2.9 vs. 0 % Increased pain 29.4 vs. 21.2 %
Seicean et al. 2013 [19]	Retrospective	32	Plexus	10 ml bupivacaine 1 % 10–15 ml alcohol	75 %	None stated
LeBlanc et al. 2011 [12]	Prospective	50	Plexus 1 vs. 2 injections	20 ml bupivacaine 0.75 % 10 ml alcohol 98 %	69 vs. 81 %	Hypotension 2 % Increased pain 33 %
Iwata et al. 2011 [18]	Retrospective	47	Plexus	2–3 ml bupivacaine <20 ml alcohol	68 %	Hypotension 17 % Diarrhea 23 % Transient inebriation 9 %
Ascunce et al. [26]	Retrospective	64	Ganglia vs. plexus (bilateral)	10 ml lidocaine 1 % 20 ml alcohol 98 %	65 % vs. 25 %	Hypotension 2 % Increased pain 2 % Diarrhea 23 %
Sakamoto et al. 2010 [15]	Retrospective	67	Plexus (bilateral) vs. broad plexus (around SMA)	3 ml lidocaine 1 %; 9 ml alcohol; 1 ml contrast	50 vs. 76 %	No major complications
Sahai et al. 2009 [11]	Prospective	160	Plexus (central) vs. plexus (bilateral)	10 cc bupivacaine 0.5 % 20 cc alcohol	50.7 vs. 77.5 %	Retroperitoneal bleed 0.7 %
Levy et al. 2008 [25]	Retrospective	17	Ganglia	8 ml Bupivacaine 0.25 % 12 ml alcohol 99 %	94 %	Hypotension 35 % Increased pain 41 %
Gunaratnam et al. 2001 [17]	Prospective	58	Plexus (bilateral)	6–12 ml bupivacaine 0.25 % 20 ml alcohol 98 %	78 %	Hypotension 20 % Increased pain 9 % Diarrhea 17 %

Case Concluded

In the case of Mr. H, celiac neurolysis appears to be an ideal choice for pain relief. His cancer-related pain is clearly not optimized with oral narcotic agents, which are causing side effects of constipation and drowsiness. To date no trials have compared percutaneous to EUS-guided celiac neurolysis; however, our preferred approach in this patient would be EUS-guided celiac ganglion neurolysis although celiac plexus neurolysis is also reasonable. Direct visualization of the celiac ganglia can only be achieved using EUS at the current time and as a result, a non-EUS approach is limited to CPN. Additional well-designed studies are needed to further compare CGN and CPN and to determine the optimal method and timing of celiac neurolysis/block, composition of the injectate, impact on quality of life, and the benefit of this technique in chronic pancreatitis patients.

EUS-Guided Alcohol Ablation of Pancreatic Cysts

Case 2

Mrs. J is a 75-year-old female with severe chronic obstructive lung disease who recently presented to the hospital with dyspnea and underwent a high-resolution CT scan of the chest which incidentally discovered a 3.5-cm unilocular head of pancreas cyst. The patient's sister passed away from pancreatic cancer in her sixties, and she is deeply worried about this lesion in her pancreas. The patient undergoes pancreatic EUS, which shows a single 3.5-cm unilocular lesion in the head/uncinate region with no apparent communication to a non-dilated main pancreatic duct. EUS-guided cyst fluid aspiration reveals mucinous fluid with string sign of 12 mm and CEA 350 ng/ml. The patient's general gastroenterologist diagnoses her with probable branch duct intraductal papillary mucinous neoplasm (IPMN) and recommends that she undergo Whipple procedure to remove this lesion. The patient asks whether there are any other options for treatment of this lesion.

The widespread use of cross-sectional imaging has dramatically increased the number of incidentally noted pancreatic cystic lesions (Chap. 31). Recent magnetic resonance imaging (MRI) and computerized tomography (CT) studies indicate a prevalence of pancreatic cysts in up to 14% [30, 31]. Pancreatic cysts encompass a wide spectrum of histopathology and the epithelium that outlines pancreatic cystic neoplasms (PCNs) may have negligible malignant potential (serous cystadenomas) or represent premalignant lesions such as intraductal papillary mucinous neoplasms (IPMNs) or mucinous cystic neoplasm (MCNs) [32, 33].

Consensus guidelines and expert opinion recommend surgical resection of MCNs and IPMNs that are symptomatic, larger than 3 cm in diameter, contain mural nodules, or involve the main pancreatic duct (main duct IPMNs) [34, 35]. However, because of the operative risk associated with pancreatic resection there has been increasing interest to develop a minimally invasive technique to treat these lesions. Pancreatic cyst ablation may be an attractive option for patients with multiple comorbidities deemed high-risk for surgery. Potential benefits include decreasing the malignant potential of the cyst, lower cost over time due to reduced cyst surveillance, and the psychological benefit to the patient. The following will review the technique, clinical trial data, and controversies surrounding pancreatic cyst ablation.

What is the Technique of EUS-Guided Pancreatic Cyst Ablation?

All studies to date describing EUS-guided pancreatic cyst ablation have used a 22-gauge needle [36–41]. With a curvilinear-array echoendoscope, the cyst is typically punctured via a transgastric or transduodenal route. Using a syringe, cyst fluid is aspirated with the goal of near complete evacuation of the cyst. Removing the cyst fluid before injection increases the surface area directly exposed to the ablative agent and improves the efficacy of ablation. The amount of aspirated fluid, viscosity, and color should be noted. To ensure

Table 33.2 Characteristics of candidate cyst and patient for ablation

The ideal cyst for ablation	The ideal patient for ablation
A benign appearance without any malignant features	Patient who is high risk for surgery
A diameter between 2 and 4 cm	Without the presence of: ongoing pancreatitis, ascites, portal hypertension, coagulopathy
Unilocular or oligolocular morphology	
No communication with main pancreatic duct	

the cyst does not completely collapse, the needle remains within the cyst before injection of the ablative agent. With viscous cyst fluid, it may not be possible to evacuate the cyst contents as much as desired; therefore, saline may be injected into the cyst to decrease viscosity or expand a small cyst to confirm needle placement [42].

With the needle in the nearly collapsed cyst, ethanol is injected into the cyst using a volume equal to that initially aspirated from the cyst. During the procedure, the needle tip is carefully maintained within the cyst to avoid parenchymal injury or leak in the cyst wall. Studies to date have performed lavage for 5 min, alternately filling and emptying the cavity during that time. For cysts with viscous fluid, this is performed as 3–4 lavages over the 5-min period. When the cyst fluid is thin, 7–8 lavages are performed over the same period. At the completion of alcohol lavage, the cyst cavity should be completely drained of fluid as much as possible. If a chemotherapeutic agent such as paclitaxel is used after alcohol lavage, as much alcohol is removed prior to paclitaxel injection. With alcohol or paclitaxel injection, the total injection volume should not exceed the volume of aspirated fluid and hence the cyst should not be expanded beyond its original diameter. When paclitaxel is injected after alcohol lavage, it is left in place and not drained. The needle is then removed from the cyst cavity [42, 43].

What Ablative Agents are Available for Pancreatic Cyst Ablation?

Ethanol (80–98%) is an inexpensive, widely available, low-viscosity agent that is easy to inject through a small gauge needle. It is hypothesized to induce cell death by membrane lysis, protein denaturation, and vascular occlusion [44] and has been used for the destruction of solid and cystic tumors in a variety of organs [42]. The only other agent used to date for pancreatic cyst ablation has been paclitaxel, which is a hydrophobic, viscous chemotherapeutic agent that inhibits cell processes that depend on microtubule turnover. Its viscosity enables it to exert a durable effect on the epithelium within the cyst cavity with a low risk of leakage [45].

Which Cysts are Considered Candidates for Ablation?

The size, morphologic characteristics, and suspected histologic type of the cyst guide the approach to cyst injection and ablation therapy (Table 33.2). In published studies the cysts that have been treated include suspected mucinous cysts measuring between 1 and 6 cm in maximal diameter [42]. The ideal size for cyst ablation is based on two competing factors: the risk of malignancy and the success of ablation. Cysts larger than 3 or 4 cm are typically at higher risk for malignancy; however, cysts containing cancer are inappropriate for ablation. On the other hand, a cyst size of at least 2 cm is often needed to ensure feasibility and safety of the ablation procedure. As a result, the ideal cyst size for ablation is likely between 2 and 4 cm [43].

Cyst ablation has the greatest chance of success in unilocular or oligolocular cysts with fewer than 2–3 locules. In the presence of three or more locules, a single needle pass may not provide sufficient drug delivery to all locules within a cyst. It is important to determine the optimal angle at which the needle can be introduced into the maximal number of targeted locules. A second needle puncture may be considered when it can be performed without increasing the risk for adverse events [43].

The presence of a communication between the cyst and the main pancreatic duct may result in flow of the injected ablative agent through the communicating duct into the main pancreatic duct. This outflow may diminish the ablative effect and also increase risk of ductal change. Oh and colleagues [40] performed endoscopic retrograde cholangiopancreatography (ERCP) in all patients to exclude any cyst communication with the main pancreatic duct. Other studies did not perform ERCP before ablation [36, 38]. A practical point to note is if a cyst does not restore to its original size during ethanol injection, vigorous lavage with repeated injection and aspiration should be avoided because of a probable communication with the main pancreatic duct [43].

Which Patients Should be Selected for Ablation?

There is no clear consensus on whom should undergo pancreatic cyst ablation. Patients with high-risk, symptomatic, or benign cysts who refuse or are not fit for surgery may be considered for ablation (Table 33.2). Patients with imaging consistent with MD-IPMN such as a dilated main pancreatic duct or suggesting malignancy such as mass-like lesions, suspicious liver, or pulmonary lesions or enlarged lymph nodes should not be offered cyst ablation. Similarly, patients with active or ongoing pancreatitis, ascites, portal hypertension, or coagulopathy have generally been excluded from cyst ablation.

Clinical Trial Data

Cyst Resolution

To date, six published prospective studies have evaluated the role of EUS-guided pancreas cyst ablation. Table 33.3 summarizes the clinical trial data of cyst ablation in the literature currently. Endpoints in all studies include EUS or radiologic assessment of changes in baseline cyst size after ablation. For ethanol ablation alone, cyst resolution (defined as no visible residual cyst) ranged from 33 to 38% [36, 38, 41] based on cross-sectional imaging. The addition of paclitaxel appears to increase CT-defined cyst resolution (defined as size < 5% of original cyst volume) with range between 60 and 79% [37, 40, 46].

Safety

EUS-guided cyst ablation has generally been well tolerated with a low rate of adverse events. The initial pilot study that evaluated the safety of injecting increasing concentrations up to 80% ethanol found no treatment-related complications [36]. Subsequent studies have shown pancreatitis rates between 2 and 10%, abdominal pain in 2 and 20%, fever in 2% and intracystic bleeding in 2%. To date, no cases of severe pancreatitis, bleeding requiring transfusion, or deaths have been reported. Prophylactic antibiotics should be administered.

Case Concluded

After discussion with the patient, it was determined that she was a good candidate for cyst ablation with a unilocular cyst measuring 3.5 cm not communicating with the pancreatic duct and no evidence of malignancy. She was also at higher risk for Whipple surgery due to her lung disease. She agreed to try EUS-guided pancreatic cyst ablation, which was performed using monitored anesthesia care and a 22-gauge needle with a single pass into the cyst after administering intravenous ciprofloxacin. Following complete aspiration of the cyst fluid, equal volume of 80% ethanol was injected and the cyst lavaged over 5 min. She did well post-procedure with no complications. Follow-up CT scan 3 months later demonstrated decrease in size of the cyst by about half.

Future Directions

Pancreatic cysts are being encountered frequently in clinical practice, including in the elderly and patients at high risk for surgical resection. Therefore, a non-surgical treatment alternative is

Table 33.3 Clinical trial data for pancreatic cyst ablation

References	No of patients	Ablative agent	Complete resolution on imaging	Complications	Median months follow -up (range)
Gan et al. 2005 [36]	25	5–80 % ethanol	35 % (8/23)	None	At least 3 months, not stated
Oh et al. 2008 [37]	14	80/99 % ethanol with paclitaxel	79 % (11/14)	Pancreatitis (10 %)	9 (6–23)
Oh et al. 2009 [46]	10	99 % ethanol with paclitaxel	60 % (6/10)	Pancreatitis (7 %) Abdominal pain	8.5 (6–18)
DeWitt et al. 2009 [38]	42	80 % ethanol	33 % (12/36)	Pancreatitis (4.5 %) Intracystic bleeding (2 %) Abdominal pain at 2h (14 %) Abdominal pain 7d (20 %)	At least 3 months, not stated
Oh et al. 2011 [40]	47	99 % ethanol with paclitaxel	62 % (29/47)	Fever (2 %) Pancreatitis (2 %) Abdominal pain (2 %)	20 (12–24)
DiMaio et al. 2011 [41]	13	80 % ethanol	38 % (5/13)	Abdominal pain (8 %)	13 month after first lavage

desirable. EUS-guided cyst ablation is an emerging modality that may present an alternative to surgery, especially if complete ablation can be achieved in the vast majority of patients. At the present time, this is an investigational procedure and studies to date have shown that cyst ablation is relatively safe with cyst resolution in up to 67 % of patients. It is uncertain whether incomplete ablation of the neoplastic cyst lining will reduce cancer risk or whether partially treated cysts will become more difficult to monitor. Future research is now needed to focus on refinement of the technique, choice, and number of ablative agents, selection criteria of appropriate cysts for treatment, and the long-term outcomes of this treatment.

Endoscopic Ultrasound-Guided Radiofrequency Ablation

Image-guided radiofrequency ablation (RFA) is a well-recognized minimally invasive treatment modality in oncology, one that utilizes the generation of high-frequency electrical alternating current through target tissue to induce ion agitation and tissue friction ultimately leading to thermal injury and consequent coagulative necrosis. Effective ablation is achieved by optimizing heat production and minimizing heat loss with the objective of generating a clear tumor ablation margin while reducing potential side effects. The availability, safety, efficacy, and low cost of percutaneous RFA have facilitated its common utilization in conjunction with ultrasound, CT, or MRI guidance for the management of a variety of solid tumors, most commonly hepatocellular carcinoma, renal cell carcinoma, non-small-cell lung cancer, and osteoid osteoma.

RFA has also been used to treat pancreatic cancer during exploratory laparotomy or laparoscopy; a recent systemic review identified five studies including 158 patients with a median survival after RFA of 3–33 months, 0–19 % mortality, 10–43 % overall morbidity, and 4–37 % RFA-related morbidity, much of which was related to collateral injury to adjacent tissues [47]. Given its minimally invasive nature and superior imaging capabilities of the pancreas, endoscopic ultrasound potentially provides an ideal vehicle for delivering RFA to pancreatic cancer as well as other percutaneously inaccessible tumors.

Animal Studies

Eight studies, six utilizing porcine models, of EUS-guided RFA have been conducted to date (Table 33.4). Using a modified 19-gauge needle electrode connected to a monopolar

Table 33.4 Summary of animal and human studies evaluating EUS-guided radiofrequency ablation

Reference	Year	Probe design/ technique	Subjects	Target organ	Maximum diameter/ area of ablated area at EUS	Maximum diameter/ area of ablated area at histology	Complications	Follow up
Goldberg [48]	1999	Monopolar 19-guage needle electrode	13 pigs	Pancreas (tail)	10–15 mm	12 mm	Transmural gastric wall burns (n=3); Intestinal serosal burn (n=1); Asymptomatic pancreatic fluid collection (n=1)	Variable; up to 14 days
Carrara [49]	2008	Hybrid bipolar RFA-carbon dioxide cryoprobe	14 pigs	Pancreas (body)	900 mm^2	4000 mm^2	Necrotic pancreatitis with peritonitis (n=1); Asymptomatic pancreatitis (n=1); Gastric wall burn (n=1); Adhesion between the pancreas and gut (n=4)	Variable; up to 14 days
Carrara [50]	2008	Hybrid bipolar RFA-carbon dioxide cryoprobe	19 pigs	Liver spleen	500 mm^2 600 mm^2	400 m^2 500 mm^2	None	Variable; up to 14 days
Varadarajulu [52]	2009	Umbrella-shaped retractable monopolar electrode deployed through a 19-gauge needle	5 pigs	Liver	23 mm	26 mm	None	7 days in 4/5 pigs
Petrone [51]	2010	Hybrid bipolar RFA-carbon dioxide cryoprobe; ultrasound- guided	16 humans with pancreatic adenocarcinoma (ex vivo)	Pancreas	Not stated	10–20 mm (depending on application time)	N/A	N/A
Gaidhane [53]	2012	1 Fr monopolar probe deployed through a 19-gauge needle	5 pigs	Pancreas (head)	Not stated	Not stated	Asymptomatic histologic pancreatitis (n=5)	6 days

Table 33.4 (continued)

Reference	Year	Probe design/ technique	Subjects	Target organ	Maximum diameter/ area of ablated area at EUS	Maximum diameter/ area of ablated area at histology	Complications	Follow up
Kim [54]	2012	18-gauge electrode with saline pump cooling	10 pigs	Pancreas (body and tail)	14.5 mm	23 mm	Asymptomatic retroperitoneal fibrosis (n=1) asymptomatic adhesions between pancreas and stomach or bowel (n=2)	7 days
Arcidiacono [55]	2012	Hybrid bipolar RFA-carbon dioxide cryoprobe	22 humans with unresectable stage III pancreatic adenocarcinoma	Pancreas	Uncertain	Uncertain	Failed probe deployment (n=6) mild abdominal pain (n=3, 1 with pancreatitis) duodenal bleed (n=1) obstructive jaundice (n=2) duodenal stricture (n=1) asymptomatic pancreatic cystic collection (n=1)	Uncertain; at least 15 months

radiofrequency generator, Goldberg et al in 1999 first demonstrated the feasibility of EUS-guided RFA of the pancreas in 13 pigs [48]. The maximum diameter of the ablated area was 10–15 mm by EUS and 12 mm by histology. Correlation between EUS or CT and gross pathologic findings for size of the ablated region was excellent for all areas larger than 5 mm; size of the ablated zone at pathologic examination was within 2 mm of that visualized on imaging. Complications included three transmural gastric wall burns, an intestinal serosal burn, and an asymptomatic pancreatic fluid collection.

In an attempt to improve ablation efficiency while reducing collateral thermal injury, Carrara et al used a hybrid cryotherm (CT) probe combining bipolar radiofrequency current with carbon dioxide cryotherapy to ablate the body of the pancreas in 14 pigs; they achieved a larger ablation zone (18 vs. 10 mm) with a 300 s application than that obtained with a 360 s application using the monopolar system from the Goldberg et al study [49]. However, similar side effects, most reflecting longer application duration, were encountered including two cases of pancreatitis (one necrotizing and the other asymptomatic), a gastric wall burn, and four cases of adhesions between the pancreas and the gut. The same group demonstrated the feasibility of using the CT probe in EUS-guided RFA of the liver and spleen in porcine models with no reported complications [50]. Ultrasound-guided RFA with the CT probe of 16 human explanted pancreatic tumors with a mean diameter of 29 mm produced ablation zone diameters of 10–20 mm with size of the ablated area correlating with duration of ablation [51].

Varadarajulu et al. used an EUS-guided umbrella-shaped retractable monopolar electrode array to ablate five porcine livers, generating ablation zone diameters of 23 mm at EUS and 26 mm at histology without any complications [52]. Gaidhane et al. deployed a 1Fr RFA probe through a 19-gauge needle to ablate 5 porcine pancreata without complications; only histological evidence of focal pancreatitis was documented [53]. Kim et al. used an 18-gauge saline pump-cooled RFA Telectrode to ablate the body or tail of pancreas of 10 pigs; ablation zone diameters of 14.5 mm at EUS and 23 mm at histology were achieved [54]. Complications included three cases of asymptomatic retroperitoneal fibrosis or pancreato-gastric adhesions.

Human Studies

Human study employing EUS-guided radiofrequency ablation is limited. Arcidiacono et al. ablated 16 unresectable stage III pancreatic cancers with a mean diameter of 35.7 mm using the CT probe; RFA could not be deployed in six additional patients because of gastroduodenal wall or tumor stiffness. Complications included mild abdominal pain in three patients, one of whom had pancreatitis; a duodenal bleed requiring endotherapy; two cases of obstructive jaundice requiring stenting; a duodenal stricture treated with stenting; and an asymptomatic pancreatic cystic collection. Median post-ablation survival time was 6 months. Abdominal CT imaging could clearly define the tumor margins in only 6 of 16 ablated patients, whereby reduction or no change in tumor size, albeit insignificant, was seen for up to 78 days [55].

Future Directions

At present, EUS-guided RFA remains a research tool that requires further assessment, refinement, and validation of its safety and efficacy in well-designed randomized controlled studies before it can be formally recommended for use in clinical practice. In particular, future studies will need to address the development of sharper probe design possibly equipped with cutting current to facilitate transluminal access; the appropriate radiologic modality and time interval for assessing tumor response, in addition to the optimal settings for treatment duration, generator power, and gas coolant pressure for effective ablation of pancreatic cancer as opposed to healthy pancreatic tissue.

Endoscopic Ultrasound-Guided Fiducial Marker Placement

Case

Mr. F is an 82-year-old male who presented with painless jaundice and a mass at the head of the pancreas. Initial EUS-FNA secured the diagnosis and a plastic biliary stent was placed as EUS staging at the time was T3N0Mx. The patient subsequently refused surgery and chemotherapy but opted for palliative radiotherapy; therefore, a second EUS was performed for fiducial marker placement. Three 0.8 mm × 5 mm fiducial markers were placed via a 19-g needle under EUS guidance (Fig. 33.3) with placement confirmed by fluoroscopy (Fig. 33.4) without complications. Placement of the markers facilitated treatment with Cyberknife (Accuray, Sunnyvale, California), which the patient has tolerated well.

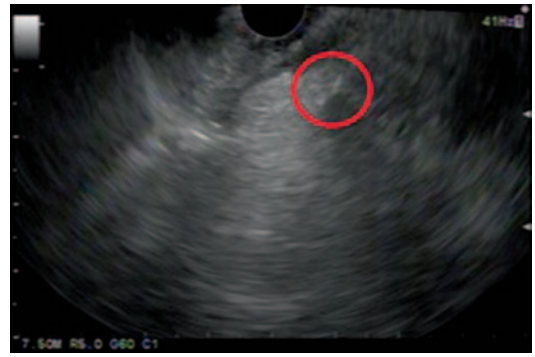

Fig. 33.3 EUS image of fiducial marker (*within red circle*) in the periphery of the pancreatic mass

Introduction

Fiducial markers are radiopaque coils or rods, which assist in the targeting of cancer radiation therapy. Traditionally placed intra-operatively or percutaneously under radiology guidance, in more recent years EUS placement via a FNA needle has been a less invasive method for fiducial marker placement into gastrointestinal malignancies which include esophageal, cholangiogiocarcinoma, stomach, pancreatic, and malignant lymph nodes [56, 57, 58]. In esophageal cancer, when there is a malignant lymph node far from the tumor, it is our practice to place fiducial markers into the lymph node to ensure radiation treatment to this region as well. There may be particular advantages for EUS placement into the

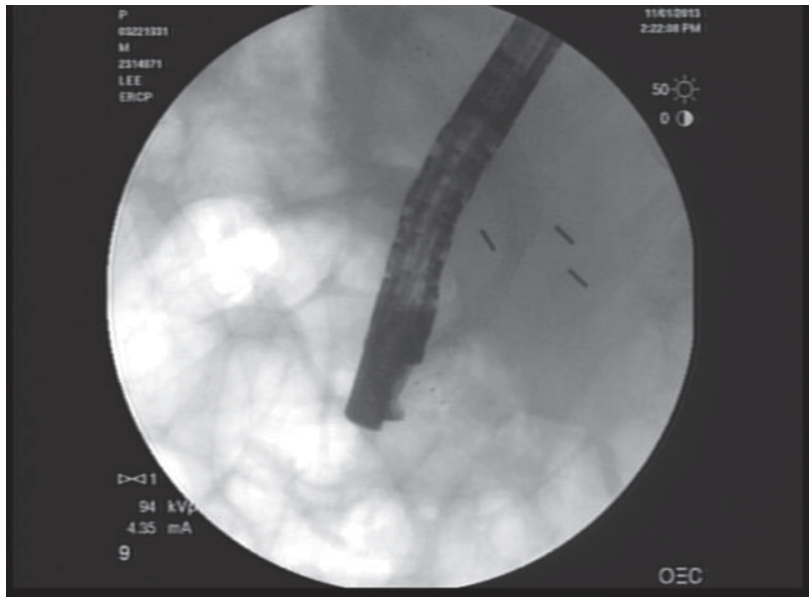

Fig. 33.4 Fluoroscopic image of all three fiducial markers in the head of pancreas with a metal biliary stent coursing through the cancer

Table 33.5 Fiducials available in the United States

Fiducial marker	Size(s)	FNA needle gauge required
Alpha-omega services (Bellflower, CA, USA)	0.8 × 2.5–5 mm	19 gauge
Visicoil, core oncology (Santa Barbara, CA, USA)	10 × 0.35 mm	22 gauge
Best medical international (Springfield, VA, USA)	0.8 × 3 mm	19 gauge
Cook medical (Bloomington, IN, USA)	0.43 × 5 mm	22 gauge

pancreas with possibly lower likelihood of peritoneal seeding compared to the percutaneous approach [59, 60].

Placement of fiducial markers allows accurate demarcation of the location and peripheral extent of the tumor in real time by image guided radiotherapy (IGRT), which is a prerequisite to facilitating stereotactic body radiotherapy (SBRT). This allows multiple beams of radiation to be delivered with extreme accuracy and consistency by quantifying respiratory motion and tumor extent, therefore maximizing radiation delivery to the tumor and minimizing collateral damage to the normal surrounding parenchyma [61]. This technique has also been used for intra-operative localization of small neuroendocrine tumors to allow parenchymal sparing resections [62, 63].

Fiducial Characteristics

Composition

Fiducial markers can be made of gold, carbon, or polymer [64]. Gold markers are more commonly used as they are most easily visualized and provide the highest level of contrast. Gold fiducial markers can also produce more artifact, but fortunately this can be minimized by employing the metal artifact reduction (MAR) methods to improve CT image quality [65].

Physical Dimensions

The size of fiducial markers can vary. Length is anywhere from 2.5 to 10 mm and diameter can range between 0.35and 0.8 mm, which dictates the gauge of needle used for delivery. Table 33.5 lists several examples of fiducials available in the United States.

Shape

The shape of fiducials can be cylindrical (rod) or coiled. A recent comparison study demonstrated that rod-shaped fiducials were significantly more visible than the coiled variety without significant differences in the rate of migration [66].

Placement of Fiducial Marker

Technique

Fiducial markers can be delivered via a 19- or 22-gauge needle. The advantage of the 22-gauge delivery system is ease and success of deployment especially in technically more difficult locations such as targeting the head or uncinate process of the pancreas. DiMaio et al [58] reported a 97% technical success rate with the 22-gauge system for gastrointestinal-related malignancies, and Ammar et al [57] reported a 100% technical success rate in tumors and lymph nodes.

At the present time, the technique for placement involves a single loading system whereby the sterile fiducial marker is loaded at the needle tip either anterograde [57] or retrograde [67] and secured with sterile bone wax placed at the very end of the needle. In our practice, retrograde loading is preferred. Once the lesion of interest is punctured, the stylet is pushed completely into the needle to deploy the fiducial marker. Saline flush is sometimes required instead of the stylet in situations where difficult stylet maneuverability is anticipated (e.g., uncinate process targets) [68]. In general, this technique produces very high success rates of deployment with normal anatomy, but in the setting of altered or post-surgical anatomy, success rates have decreased to 73% [69]. A new multi-fiducial system has

demonstrated a 95% success rate in porcine models with four fiducials placed sequentially in under 1 min [70]. This device has a narrowing or waist near the tip to provide the endoscopist tactile feedback indicating successful deployment of each individual fiducial marker.

Ideal Fiducial Geometry

Ideal fiducial geometry (IFG) is defined as having a minimum of three fiducials, at least 2 cm apart and interfiducial angles greater than 15°. Surgical placement has more consistently achieved IFG than EUS-guided methods, although IFG may not be necessary as both surgical and EUS-guided methods achieve high visibility under Cyberknife imaging [71]. Placement protocols vary among centers, particularly regarding the actual number of fiducials placed. In most centers, including our own, 3–4 fiducial markers are inserted between 1.5–2 cm apart and around the periphery of the tumor. We aim for IFG if the tumor is large enough to allow adequate spacing of the fiducials, regardless of the type of tumor. Smaller lesions may only allow 1 or 2 fiducials to be inserted. Also, small cancers are more likely to be resectable; therefore, fiducial marker placement may be unnecessary.

Complications

Complications related to fiducial marker placements are rare. The most common is migration at 1 week post placement when IGRT typically commences. The median migration distance has been reported to be within 1.3 mm [66]; however, total migration to the extent whereby the fiducial marker is not seen at IGRT and the quality of IGRT is compromised has been reported in up to 7% of cases [69].

Other reported complications include infection in two patients [58, 59] who were managed without intravenous antibiotics or hospital admission. Given the overall low risk of infection with this procedure, we do not routinely administer antibiotic prophylaxis following EUS-guided fiducial marker placement for GI malignancy in our practice. There was one report of post-procedural abdominal pain which was ultimately diagnosed as mild pancreatitis [69]. Bleeding occurred on one occasion which was minor and did not require blood transfusion [68].

Summary

Fiducial markers play an integral part in precise delivery of high-intensity radiotherapy by Cyberknife. These markers can be placed surgically, radiologically, or under endoscopic ultrasound guidance. The EUS method is particularly useful in deeper targets, particularly the pancreas, and has proven to be very safe and effective.

Endoscopic Ultrasound–Guided Antitumor Agents

With celiac ganglion neurolysis, EUS-guided fine-needle injection (EUS-FNI) demonstrated the feasibility and safety of delivering medication into a localized region and structure. As a result, EUS-FNI has received attention as a method for antitumor agent delivery, particularly for intratumoral and combination therapy against esophageal and pancreatic cancer. The evidence supporting the feasibility of EUS-FNI of antitumor agents has been expanding with promising results.

The concept of EUS-FNI for antitumor agent delivery has been studied largely in pancreatic cancer treatment mainly due to its accessible anatomic location by EUS and the dismal prognosis of this cancer. Various organs and major vessels surrounding the pancreas make access to it difficult for modalities such as CT while EUS provides excellent access to all regions of the pancreas. Despite extensive basic and clinical research, the prognosis of pancreatic cancer remains bleak and surgical resection represents the only possibility of cure. One of the reasons for the poor response to chemotherapy in pancreatic cancer is because of poor drug delivery due to abundant desmoplasia and the hypovascular nature of the

tumor. By injecting antitumor agents directly into the tumor under EUS guidance, these hurdles can be overcome less invasively.

Early Experience

Our first study testing the concept of EUS-FNI for antitumor agent delivery involved injection of allogenic mixed lymphocyte culture (cytoimplant) into pancreatic tumors. Despite the early termination of a randomized controlled trial employing EUS-guided cytoimplant versus conventional therapy, this experience clearly demonstrated the feasibility of EUS-FNI as a delivery method for an antitumor agent [72].

Subsequent studies included EUS-FNI of "gene therapy" with ONYX-015 [73, 74], a gene-deleted replication-selective adenovirus that preferentially replicates in and kills malignant cells. A phase I/II trial testing feasibility, tolerability, and efficacy of EUS-FNI of ONYX-015 into unresectable pancreatic carcinomas evaluated 21 patients. Objective partial regressions were seen in only 2 patients, but this study again further supported the feasibility and safety of EUS-FNI antitumor therapy and set the stage for more advanced gene therapy studies discussed below.

TNFerade Gene Therapy

Tumor necrosis factor-α (TNF-α) has potent antitumor properties through its effect on tumor vasculature and direct cytotoxic effect. TNF-α may also function as a radiosensitizer by increasing levels of hydroxyl radicals, thereby enhancing the oxidative damage produced by radiation. Clinical studies with TNF-α have been limited due to severe systemic toxicity. TNFerade was constructed as a second generation adenovector, which expresses the complementary DNA (cDNA) encoding human TNF as a novel means to selectively deliver TNF to tumor cells using gene transfer [75]. To optimize local effectiveness and minimize systemic toxicity, the radiation-inducible immediate response early growth response (Egr)-1 promoter was placed upstream of the transcriptional start site of the human TNF cDNA. This vector was engineered to ensure that maximal gene expression and subsequent TNF secretion are constrained in space and time by radiation therapy. Human clinical trials have been performed in pancreatic, esophageal, and rectal cancers.

In patients with locally advanced pancreatic cancer, long-term results of phase I/II study of EUS or percutaneous transabdominal delivery of TNFerade with chemoradiation were reported [75]. TNFerade was injected into locally advanced pancreatic carcinomas once a week for 5 weeks together with 50.4 Gy of radiation and 5-fluorouracil (5-FU) 200 mg/m^2 daily over 5.5 weeks. Dose levels from 4×10^9–1×10^{12} particle units (PU) were studied. TNFerade was delivered with a single needle pass by percutaneous transabdominal approach whereas up to four injections were given by EUS. Figures 33.5, 33.6 and 33.7 show a TNFerade patient pre- and post-treatment). Fifty patients completed this dose-escalation study with 27 patients undergoing EUS-guided injection. Dose-limiting toxicities occurred in 3 EUS patients at 1×10^{12} PU (2 patients with pancreatitis and one patient with cholangitis). Major grade 3–4 adverse events were gastrointestinal bleeding, deep vein thrombosis and pulmonary emboli, pancreatitis, and cholangitis. The median time to tumor progression was 108 days (95% CI 67–198 days), and the median overall survival was 297 days (95% CI 201–316 days). The best median survival was seen in the 4×10^{11} PU cohort of 332 days (95% CI 154–316). Seven patients underwent surgical resection after treatment and six had negative surgical margins with one patient demonstrating a complete pathologic response. Given the high rate of pathologically negative surgical resection after downstaging, this treatment seemed promising.

Subsequently, a phase II/III randomized controlled trial of standard of care (SOC—chemoradiation therapy) with and without TNFerade was conducted [76]. In this study, 198 patients were assigned to the SOC + TNFerade and 90 to SOC. Median overall survival was 10 months for patients in both the SOC + TNFerade and SOC arms (hazard ratio 0.90; 95% CI 0.66–1.22; p = 0.26). Median progression-free survival was 6.8 months

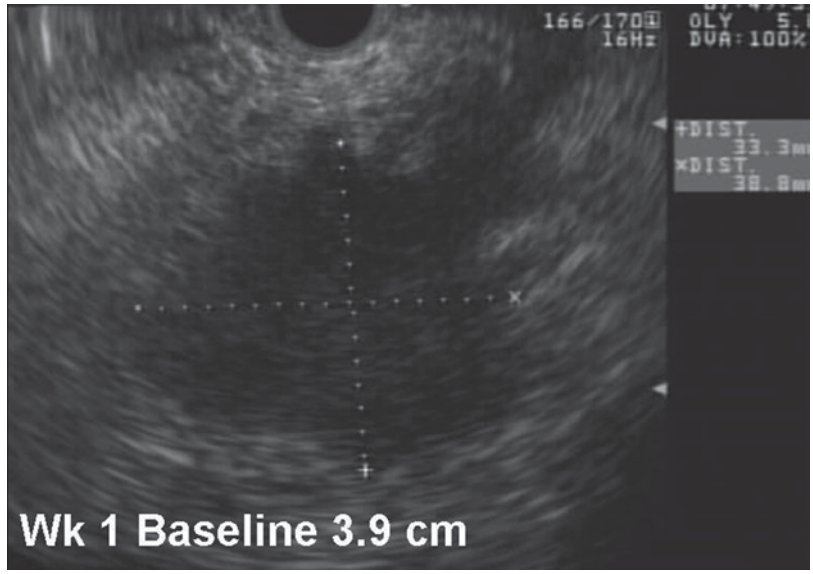

Fig. 33.5 A 71 year old man with T4 adenocarcinoma in the neck of the pancreas. Pre-treatment tumor size was 3.9 × 3.3 cm

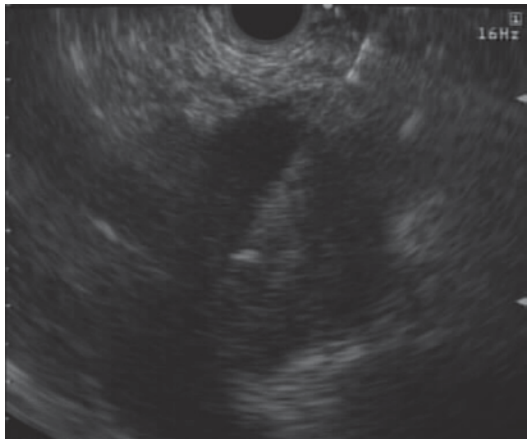

Fig. 33.6 EUS-guided fine-needle injection of TNFerade

for SOC + TNFerade versus 7.0 months for SOC (HR, 0.96; 95 % CI 0.69–1.32; p = 0.51). Patients in the SOC + TNFerade arm experienced more grade 1–2 fevers and chills than those in the SOC arm ($p < 0.001$) but both arms had similar rates of grade 3–4 toxicities. Although overall results did not show a difference in survival, a subgroup analysis revealed that patients with T1–T3 tumors and cancer antigen (CA) 19 − 9 levels less than 1000 U/ml had longer survival with the addition of TNFerade (10.9 vs. 9.0 months; p = 0.04) [77]. Thus, patient selection may be especially important with TNFerade therapy.

In locally advanced esophageal cancer, a multicenter phase 1 dose-escalating trial of intratumoral injection of TNFerade was performed [78]. TNFerade, with doses escalated logarithmically from 4×10^8–4×10^{11} PU, was given in combination with cisplatin 75 mg/m^2 and 5-FU 1000 mg/m^2/day for 96 h on days 1 and 29 with concurrent radiotherapy (RT) to 45 Gy. Surgery was performed 9–15 weeks after treatment. Six patients (29 %) had pathologic complete response among the 21 patients that underwent surgical evaluation (20 from esophagectomy and 1 from autopsy). Dose-limiting toxicities were not observed. The most frequent adverse events were fatigue (54 %), fever (38 %), nausea (29 %), vomiting (21 %), esophagitis (21 %), and chills (21 %). At the top dose of 4×10^{11} PU, 5 of 8 patients developed thromboembolic events. The median overall survival was 47.8 months. The 3- and 5-year overall and disease-free survival rates were 54 and 41 and 38 and 38 %, respectively. These results, especially the long-term prognosis, are encouraging and warrant further study with a randomized controlled trial.

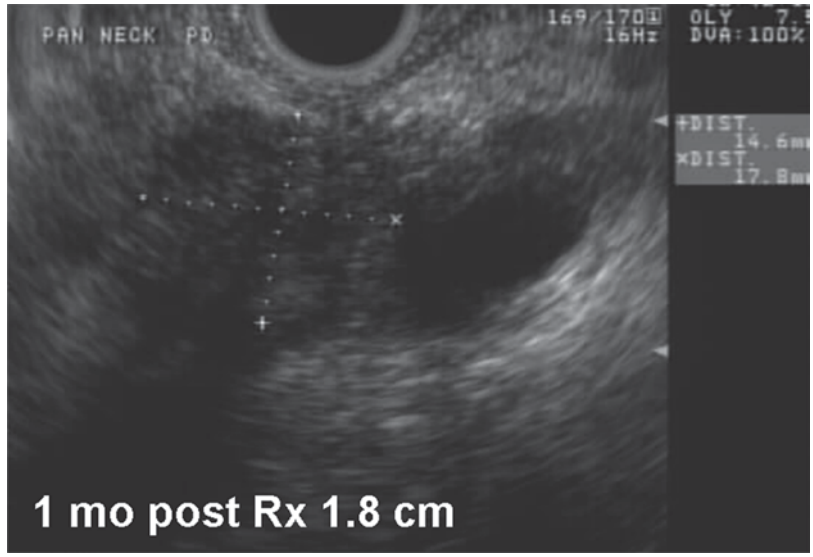

Fig. 33.7 EUS at 4 weeks following EUS-FNI showed a marked decrease in tumor size to 1.8 × 1.5 cm

A pilot study of TNFerade with capecitabine and radiation therapy as neoadjuvant chemoradiation therapy was performed in nine patients with T3, T4 or N1 rectal cancer [79]. Patients received RT to a total dose of 50.4 to 54 Gy in combination with capecitabine 937.5 mg/m2 orally twice daily. TNFerade at a dose of 4×10^{10} PU was injected into the rectal tumor on the first day of RT and weekly for a total of five injections. Surgery was performed 5–10 weeks after completion of chemoradiation. Eight patients completed all treatments. Grade 3 hematologic toxicity was observed in 2 patients. Discontinuation of treatment was necessary in 1 patient with grade 3 hematologic toxicity and concurrent ileitis. One grade 2 catheter-associated thrombosis was observed. No toxicity was directly attributable to the FNI procedure. A complete pathologic response was observed in 2 of 9 patients. This study confirmed the feasibility of EUS-FNI of antitumor agents in rectal cancer.

EUS-Guided Immunotherapy

EUS-guided immunotherapy has been considered an attractive option, especially in patients with pancreatic cancer, which is usually refractory to conventional chemotherapy. Tumor antigen-loaded dendritic cells (DCs) have been studied as a therapeutic vaccine for inducing tumor-specific immunity because DCs are the most potent antigen-presenting cells.

Irisawa and colleagues reported a pilot trial with EUS-FNI of unpulsed immature DCs in seven patients with unresectable stage IV pancreatic cancer refractory to gemcitabine [80]. Five patients received radiation to induce apoptosis and necrosis before initial EUS-FNI of DCs. Patients received intratumoral injection of 10 billion or more immature DCs at 2–3 sites on days 1, 8, and 15. The cycles were repeated every 28 days for as long as possible. No complication with EUS-FNI was noted. Median survival was 9.9 months with CA 19−9 level decreasing in three patients and three having a mixed response defined as regression of the main tumor, with other metastatic lesions remaining stable or progressing.

Subsequently, Hirooka and colleagues performed a pilot trial of combination therapy of gemcitabine and immunotherapy using OK432-pulsed DCs in five patients with inoperable locally advanced pancreatic cancer. OK432 is a widely used maturation stimulus for DCs. In this trial, patients received gemcitabine at 1000 mg/m^2 (day 1) and EUS-FNI of OK432-pulsed DCs into the tumor, followed by intravenous infusion of

lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody (day 4) at 2-week intervals. No serious treatment-related adverse events were observed. One patient had partial response and 2 had sustained stable disease for over 6 months.

Despite being small, these studies suggest that immunotherapy via intratumoral injection of DCs under EUS guidance should be further explored in larger clinical trials.

Future Directions

Many of the clinical studies mentioned are still experimental with small study populations. Prospective randomized controlled trials with large study populations are necessary to confirm the role of EUS-FNI in cancer treatment. Unlike systemic chemotherapy, EUS-FNI of an antitumor agent only exerts antitumor effects locally. Therefore, appropriate patient selection with truly local disease is important. EUS-FNI antitumor therapy cannot be offered as monotherapy, but as part of combination treatment including systemic therapy.

In conclusion, although EUS-FNI of antitumor agents has not yet been established as a standard option in cancer treatment, its feasibility and safety have been proven in both animal and human studies. The task at hand is to develop effective biologic and non-biologic local therapies. Once these agents are identified, large prospective randomized controlled trials will be needed to prove efficacy over standard therapy. We remain optimistic that EUS-FNI will play in important role in future cancer therapy.

Key Points

- EUS-guided celiac plexus block/neurolysis and more recently celiac ganglion neurolysis offer alternatives to opiate pain management in patients with pancreatic cancer or chronic pancreatitis pain. Efficacy appears higher for pancreatic cancer patients with lower response rates and durability in chronic pancreatitis patients.
- For EUS-CPN, usually a combination of bupivacaine and 98 % alcohol is injected while for EUS-CPB, bupivacaine with triamcinolone are administered.
- Whether bilateral injection is superior to unilateral remains unclear with studies supporting both techniques in celiac plexus block and neurolysis.
- Directly injecting alcohol into the celiac ganglia may improve pain relief although further studies are necessary.
- EUS-guided pancreatic cyst ablation with alcohol or a combination of alcohol and paclitaxel appears safe in select patients with benign unilocular cysts less than 6 cm in size without communication with the main pancreatic duct.
- EUS-guided placement of fiducial markers into a variety of gastrointestinal malignancies helps target radiation treatment. Smaller diameter fiducials allow the use of 22-gauge needles for placement.
- EUS-guided radiofrequency ablation of pancreatic tumors remains investigational.
- EUS-FNI of antitumor agents appears safe and feasible but awaits the development of optimal therapeutic agents.

References

1. Yan BM, Myers RP. Neurolytic celiac plexus block for pain control in unresectable pancreatic cancer. Am J Gastroenterol. 2007;102(2):430–8.
2. Ventafridda V, et al. A validation study of the WHO method for cancer pain relief. Cancer. 1987;59(4):850–6.
3. Levy MJ, Chari ST, Wiersema MJ. Endoscopic ultrasound-guided celiac neurolysis. Gastrointest Endosc Clin N Am. 2012;22(2):231–47, viii.
4. Yeager MP, et al. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. Anesthesiology. 1995;83(3):500–8.
5. Ward EM, et al. The celiac ganglia in man: normal anatomic variations. Anesth Analg. 1979;58(6):461–5.
6. Brown DL, Moore DC. The use of neurolytic celiac plexus block for pancreatic cancer: anatomy and technique. J Pain Symptom Manage. 1988;3(4):206–9.
7. Arcidiacono PG, et al. Celiac plexus block for pancreatic cancer pain in adults. Cochrane Database Syst Rev. 2011;(3):CD007519.
8. Eisenberg E, Carr DB, Chalmers TC. Neurolytic celiac plexus block for treatment of cancer pain: a meta-analysis. Anesth Analg. 1995;80(2):290–5.

9. Wiersema MJ, Wiersema LM. Endosonography-guided celiac plexus neurolysis. Gastrointest Endosc. 1996;44(6):656–62.
10. Puli SR, 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(11):2330–7.
11. Sahai AV, 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(2):326–9.
12. LeBlanc JK, et al. A prospective, randomized study of EUS-guided celiac plexus neurolysis for pancreatic cancer: one injection or two? Gastrointest Endosc. 2011;74(6):1300–7.
13. LeBlanc JK, et al. A prospective randomized trial of 1 versus 2 injections during EUS-guided celiac plexus block for chronic pancreatitis pain. Gastrointest Endosc. 2009;69(4):835–42.
14. Tellez-Avila FI, et al. Central is as effective as bilateral endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. Endosc Ultrasound. 2013;2(3):153–6.
15. Sakamoto H, et al. EUS-guided broad plexus neurolysis over the superior mesenteric artery using a 25-gauge needle. Am J Gastroenterol. 2010;105(12):2599–606.
16. Gleeson FC, et al. Frequency of visualization of presumed celiac ganglia by endoscopic ultrasound. Endoscopy. 2007;39(7):620–4.
17. Gunaratnam NT, et al. A prospective study of EUS-guided celiac plexus neurolysis for pancreatic cancer pain. Gastrointest Endosc. 2001;54(3):316–24.
18. Iwata K, et al. Predictive factors for pain relief after endoscopic ultrasound-guided celiac plexus neurolysis. Dig Endosc. 2011;23(2):140–5.
19. Seicean A, et al. Pain palliation by endoscopic ultrasound-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer. J Gastrointestin Liver Dis. 2013;22(1):59–64.
20. Kaufman M, 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(2):127–34.
21. Wyse JM, 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(26):3541–6.
22. Santosh D, et al. Clinical trial: a randomized trial comparing fluoroscopy guided percutaneous technique vs. endoscopic ultrasound guided technique of coeliac plexus block for treatment of pain in chronic pancreatitis. Aliment Pharmacol Ther. 2009;29(9):979–84.
23. Gress F, 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(2):409–16.
24. Doi S, et al. Endoscopic ultrasound-guided celiac ganglia neurolysis vs. celiac plexus neurolysis: a randomized multicenter trial. Endoscopy. 2013;45(5):362–9.
25. Levy MJ, et al. Initial evaluation of the efficacy and safety of endoscopic ultrasound-guided direct Ganglia neurolysis and block. Am J Gastroenterol. 2008;103(1):98–103.
26. Ascunce G, et al. EUS visualization and direct celiac ganglia neurolysis predicts better pain relief in patients with pancreatic malignancy (with video). Gastrointest Endosc. 2011;73(2):267–74.
27. O'Toole TM, Schmulewitz N. Complication rates of EUS-guided celiac plexus blockade and neurolysis: results of a large case series. Endoscopy. 2009;41(7):593–7.
28. Alvarez-Sanchez MV, et al. Interventional endoscopic ultrasonography: an overview of safety and complications. Surg Endosc. 2013;28:712–34.
29. 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(1):151–2.
30. Lee KS, et al. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. Am J Gastroenterol. 2010;105(9):2079–84.
31. Laffan TA, et al. Prevalence of unsuspected pancreatic cysts on MDCT. AJR Am J Roentgenol. 2008;191(3):802–7.
32. Al-Haddad M, et al. Diagnosis and treatment of cystic pancreatic tumors. Clin Gastroenterol Hepatol. 2011;9(8):635–48.
33. Brugge WR, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. Gastroenterology. 2004;126(5):1330–6.
34. Tanaka M, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012;12(3):183–97.
35. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007;102(10):2339–49.
36. Gan SI, et al. Ethanol lavage of pancreatic cystic lesions: initial pilot study. Gastrointest Endosc. 2005;61(6):746–52.
37. Oh HC, et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. Gastrointest Endosc. 2008;67(4):636–42.
38. DeWitt J, et al. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. Gastrointest Endosc. 2009;70(4):710–23.
39. 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.
40. Oh HC, et al. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. Gastroenterology. 2011;140(1):172–9.

41. 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.
42. DeWitt J. Endoscopic ultrasound-guided pancreatic cyst ablation. Gastrointest Endosc Clin N Am. 2012;22(2):291–302, ix–x.
43. Oh HC, Brugge WR. EUS-guided pancreatic cyst ablation: a critical review (with video). Gastrointest Endosc. 2013;77(4):526–33.
44. Gelczer RK, et al. Complications of percutaneous ethanol ablation. J Ultrasound Med. 1998;17(8):531–3.
45. Rowinsky EK, Donehower RC. Paclitaxel (taxol). N Engl J Med. 1995;332(15):1004–14.
46. Oh HC, 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.
47. Fegrachi S, et al. Radiofrequency ablation for unresectable locally advanced pancreatic cancer: a systematic review. HPB (Oxford). 2014;16(2):119–23.
48. Goldberg SN, et al. EUS-guided radiofrequency ablation in the pancreas: results in a porcine model. Gastrointest Endosc. 1999;50(3):392–401.
49. Carrara S, et al. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. Endoscopy. 2008;40(4):321–6.
50. Carrara S, et al. Endoscopic ultrasound-guided application of a new internally gas-cooled radiofrequency ablation probe in the liver and spleen of an animal model: a preliminary study. Endoscopy. 2008;40(9):759–63.
51. Petrone MC, et al. US-guided application of a new hybrid probe in human pancreatic adenocarcinoma: an ex vivo study. Gastrointest Endosc. 2010;71(7):1294–7.
52. 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(2):372–6.
53. Gaidhane M, et al. Endoscopic Ultrasound-Guided Radiofrequency Ablation (EUS-RFA) of the Pancreas in a Porcine Model. Gastroenterol Res Pract. 2012;2012:431451.
54. Kim HJ, et al. EUS-guided radiofrequency ablation of the porcine pancreas. Gastrointest Endosc. 2012;76(5):1039–43.
55. Arcidiacono PG, et al. Feasibility and safety of EUS-guided cryothermal ablation in patients with locally advanced pancreatic cancer. Gastrointest Endosc. 2012;76(6):1142–51.
56. Kothary N, et al. Safety and efficacy of percutaneous fiducial marker implantation for image-guided radiation therapy. J Vasc Interv Radiol. 2009;20(2):235–9.
57. Ammar T, et al. Fiducial placement for stereotactic radiation by using EUS: feasibility when using a marker compatible with a standard 22-gauge needle. Gastrointest Endosc. 2010;71(3):630–3.
58. DiMaio CJ, et al. EUS-guided fiducial placement for image-guided radiation therapy in GI malignancies by using a 22-gauge needle (with videos). Gastrointest Endosc. 2010;71(7):1204–10.
59. Pishvaian AC, et al. EUS-guided fiducial placement for CyberKnife radiotherapy of mediastinal and abdominal malignancies. Gastrointest Endosc. 2006;64(3):412–7.
60. Micames C, et al. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. Gastrointest Endosc. 2003;58(5):690–5.
61. Timmerman RD, et al. Stereotactic body radiation therapy in multiple organ sites. J Clin Oncol. 2007;25(8):947–52.
62. Ramesh J, Porterfield J, Varadarajulu S, Endoscopic ultrasound-guided gold fiducial marker placement for intraoperative identification of insulinoma. Endoscopy 2012; 44(Suppl 2) UCTN: E327–8.
63. Law JK, et al. Endoscopic ultrasound (EUS)-guided fiducial placement allows localization of small neuroendocrine tumors during parenchymal-sparing pancreatic surgery. Surg Endosc. 2013;27(10):3921–6.
64. Handsfield LL, et al. Determination of optimal fiducial marker across image-guided radiation therapy (IGRT) modalities: visibility and artifact analysis of gold, carbon, and polymer fiducial markers. J Appl Clin Med Phys. 2012;13(5):3976.
65. Kassim I, et al. Implications of artefacts reduction in the planning CT originating from implanted fiducial markers. Med Dosim. 2011;36(2):119–25.
66. Khashab MA, et al. Comparative analysis of traditional and coiled fiducials implanted during EUS for pancreatic cancer patients receiving stereotactic body radiation therapy. Gastrointest Endosc. 2012;76(5):962–71.
67. Owens DJ, Savides TJ. EUS placement of metal fiducials by using a backloaded technique with bone wax seal. Gastrointest Endosc. 2009;69(4):972–3.
68. Park WG, et al. EUS-guided gold fiducial insertion for image-guided radiation therapy of pancreatic cancer: 50 successful cases without fluoroscopy. Gastrointest Endosc. 2010;71(3):513–8.
69. Sanders MK, et al. EUS-guided fiducial placement for stereotactic body radiotherapy in locally advanced and recurrent pancreatic cancer. Gastrointest Endosc. 2010;71(7):1178–84.
70. Draganov PV, Chavalitdhamrong D, Wagh MS. Evaluation of a new endoscopic ultrasound-guided multi-fiducial delivery system: a prospective non-survival study in a live porcine model. Dig Endosc. 2013;25(6):615–21.
71. Majumder S, et al. Endoscopic ultrasound-guided pancreatic fiducial placement: how important is ideal fiducial geometry? Pancreas. 2013;42(4):692–5.
72. Chang KJ, 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.

73. Mulvihill S, et al. Safety and feasibility of injection with an E1B-55 kDa gene-deleted, replication-selective adenovirus (ONYX-015) into primary carcinomas of the pancreas: a phase I trial. Gene Ther. 2001;8(4):308–15.
74. Hecht JR, 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(2):555–61.
75. Hecht JR, et al. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. Gastrointest Endosc. 2012;75(2):332–8.
76. Herman JM, et al. Randomized phase III multi-institutional study of TNFerade biologic with fluorouracil and radiotherapy for locally advanced pancreatic cancer: final results. J Clin Oncol. 2013;31(7):886–94.
77. Nakai Y, Chang KJ. Endoscopic ultrasound-guided antitumor agents. Gastrointest Endosc Clin N Am. 2012;22(2):315–24, x.
78. Chang KJ, et al. Phase I evaluation of TNFerade biologic plus chemoradiotherapy before esophagectomy for locally advanced resectable esophageal cancer. Gastrointest Endosc. 2012;75(6):1139–46 e2.
79. Citrin D, et al. A pilot feasibility study of TNFerade biologic with capecitabine and radiation therapy followed by surgical resection for the treatment of rectal cancer. Oncology. 2010;79(5–6):382–8.
80. Irisawa A, 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(2):189–90.

EUS-Guided Bilio-Pancreatic Drainage

34

Marc Giovannini, Erwan Bories and Felix Tellez

Introduction

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

Using EUS guidance and dedicated accessories, bilio-digestive anastomoses can be created.

The aim of this section is to:

1. Describe the material needed for such procedures
2. Detail the technique of biliary drainage under EUS guidance
3. Discuss the place of these techniques today in comparison with ERCP

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Case Report

An 89 year-old-male with painless jaundice underwent an abdominal (computed tomography) CT that revealed a 5.6 cm mass in the head of the pancreas with diffuse biliary dilation leading to an abrupt cutoff in the distal bile duct and several liver lesions. He was referred for EUS and ERCP. EUS-FNA was performed of a hepatic lesion and the pancreatic mass with preliminary cytology evaluation confirming pancreatic adenocarcinoma. ERCP was attempted on two separate occasions to establish biliary drainage, but was unsuccessful. The patient refused a percutaneous biliary drain. The possibility of performing EUS-guided biliary drainage was discussed with the patient who agreed to this.

What Tools Are Necessary to Perform EUS-Guided Biliary Drainage?

Interventional Echoendoscopes

Around 1990, the Pentax-Corporation developed an electronic convex curved linear array echoendoscope (FG32UA) with an imaging plane in the long axis of the device that overlaps with the instrumentation plane. This echoendoscope, equipped with a 2.0 mm working channel, enabled fine needle biopsy under EUS guidance. However, the relatively small working channel of the FG32UA was a drawback for performing pseudocyst drainage because it necessitated

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exchanging the echoendoscope for a therapeutic duodenoscope to insert either a stent or nasocystic drain. To enable stent placement using an echoendoscope, the EUS interventional echoendoscopes (FG38X, EG 38-UT and EG-3870UTK) were developed by Pentax-Hitachi. The FG38X has a working channel of 3.2 mm, which allows the insertion of an 8.5F stent or nasocystic drain, and the EG38-UTand EG-3870UTK have a larger working channel of 3.8 mm with an elevator allowing the placement of a 10F stent [1, 2].

The Olympus Corporation has also developed convex linear array echoendoscopes. The GF UC 160P OL5 has a biopsy channel of 2.8 mm, which enables the placement of a 7F stent or nasocystic catheter, and the instrument is equipped with an elevator. The GF UCT 180 also has an elevator and a larger working channel of 3.7 mm allowing the placement of 10 F stents. The main drawback of convex linear array echoendoscopes is the more limited imaging field (120° using the Pentax and 180° using the Olympus) produced by an electronic transducer. These instruments are coupled with the Aloka processor or with a smaller processor (Suzie).

Needles and Accessories for Drainage

In standard EUS-guided fine needle aspiration (FNA), the 22G needle is well visualized sonographically and can be used for pseudocyst puncture. The drawback of this needle is the small caliber that will accept only an 0.018 in. guidewire. Using a 19G FNA needle, a 450 cm long hydrophilic 0.035 in. guidewire can be inserted through the needle into the dilated bile duct. The needle should be primed with contrast before insertion. One of the main problems during EUS-guided hepaticogastrostomy, is the difficulty in manipulating the guidewire through the 19G EUS needle. The principal trouble is "stripping" the coating of the guidewire, which in turn creates a risk of leaving part of the wire coating in the patient and also the impossibility of continuing the procedure to insert the stent.

To solve this problem, we worked with Cook Medical to design a special needle called the EchoTip® Access Needle. This needle is original because the stylet is sharp and it is relatively easy to insert the needle into the bile duct, pancreatic duct, or a pseudocyst. When the stylet is withdrawn, the needle left in place is smooth, manipulating the guidewire is easy, and the device is designed to decrease the possibility of wire stripping. If this needle is not available, a thinner 0.025 in. guidewire may reduce friction between the wire and edge of the needle, and the guidewire should not be pulled back. Guidewires used with success in various reports include Radiofocus (Terumo, Tokyo, Japan), Dreamwire (Boston Scientific, Marlborough, MA, USA), RevoWave (Piolax Medical, Kanagawa, Japan), and VisiGlide (Olympus Medical, Tokyo, Japan). The Terumo wire had the best torque rotation control. [3]

Some authors have used needle knife catheters, but the needle can be difficult to visualize endosonographically. The "Zimmon" needle knife (Cook Medical, Bloomington, IN, USA) has a large gauge needle that is easier to visualize. Diathermy is occasionally required to penetrate the bile duct although should be avoided due to higher rate of complications associated with the use of a needle knife for fistula dilation (Fig. 34.1) [4–36].

Dilators are required to enlarge the fistula tract following puncture. Bougie (6-7F) or balloon (4–6 mm) dilators such as the Soehendra biliary dilation catheter (Cook Medical) or Hurricane biliary balloon dilatation catheter (Boston Scientific) may be used. To minimize pneumoperitoneum following EUS-guided biliary drainage, CO_2 should be used for insufflation during all these procedures. [26] Prophylactic antibiotics should also be administered to all patients.

What Is the Technique of EUS-Guided Biliary Access?

There are a variety of ways to access the biliary system and establish drainage. No single approach appears superior based on current studies, [26] and the decision to choose a particular approach is individualized to the patient. The extrahepatic or intrahepatic bile duct can be

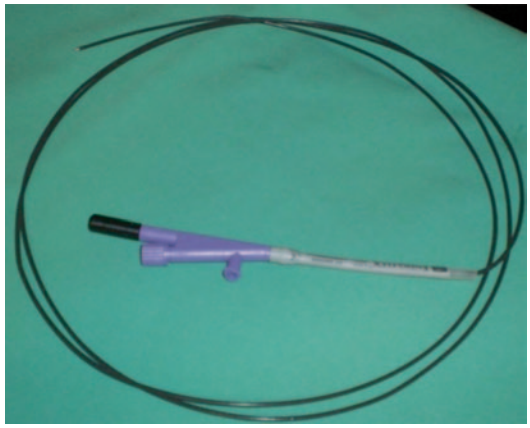

Fig. 34.1 6F cystostome (Endoflex Company)

punctured and a stent can be deployed in the usual retrograde fashion during a rendezvous, antegrade across the gastrointestinal wall and down the stricture, or through the gastrointestinal wall to create a bilio-enteric fistula. With the extrahepatic approach, usually the duodenal bulb is punctured, although, rarely the antrum is traversed. With the intrahepatic approach, the left intrahepatic ducts are accessed through the gastric fundus about 2–3 cm below the cardia along the lesser curvature and rarely through the distal esophagus or jejunum in postsurgical anatomy.

EUS-Guided Rendezvous (Fig. 34.2)

This figure illustrates the EUS-guided rendezvous technique. If the papilla is accessible, this is the preferred approach. Either an intrahepatic or extrahepatic puncture can be performed to access the bile duct. Some experts prefer the intrahepatic approach as it is thought to cause less bile leak than the extrahepatic approach. [24] In the intrahepatic approach, the therapeutic linear echoendoscope is positioned in the stomach along the mid-lesser curvature, and after puncturing the left hepatic biliary system using a 19G needle, bile is aspirated and contrast injected. Then a long 0.035 in. hydrophilic guidewire (Tracer Metro Direct, Cook Endoscopy or Jagwire, Boston Scientific, Paris, France) is inserted into the bile duct and looped inside the duodenum. Advancing the guidewire through the needle and down the intrahepatic ducts through the stricture and out the ampulla is often the most difficult part of the procedure. Because of the long distance the wire needs to travel with this intrahepatic approach; pushability and transmission of torque are often limited in advancing it through a tight stricture.

On the other hand, the extrahepatic approach has its own issues. Puncturing through the duodenal bulb for an extrahepatic approach may be challenging due to the long position of the echoendoscope making maneuvering a 19G needle difficult, and from this position, the wire will have a tendency to head towards the hilum rather than the ampulla. In order to advance the wire out the ampulla, a short scope position is preferred. Before puncturing the bile duct, the position of the needle can be checked with fluoroscopy. Then the needle is withdrawn and the echoendoscope with the needle are gently withdrawn leaving the guidewire in place. Afterwards, a duodenoscope is advanced to the second/third portion of the duodenum, parallel to the guidewire in the duodenum. Cannulation can be attempted alongside the guidewire, or the guidewire is captured with a standard snare or forceps and pulled out through the working channel of the duodenoscope. An ERCP cannula is advanced over the guidewire, and the ERCP can be completed in usual retrograde fashion.

The rendezvous technique, although attractive because it preserves the normal anatomy without creating a new fistulous communication between the biliary tree and gastrointestinal lumen, is potentially fraught with difficulties at several steps. If the intrahepatic approach is used, advancing the guidewire, the long distance through the papilla can be arduous. With the extrahepatic approach, several punctures into the bile duct may be necessary before being able to direct the guidewire out the papilla. Similarly, once the guidewire has been looped in the duodenum, exchanging the echoendoscope for the duodenoscope can be cumbersome. If the rendezvous approach fails or is not possible due to duodenal obstruction, EUS-guided bilioenteric anastomoses may be attempted.

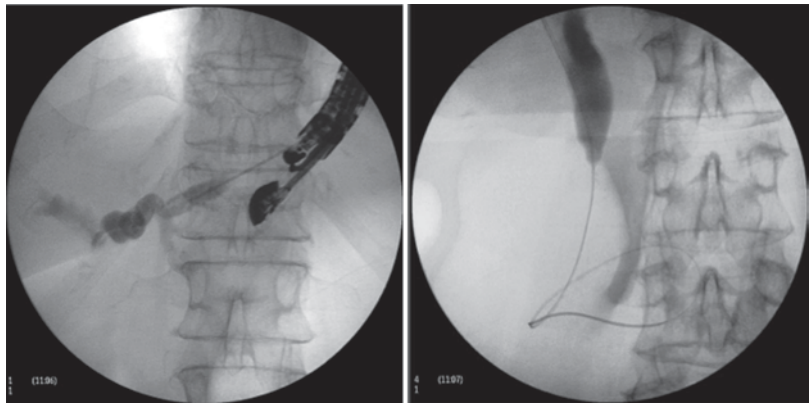

Fig. 34.2 Rendezvous technique using EUS guidance: *Left panel* shows EUS-FNA using 19G needle to puncture dilated left intrahepatic bile duct followed by bile aspiration and then contrast injection. *Right panel* shows long guidewire advanced antegrade down through the distal biliary stricture and coiling out in the duodenum

EUS-Guided Bilioenteric Anastomoses

Choledochoduodenostomy (CD) (Video 34.1)

The formation of permanent bilioenteric fistulae whether a choledochoduodenostomy or hepaticogastrostomy should be reserved in patients with unresectable malignancies. In choledochoduodenostomy, a 19 G needle is inserted transduodenally into the bile duct under EUS guidance. Bile is aspirated and contrast is injected into the bile duct for cholangiography. A 450-cm long, 0.035-in. guidewire is inserted through the 19 G needle into the bile duct. With the echoendoscope in a long position in the proximal duodenum, advancing the wire towards the hilum usually allows an easier angle to advance the stent. Only after the wire position is secured should dilation be performed to decrease risk of bile leakage. The choledochoduodenal fistula is dilated using a 6–to 7F biliary bougie dilator (Soehendra biliary dilator; Cook Medical), 4–6 mm balloon dilator, or a 6Fr cystostome (Endoflex, Germany). Overdilation should be avoided to decrease the risk of bile leakage. A 7F–10F biliary plastic stent or a covered self-expandable metallic stent (SEMS) is placed through the choledochoduodenostomy site into the extrahepatic bile duct. Uncovered metal stents should not be used to create bilioenteric fistulae due to the potential risk of bile leakage and peritonitis.

Left Hepaticogastrostomy (HGE) (Fig. 34.3)

EUS-guided hepaticogastrostomy was first reported by Burmester *et al*. [7] in 2003. The technique is basically similar to EUS-guided drainage of pancreatic pseudocysts. By using an interventional echoendoscope, the dilated left hepatic duct (segment III) is well visualized. Hepaticogastrostomy is then performed under combined fluoroscopic and ultrasound guidance, with the tip of the echoendoscope positioned such that the inflated balloon is in the middle part of the lesser curvature of the stomach. A 19G needle (EchoTip® Access Needle, Cook Ireland Ltd., Limerick, Ireland) is inserted transgastrically into the distal part of the left hepatic duct and following aspiration of bile, contrast medium is injected. Opacification demonstrates dilated biliary ducts proximal to the complete obstruction. The needle is exchanged over a guidewire (0.02 in. diameter, Terumo Europe, Leuven, Belgium) for a 6.5F diathermic sheath (prototype Cysto-Gastro set, EndoFlex, Voerde, Germany), which is then used to enlarge the channel between the stomach and the left hepatic duct. The sheath was introduced by using cutting current in this figure. However, electrocautery is usually not necessary and following needle puncture, dilation can be performed using a bougie or balloon dilator. After exchange over a guidewire (TFE-coated 0.035 in. diameter, Cook Europe, Bjaeverskov, Denmark),

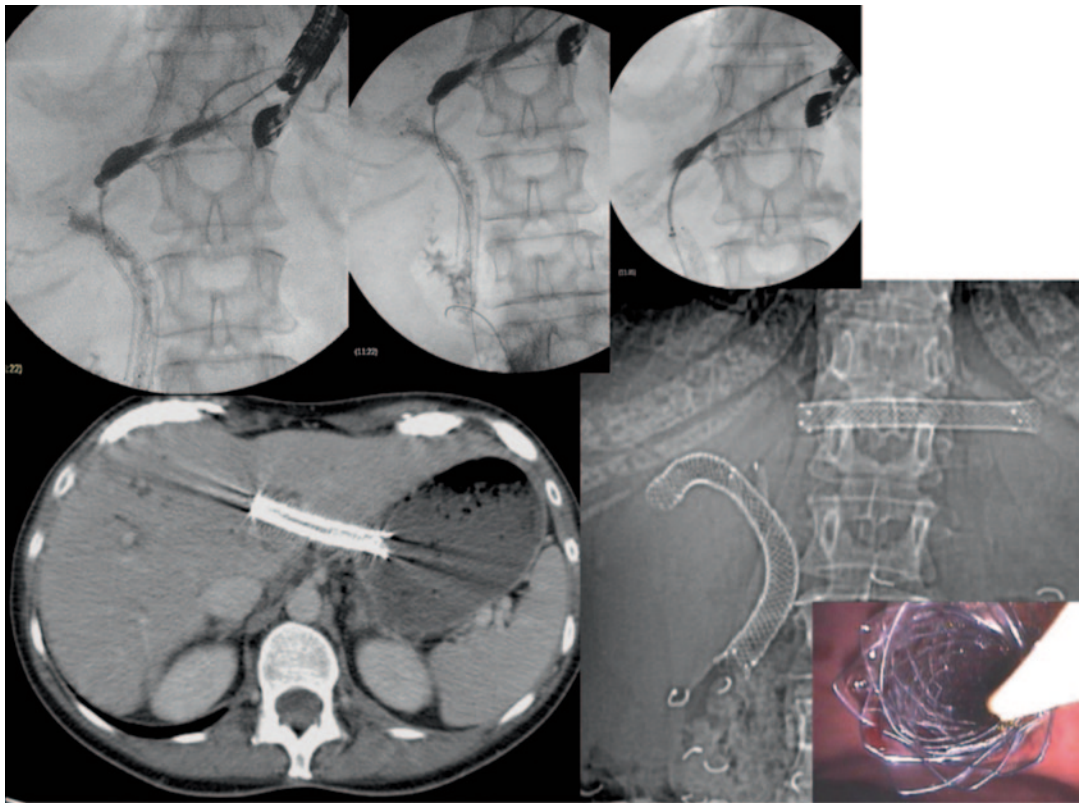

Fig. 34.3 Hepaticogastrostomy performed after ERCP failed to drain the left hepatic lobe in patient with a Klatskin Tumor. *Top panels* show two overlapping metal biliary stents in right main hepatic duct with EUS-FNA using a 19G needle into the left intrahepatic duct showing a mildly dilated left hepatic duct. A long guidewire is advanced antegrade into the duodenum, the tract is dilated using a 6.5 Fr diathermic sheath, and then a fully covered metal stent is inserted. *Bottom panels* show abdominal CT scan, fluoroscopic, and endoscopic image of metal stent deployed to create hepaticogastrostomy

an 8.5 F by 8 cm long hepatico-gastric stent or a 10 mm by 8 cm long covered SEMS (Boston Scientific) is positioned. As observed by fluoroscopy, contrast is emptied from the stent into the stomach. To prevent bile leakage, a 6 or 7F nasobiliary drain can be left through the metallic stent for aspiration during the ensuing 48 h. More recently we decided to insert a covered stent within an uncovered stent to prevent bile leakage. Hepaticogastrostomy may be combined with placement of an additional metallic stent bridging the distal stricture as described below.

Antegrade Approach

This approach refers to the formation of a temporary bilioenteric fistula followed by management of the stricture in an antegrade fashion. The technique involves access to the left intrahepatic ducts as described above using a 19G FNA needle and a 450 cm long 0.035 in. guidewire advanced through the stricture into the duodenum, similar to during a rendezvous using the intrahepatic approach. This is followed by dilation of the fistula tract using a bougie or balloon dilator, and then placement of a metal stent in an antegrade fashion. The presence of the dilating catheter through which the wire can be manipulated facilitates advancement of the wire, unlike during a rendezvous procedure. Theoretical concern for bile leakage exists if a second stent is not placed bridging the left intrahepatic bile ducts and the stomach although this has not been reported in the literature. Extrahepatic biliary puncture is not recommended in the antegrade approach because

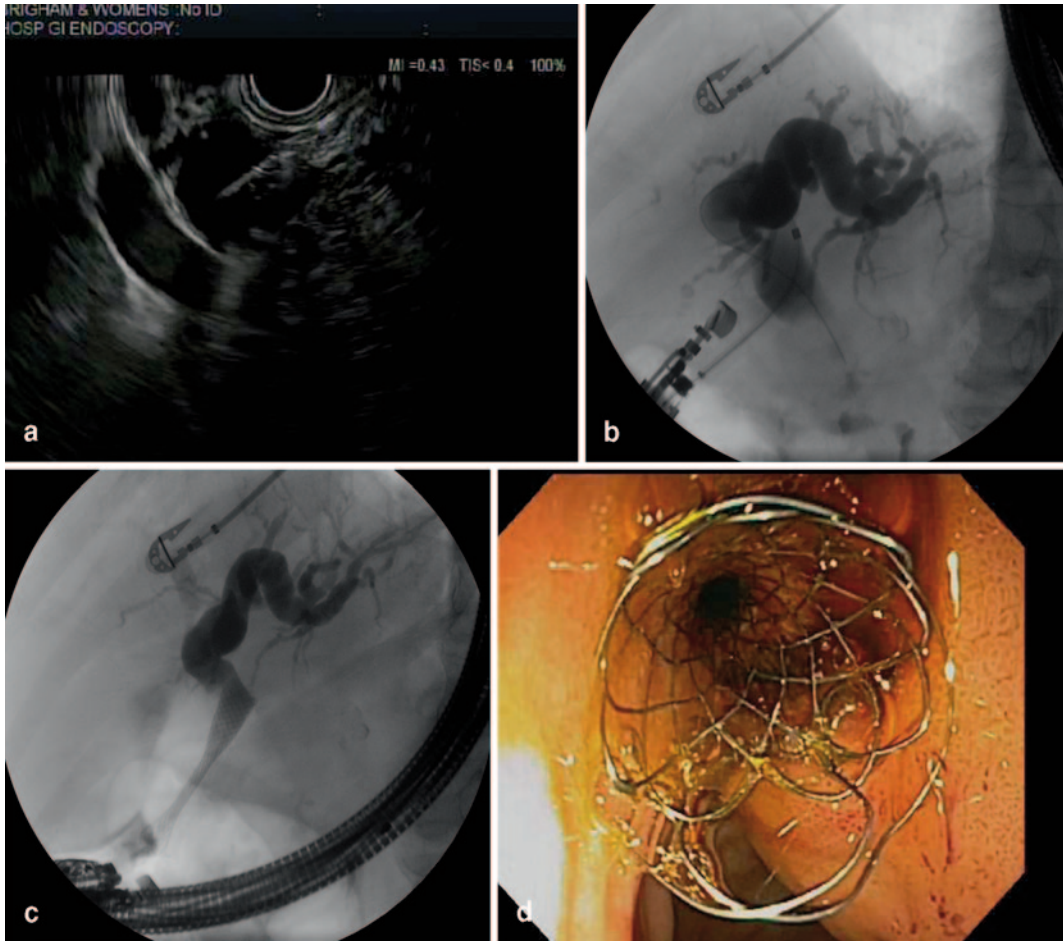

Fig. 34.4 **a** EUS-guided choledochoduodenostomy with 19G needle punctured into dilated common bile duct. **b** Contrast injection shows diffusely dilated proximal extrahepatic and intrahepatic bile duct with no contrast exiting the ampulla. Long 0.035 in. dreamwire guidewire (Boston Scientific) is in the bile duct with a 7Fr Soehendra catheter dilator (Cook Medical) advanced across the choledochoduodenostomy site. **c** Fluoroscopic view of fully covered SEMS deployed to establish the choledochoduodenostomy. **d** Endoscopic view of fully covered SEMS with distal end in duodenal bulb. (Courtesy Dr. Christopher Thompson, Brigham and Women's Hospital, Boston, MA)

advancing the stent is often challenging due to the angle the stent needs to traverse.

Case Continued

EUS-guided biliary drainage was performed using general anesthesia and CO2 insufflation after administering intravenous ciprofloxacin. EUS revealed a 2 cm common bile duct. Because the papilla was accessible, the rendezvous approach was initially chosen. However, despite multiple attempts at positioning the therapeutic linear echoendoscope to allow the guidewire to be advanced out the papilla, this could not be achieved. Therefore, the decision was made to perform a choledochoduodenostomy. With the echoendoscope in the duodenal bulb in the long position, the 19G needle punctured the CBD (Fig. 34.4a), bile was aspirated, and contrast injected. A long 0.035 in. dreamwire guidewire (Boston Scientific) was advanced into the biliary system. The needle was removed and the transmural tract dilated using a Soehendra dilation catheter up to 7Fr (Fig. 34.4b).

A 10 mm × 4 cm long fully covered SEMS was deployed with the distal end in the duodenal bulb and good bile drainage (Fig. 34.4c, d).

What Are the Role, Success, and Complications of EUS-Guided Biliary Access

ERCP is the gold standard technique for the drainage of obstructive jaundice due to malignant or benign etiologies. The success rate of biliary stenting by ERCP is around 80–85 % with unsuccessful ERCPs resulting from either failed cannulation of the papilla or inability to reach the papilla due to intestinal obstruction or surgically altered anatomy. Percutaneous biliary drainage is the accepted alternative, but carries a high complication rate from bleeding or peritoneal bile leakage (20–30 %). The morbidity and mortality of surgery as a palliative procedure are 35–50 % and 10–15 %, respectively. Therefore, these new techniques of biliary drainage using EUS guidance could provide another option. A small retrospective study of patients with inaccessible papilla compared 25 patients undergoing EUS-guided biliary drainage using either the antegrade approach or the creation of a bilioenteric fistula to 26 patients having percutaneous biliary drainage. [37] Both clinical access at achieving internal biliary drainage with stents (92 % vs. 46 %, $p < 0.05$) and complications (20 % vs. 46 %, $p < 0.05$) were favorable with the EUS arm. There was a death following the EUS approach and two deaths after percutaneous drainage. Another small retrospective series comparing EUS to percutaneous biliary drainage in failed ERCPs for distal biliary strictures found greater technical success with the percutaneous approach (100% versus 86%, p=0.007) with a trend towards increased adverse events in the percutaneous groups (39% versus 18%, p=0.08). [38] Further rigorous randomized studies are necessary to compare the EUS to the percutaneous approach.

To date, 549 patients with EUS-guided bile duct drainage (EUS-CD = 284; EUS-HGE = 265, and EUS rendezvous = 33) have been reported in 30 studies (Table 34.1). [4–36] A 19 gauge or 22 gauge fine needle followed by balloon dilatation, needle knife, or cystotome were used to puncture the intrahepatic bile ducts in all these patients. We recently published a large multicenter study including 240 patients in whom ERCP failed due to tumor infiltration at the papilla, duodenal obstruction, inability to advance the guidewire through the stricture, and postsurgical anatomy, and EUS-guided biliary access was employed. [39] Over 80 % of the patients had malignant biliary obstruction. The intrahepatic approach was used in 60 % of patients with 90 % success, which was similar to the 84 % success with the extrahepatic approach. Complications occurred in about 31 % of patients with similar rates for both the intrahepatic and extrahepatic routes as well as for plastic and metal stents, although there was a higher rate of cholangitis with plastic stents (11 % versus 3 %, $p = 0.02$).

Choledochoduodenostomy

Patients who have undergone this technique have high technical success (265/284 = 93.3 %) and clinical success (219/265 = 81.5 %). The rate of complications is 51/284 (17.9 %). Less than 2 % of the patients with complications needed invasive treatment, according to the obtained data. The main reported complication was the bile leakage 29/51 (56.9 %). Compared to ERCP, EUS-guided biliary drainage of 104 distal biliary strictures had similar rates of clinical success (92–93%) and adverse events (9%). As expected, a much higher rate of success occurred in patients with duodenal obstruction undergoing EUS-guided drainage rather than ERCP (91% versus 57%, p=0.0003). [40]

Hepaticogastrostomy

Hepaticogastrostomy was successful in 251/265 cases (94.7 %) with clinical success in 80.8 % (203/251). Various types of stents, including plastic stents, uncovered metal stents, and covered metal stents were used for the drainage. The rate of complications was 80/265 (30.1 %).

Table 34.1 Summary of the published literature on EUS-guided biliary drainage (HGE, CD, and rendezvous technique)

First author, year	*n*	Device for puncture	Technical success,*n*	Clinical success, *n*	Initial stent		Early complications (*n*)
					Plastic, French	SEMS, mm	
EUS-guided choledochoduodenostomy							
Giovannini 2001 [6]	1	NK	1/1	1/1	10	–	None
Burmester 2003 [7]	2	19G FT	1/2	1/1	8.5	–	Bile peritonitis (1)
Puspok 2005 [8]	5	NK	4/5	4/4	7−10	–	None
Kahaleh 2006 [9]	1	19G FN	1/1	1/1		10	Pneumoperitoneum (1)
Yamao 2008 [10]	5	NK	5/5	5/5	7–8.5	–	Pneumoperitoneum (1)
Ang 2007 [11]	2	NK	2/2	2/2	7	–	Pneumoperitoneum (1)
Fujita [12]	1	19G FN	1/1	1/1	7	–	None
Tarantino 2008 [13]	4	19G, 22G FN/NK	4/4	4/4	–[a]	–	None
Itoi 2008 [14]	4	NK (2), 19 G FN (2)	4/4	4/4	7, NBD	–	Bile peritonitis (1)
Horaguchi 2009 [15]	8	19G	8/8	8/8	7	–	Peritonitis (1)
Hanada 2009 [16]	4	19G FN	4/4	4/4	6–7	–	None
Park 2009 [17]	4	19G FN/NK	4/4	4/4	–	10	None
Brauer 2009 [18]	3	19G, 22G FN/NK	2/3	2/2	10	–	Pneumoperitoneum Cardiac failure
Maranki 2009 [19]	4	19G, 22G		0	10	10	0
Artifon 2010 [20]	3	19G	3/3	3/3	–	10	None
Eum 2010 [21]	2	19G	2/2	2/2	–	10	None
Hara 2011 [22]	18	22G	17/18	17/17	7–8.5	–	Focal peritonitis (2) Hemobilia (1)
Ramírez-Luna 2011 [23]	9	19G	9/9	8/9	7–10	–	Biloma (1)
Park 2011 [5]	24	19G	22/24	20/22	7	10	Pneumoperitoneum (7) Bile peritonitis (2) Bleeding (2)
Shah 2012 [24]	70	19G, 22G	Δ				None
Kawakubo 2013 [25]	44	19G/NK	42/44	33/42	23	19	Bile leakage (4) Perforation (2) Bleeding (1)
Khashab et al 2013 [26]	20	19G	20/20	18/20	0	20	Perforation(1)
Dhir 2013 [27]	31	19G/NK	30/31	27/30	0	30	Bile leakage (2) Perforation (1)
Gupta 2013 [28]	89	19G/NK	75/89	46/75	25	50	Bile leakage (13) Bleeding (8) Cholangitis (4)
EUS-guided hepaticogastrostomy							
Burmester 2003 [7]	1	19G FT	1/1	1/1	8.5		None
Kahaleh 2006 [9]	2	19G, 22G FN	2/2	2/2	10		None
Artifon 2007 [29]	1	19G FN	1/1	1/1	–	10	None
Bories 2007 [30]	11	19G, 22G FN/CT	10/11	10/10	7	10	Cholangitis (2) Ileus (1) Biloma (1)

Table 34.1 (continued)

First author, year	*n*	Device for puncture	Technical success,*n*	Clinical success, *n*	Initial stent		Early complications (*n*)
					Plastic, French	SEMS, mm	
Will 2007 [31]	4	19G FN	4/4	3/4	–	10	Cholangitis (1)
Chopin-Laly 2008 [32]	1	–	1/1	1/1	–	–[a]	None
Park 2009 [17]	9	19G FN/NK	9/9	9/9		10	None
Horaguchi 2009 [15]	6	19G	6/6	5/6	7	–	None
Maranki 2009 [19]	3	19G, 22G	3	δ	10	10	δ
Park 2010 [33]	5	19G	5/5	5/5	–	10	None
Martins 2010 [34]	1	19G	1/1	0/1	–		Death (1)
Eum 2010 [21]	1	19G	1/1	1/1	–	10	None
Artifon 2011 [35]	1	19G	1/1	1/1	–	10	None
Ramírez-Luna 2011 [23]	2	19G	2/2	2/2	7	–	Stent migration (1)
Park et al 2011 [5]	17	19G	17/17	13/17	7	10	Pneumoperitoneum (4) Bleeding (2)
Shah 2012 [25]	16	19G, 22G	13/16	13/16	10	10	Hepatic hematoma (1) Infection (1)
Kawakubo 2013 [25]	20	19G/NK	20/20	14/20	4	16	Bile leakage (5) Cholangitis (1)
Dhir 2013 [27]	34	19G/NK	34/34	31/34	0	34	Cholangitis (5) Perforation (3) Bile leakage (2) Bleeding (1)
Gupta 2013 [28]	146	19G/NK	132/146	80/132	52	80	Bleeding (18) Bile leakage(14) Perforation (11) Cholangitis (7)
EUS-guided rendezvous							
Will et al 2007 [31]	1	19G FN	–	–	–	–	–
Maranki et al 2009 [19]	32	19G, 22G	–	0	10	10	0
Shah 2012 [24]	50	19G, 22G	37/50	37/50	10	10	Pancreatitis (1) Bile leak (1) Perforation (1)
Kahaleh 2013 [36]	13	19G	13/13	13/13	0	13	Pancreatitis(1) Cholecystitis (1)

HGE hepaticogastrostomy; *CD* choledochoduodenostomy; *NK* needle knife; *FT* fistulotome; *FN* fine needle; *SEMS* self-expanding metal stent; *NBD* nasobiliary drainage; *CT* cystotome

[a] Unspecified

δ Data are presented as an intrahepatic vs extrahepatic approach (these included CD, HGE, and rendezvous technique). We cannot obtain the raw data

Δ Data presented as direct EUS intervention (including CD and HE) and rendezvous technique

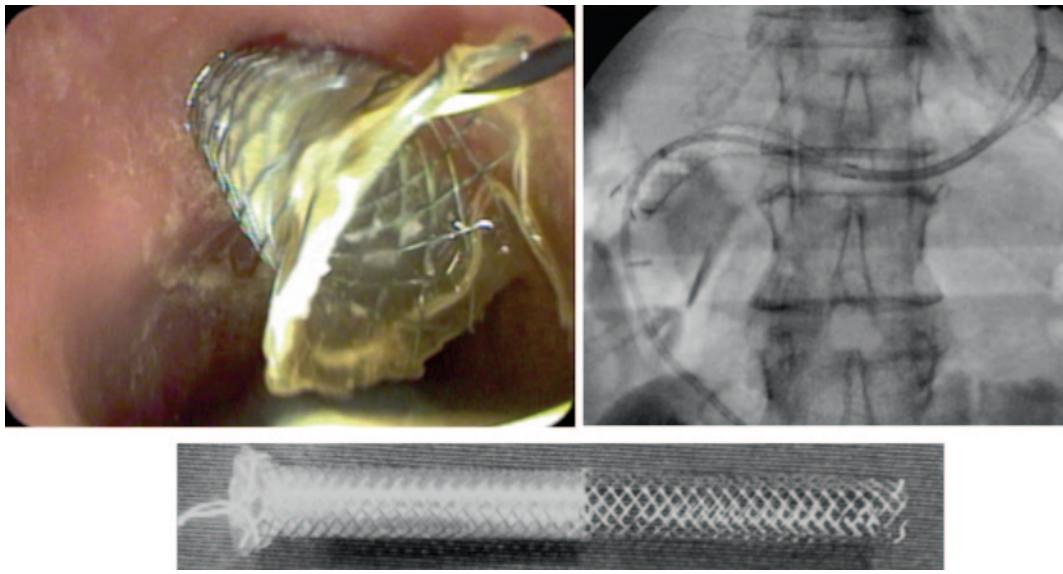

Fig. 34.5 Half-covered metal stent for hepaticogastrostomy

None of the patients with complications, according to the obtained data, needed invasive treatment. Main complications reported were bleeding 21/80 (26.2%), bile leakage 14/80 (17.5%), cholangitis 14/80 (17.5%) and perforation 11/80 (13.7%). Other complications included peritonitis, cholecystitis, pancreatitis, pneumoperitoneum, abdominal pain, and stent migration.

Kahaleh et al. described that the advantages of EUS-guided hepaticogastrostomy over percutaneous transhepatic drainage included puncture of the biliary tree with real-time US while using color Doppler information to limit the possibility of vascular injury, the absence of ascites in the interventional field, and the lack of an external drain. Based on their experience, they also pointed out the extrahepatic approach has a greater risk of complication than the intrahepatic approach [36] although this was not confirmed in our recent multicenter retrospective study. Itoi et al. reported the limitations of this technique as follows: (i) nonapposed gastric wall and the left liver lobe causing displacement between the puncture site of the gastric wall and intrahepatic bile duct, resulting in the possibility of a failed procedure; (ii) risk of mediastinitis following a transesophageal approach; (iii) difficulty with puncturing a cirrhotic liver; (iv) risk of injuring the portal vein; and (v) the use of small-caliber stents or metal stents with a small diameter delivery device) [41].

This review of the literature showed fewer complications with choledochoduodenostomy compared to hepaticogastrostomy with the same success rate. This difference is due to the technique used with less dilatation and more fully covered metallic stents in the duodenal route than the transgastric approach, which limits the risk of perforation and bile leakage. But today, the use of partially covered expandable metal stents (Fig. 34.5) for hepaticogastrostomy could decrease the rate of complications.

What Stent Should Be Used?

From a clinical standpoint, the most relevant technical choice is the type of stent used. It is difficult to draw significant conclusions from the published reports since no formal comparisons have been made among the different kinds of stents. Covered (total or partially) SEMS appears to be a better option for three reasons. First, upon full expansion covered SEMS effectively seal the

puncture/dilation tract, which would in theory prevent bile leakage. Second, their larger diameter provides better long-term patency, which would decrease the need for stent revisions. Finally, if dysfunction by ingrowth or clogging occurs, management is somewhat less challenging than with plastic stents since a new stent (plastic or SEMS) can easily be inserted through the previously placed occluded SEMS. By contrast, exchanging a clogged plastic transmural stent usually requires over-the-wire replacement to maintain transmural access because free-hand removal risks track disruption with subsequent guidewire passage into the peritoneum, which would then require a repeat EUS-guided biliary drainage procedure. [42] Uncovered SEMS could allow bile leakage into the peritoneum and possibly subsequent biloma formation. On the other hand, with covered SEMS, foreshortening, the risk of immediate or delayed migration, and the possibility of occluding secondary bile ducts must be appreciated. [34] Insertion and deployment of SEMS transmurally is more demanding than during ERCP.

The best indication today for EUS-guided biliary drainage is to decompress the left lobe of the liver or to establish biliary drainage when accessing the papilla is impossible either due to malignant intestinal obstruction or previous surgery (e.g., gastrectomy, Whipple, Roux-en-Y gastric bypass). In cases of failed cannulation, PTC may still be recommended with a rendezvous technique until we have results of randomized studies comparing EUS-guided biliary drainage to PTC.

EUS-Guided Pancreatic Drainage

The experience and literature about EUS-guided pancreatic drainage is sparser than EUS-guided biliary drainage. Unlike with biliary drainage, the primary indications for pancreatic drainage are benign etiologies including acute recurrent pancreatitis, chronic abdominal pain, and/or chronic pancreatitis with anastomotic or nonanastomotic stricture. In addition most patients will require more than one procedure to remove the stent placed, and the procedures are long, averaging 148 min. [43] In a large series of 45 patients undergoing EUS-guided pancreatic drainage, overall technical success was 74% with fairly even distribution of retrograde and antegrade placed stents. As expected, post-surgical patients were more likely to undergo antegrade stent placement, and the majority of these stents crossed the papilla or anastomosis. The only factor predictive of failed EUS procedure was attempted ERCP immediately before the EUS. Although main pancreatic duct diameter was not associated with procedure failure in this study, experts believe EUS-guided drainage is usually successful with a dilated main pancreatic duct ($\geq$ 4 mm) [44]. Clinical success was achieved in 83% of patients while the stents were in place with 17% recurrence following stent removal over median 32-month follow-up. Serious complications occurred in 6% and included peripancreatic abscess and pancreatitis. A 3 cm long piece of guidewire coating had been stripped off and retained in the retroperitoneum of one patient without apparent symptoms. Overall complication rate was 19% from 132 patients published with this technique and also included fever, bleeding, and perforation [44].

The technique of EUS-guided pancreatic drainage is analogous to biliary drainage. CO_2 insufflation and prophylactic antibiotics are recommended. A therapeutic linear echoendoscope is used to visualize the main pancreatic duct and a 22G or 25G needle may be inserted first to obtain a pancreatogram. Otherwise, if pancreatic drainage is indicated, a 19G needle is introduced followed by long guidewire placement and retrograde or antegrade stent placement. With antegrade stent placement, transmural access is secured by using a cystotome with cutting current to introduce the sheath (prototype Cysto-Gastro set, EndoFlex, Voerde, Germany) or by dilating with a dilating balloon, dilating cathether, cannula, or rarely wire-guided needle knife catheter where cautery was only used if necessary. Some experts believe the diathermic technique leads to lower rates of pancreatic juice leakage than balloon dilation.

The role of EUS-guided pancreatic drainage remains uncertain and likely is best indicated for post-Whipple anastomotic strictures while pa-

tients with chronic pancreatitis-related strictures may require surgery. Given the relatively high complication rates, these procedures should only be performed in highly experienced therapeutic endoscopy centers.

Conclusion

EUS-guided biliary management is useful following failed ERCP with a high rate of technical success and clinical efficacy. It provides a new way to achieve biliary drainage that may be complementary to the percutaneous approach. The morbidity rate is high with EUS-guided biliary drainage and requires an experienced team. Further technical improvements are mandatory to reduce the number of adverse events. In addition, randomized studies comparing the EUS-guided approach to PTC are needed to define the place of this technique of bile duct drainage. EUS-guided pancreatic drainage is feasible although also suffers from relatively high complication rate. The best indication for this procedure is a benign anastomotic stricture following Whipple surgery. These EUS-guided procedures should be performed in carefully selected patients by experienced therapeutic endoscopists in a multidisciplinary team.

Key Points

- EUS-guided biliary drainage requires specific equipment including a therapeutic linear echoendoscope, 19G needle, long guidewires, dilating accessories, and stents.
- A variety of routes are available to gain biliary access with the choice individualized to the patient and no one approach appearing superior.
- When the papilla is accessible, the rendezvous approach is preferred. If this technically demanding approach is not feasible, options include intrahepatic antegrade stent placement either across the stricture and/or with creation of a hepaticogastrostomy and choledochoduodenostomy.
- Morbidity of the EUS-guided biliary drainage technique remains relatively high and mainly include bile leak, cholangitis, bleeding, and perforaton.
- EUS-guided pancreatic drainage is feasible although arduous and likely most successful in patients with benign anastomotic strictures following Whipple surgery.

Video Caption

Video 34.1 EUS-FNA is performed using a 19G needle advanced into the distal CBD from the duodenal bulb in a long position. After bile is aspirated, contrast is injected to perform a cholangiogram demonstrating a diffusely dilated biliary system with no contrast exiting the papilla. A long 0.035 in. guidewire is advanced into the right hepatic duct. Then dilation of the tract is performed using a 4 mm balloon dilator advanced across the choledochoduodenostomy. Finally a 10 mm × 4 cm fully covered metal stent is deployed across the choledochoduodenostomy with the distal end in the duodenal bulb draining bile. Courtesy, Dr. Christopher Thompson, Brigham and Women's Hospital, Boston, MA

References

1. Giovannini M, Pesenti C, Bories E, Caillol F. Interventional EUS: difficult pancreaticobiliary access. Endoscopy. 2006;38(Suppl 1):S93–5.
2. Kahaleh M. EUS-guided cholangio-drainage and rendezvous techniques. Tech Gastrointest Endosc. 2007;9:39–45.
3. Isayama H, Nakai Y, Kawakubo K, et al. The endoscopic ultrasonography-guided rendezvous technique for biliary cannulation: a technical review. J Hepatobiliary Pancreat Sci. 2013;20:413–20
4. Grimm H, Binmoeller KF, Soehendra N. Endosonography-guided drainage of a pancreatic pseudocyst. Gastrointest Endosc. 1992;38:170–1.
5. Park DH, 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(6):1276–84
6. 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 Oct;33(10):898–900.
7. Burmester E, Niehaus J, Leineweber T, Huetteroth T. EUS-cholangio-drainage of the bile duct: report of 4 cases. Gastrointest Endosc. 2003;57:246–51.

8. Puspok A, Lomoschitz F, Dejaco C, et al. Endoscopic ultrasound guided therapy of benign and malignant biliary obstruction: a case series. Am J Gastroenterol. 2005;100:1743–7.
9. Kahaleh M, Hernandez AJ, Tokar J, Adams RB, Shami VM, Yeaton P. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. Gastrointest Endosc. 2006;64(1):52–9.
10. Yamao K, Bhatia V, Mizuno N, Sawaki A, Ishikawa H, Tajika M, Hoki N, Shimizu Y, Ashida R, Fukami N. EUS-guided choledochoduodenostomy for palliative biliary drainage in patients with malignant biliary obstruction: results of long-term follow-up. Endoscopy. 2008;40(4):340–2. doi:10.1055/s-2007-995485.
11. Ang TL, Teo EK, Fock KM. EUS-guided transduodenal biliary drainage in unresectable pancreatic cancer with obstructive jaundice. JOP. 2007;8(4):438–43.
12. Fujita N, Noda Y, Kobayashi G, et al. Temporary endosonography-guided biliary drainage for transgastrointestinal deployment of a self-expandable metallic stent. J Gastroenterol. 2008;43:637–40.
13. Tarantino I, Barresi L, Repici A, Traina M. EUS-guided biliary drainage: a case series. Endoscopy. 2008 Apr;40(4):336–9. doi: 10.1055/s-2007-995455. Epub 2008 Feb 11.
14. Itoi T, Itokawa F, Sofuni A, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Endoscopic ultrasound-guided choledochoduodenostomy in patients with failed endoscopic retrograde cholangiopancreatography. World J Gastroenterol. 2008;14(39):6078–82.
15. Horaguchi J, Fujita N, Noda Y, et al. Endosonography-guided biliary drainage in cases with difficult transpapillary endoscopic biliary drainage. Dig Endosc. 2009;21:239–44.
16. Hanada K, Iiboshi T, Ishii Y. Endoscopic ultrasound-guided choledochoduodenostomy for palliative biliary drainage in cases with inoperable pancreas head carcinoma. Dig Endosc. 2009;21(Suppl 1):S75–8. doi:10.1111/j.1443–1661.2009.00855.x.
17. Park dH, Koo JE, Oh J, et al. EUS-guided biliary drainage with one-step placement of a fully covered metal stent for malignant biliary obstruction: a prospective feasibility study. Am J Gastroenterol. 2009;104:2168–74.
18. Brauer BC, Chen YK, Fukami N, Shah RJ. Single-operator EUS-guided cholangiopancreatography for difficult pancreaticobiliary access (with video). Gastrointest Endosc. 2009 Sep;70(3):471–9. doi:10.1016/j.gie.2008.12.233 (Epub 2009 Jun 27).
19. Maranki J, Hernandez AJ, Arslan B, et al. Interventional endoscopic ultrasound-guided cholangiography: long-term experience of an emerging alternative to percutaneous transhepatic cholangiography. Endoscopy. 2009;41:532–8.
20. Artifon EL, Takada J, Okawa L, Moura EG, Sakai P. EUS-guided choledochoduodenostomy for biliary drainage in unresectable pancreatic cancer: a case series. JOP. 2010;11(6):597–600.
21. Eum J, Park dH, Ryu CH, et al. EUS-guided biliary drainage with a fully covered metal stent as a novel route for natural orifice transluminal endoscopic biliary interventions: a pilot study (with videos). Gastrointest Endosc. 2010;72:1279–84.
22. Hara K, Yamao K, Niwa Y, et al. Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction. Am J Gastroenterol. 2011;106(7):1239–45.
23. Ramírez-Luna MA, Téllez-Ávila FI, Giovannini M, et al. Endoscopic ultrasound- guided biliodigestive drainage is a good alternative in patients with unresectable cancer. Endoscopy. 2011;43(9):826–30
24. Shah JN, Marson F, Weilert F, et al. Single-operator, single-session EUS-guided anterograde cholangiopancreatography in failed ERCP or inaccessible papilla. GIE. 2012;75:56–64.
25. Kawakubo K, Isayama, Hironari Kato H, et al. Multicenter retrospective study of endoscopic ultrasound-guided biliary drainage for malignant biliary obstruction in Japan. J Hepatobiliary Pancreat Sci. 2013;27:131–8
26. Khashab MA, Kord Valeshabad A, Modayil R, et al. EUS-guided biliary drainage by using a standardized approach for malignant biliary obstruction: rendezvous versus direct transluminal techniques. GIE. 2013;78(5):734–41
27. Dhir V, Artifon ELA, Gupta K, et al. Multicenter study on endoscopic ultrasound-guided expandable biliary metal stent placement: Choice of access route, direction of stent insertion, and drainage route. Dig Endosc. 2013;53:1–6
28. Gupta K, Perez-Miranda M, Kahaleh M, et al. Endosocpic Ultrasound –assisted Bile Duct Access and drainage: Multicenter, Long-Term Analysis of Approach, Outcomes, and Complications of a technique in evolution. J Clin Gastroenterol. 2013;29:121–7.
29. Artifon EL, Chaves DM, Ishioka S, et al. Echoguided hepatico-gastrostomy: a case report. Clinics (Sao Paulo). 2007;62:799–802.
30. Bories E, Pesenti C, Caillol F, Lopes C, Giovannini M. Transgastric endoscopic ultrasonography-guided biliary drainage: results of a pilot study. Endoscopy. 2007;39:287–91.
31. Will U, Thieme A, Fueldner F, et al. Treatment of biliary obstruction in selected patients by endoscopic ultrasonography (EUS)-guided transluminal biliary drainage. Endoscopy. 2007;39:292–5.
32. Chopin-Laly X, Ponchon T, Guibal A, Adham M. Endoscopic biliogastric stenting: a salvage procedure. Surgery. 2009;145:123.
33. 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.
34. Martins FP, Rossini LG, Ferrari AP. Migration of a covered metallic stent following endoscopic ultrasound-guided hepaticogastrostomy: fatal complication. Endoscopy. 2010;42(Suppl 2):E126–7.

35. Artifon EL, Okawa L, Takada J, Gupta K, Moura EG, Sakai P. EUS-guided choledochoantrostomy: an alternative for biliary drainage in unresectable pancreatic cancer with duodenal invasion. Gastrointest Endosc. 2011;73(6):131720
36. Kahaleh M, Artifon EL, Perez-Miranda M, et al. Endoscopic ultrasonography guided biliary drainage: summary of consortium meeting, May 7th, 2011, Chicago. World J Gastroenterol. 2013;19:1372–9.
37. Bapaye Dubale N, Aher A. Comparison of endosonography-guided vs. percutaneous biliary stenting when papilla is inaccessible for ERCP. United European Gastroenterol J. 2013;1:285–93.
38. Khashab MA, Valeshabad AK, Afghani E, Singh VK, Kumbhari V, Messallam A, Saxena P, Zein ME, Lennon AM, Canto MI, Kalloo AK. 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;60:557–565.
39. Gupta K, Perez-Miranda M, Kahaleh M, 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;48:80–7.
40. Dhir V, Itoi T, Khashab MA, Park DH, Teoh AYB, Attam R, Messallam A, Varadarajulu S, Maydeo A. 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 Dec 5. Epub ahead of print.
41. Itoi T, Sofuni A, Itokawa F, et al. Endoscopic ultrasonography-guided biliary drainage.J Hepatobiliary Pancreat Sci. 2010;17:611–6.
42. Fujita N, Sugawara T, Noda Y, et al. Snare-over-the-wire technique for safe exchange of a stent following endosonography-guided biliary drainage. Dig Endosc. 2009;21:48–52.
43. Fuiji L, Topazian MD, Abu Dayyeh BK, et al. EUS-guided pancreatic duct intervention: outcomes of a single tertiary-care referral center experience. Gastrointest Endosc. 2013;78:854–64.
44. Giovannini M. EUS-guided pancreatic duct drainage: ready for prime time? Gastrointest Endosc. 2013;78:865–7.

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