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Meet the editors

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Contents

Preface

With the rapid development of modern medical technology, endoscopic technology has also achieved unprecedented development. Its fields cover examination, treatment, surgery, and even molecular imaging diagnosis. Endoscopy technology brings a minimally invasive diagnosis and treatment experience to patients. Invasive treatment and examination of digestive surgery has changed from large incisions to several Trocar holes, from surgery to endoscopic treatment, and from laparotomy to endoscopy or laparoscopy, which has changed the diagnosis treatment and management of digestive surgery, enhanced the recovery after surgery, and benefited the patients needing to undergo surgical procedures. It is for this reason that we plan to introduce the development of endoscopic and laparoscopic surgery in digestive surgery and enhanced rehabilitation medicine.

With the latest improvements, the different types of endoscopy are classified according to the sites of the body or the techniques of the system, including endoscope, laparoscope, and microscope. In its infancy, an endoscope was mainly used to examine the gastrointestinal trunk and later it was applied in many other systems with a canal or cavity, and even an iatrogenic one. In addition to this, endoscopy also became a treatment approach, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic hemostasis, and so on, therefore not only limited to examinations. Laparoscopes are mostly manipulated by surgeons to finish an operation instead of laparotomies, minimizing the trauma from surgery itself, benefiting the patients suffering from general surgery diseases, and achieving enhanced recovery after surgery (ERAS). All the applications of endoscopy are covered in the chapters of this book.

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Section 1

Introduction: The Advance of Endoscopy

Chapter 1

Introductory Chapter: Endoscopy and ERAS

Qiang Yan

1. The history of endoscopy

I am honored that the editorial department gave me this opportunity and provided a platform for me to write this book *Endoscopy*. I have been majoring in Hepatobiliary and Pancreatic Surgery for more than 20 years. I have witnessed the vigorous development of modern medicine and experienced the rise of minimally invasive treatment of digestive surgery. Invasive treatment and examination of digestive surgery have passed from large incisions more than 20 cm to several 1 cm-length Trocar holes, from surgery to endoscopic treatment, and from laparotomy to endoscopy or laparoscopy, which have changed the idea of the diagnosis treatment and management of digestive surgery, enhanced the recovery after surgery, and benefited the patients needing to undergo surgical procedures. It is for this reason that I plan to introduce the development of endoscopy and laparoscopy in digestive surgery and enhanced rehabilitation medicine.

An endoscope is a tube equipped with a light that can enter the body through the natural orifice of the body or through a small incision made by surgery. The original endoscope was made of hard tubes and was invented more than two centuries ago. Endoscopes are inserted into a canal or cavity to examine and obtain medical images directly, compared to other imaging techniques. With the improvement, the endoscopy varies into different types according to the sites of the body or the techniques of the system. The electronic endoscopy system is the most popular nowadays, which is mainly composed of three main parts: endoscope, video information system center, and television monitor.

Although had the first generational endoscopy gradually improved since the invention, they had still not been widely used. Later, Philipp Bozzini developed the first endoscope with a light conductor, which made the examination of orifice visible in 1806. In the 1950s, endoscopes were made of hoses, so they could easily bend around every corner of the body. In 1965, Harold Hopkins installed a lens on the endoscope to make the field of vision clearer. Today's endoscopes usually have two fiberglass tubes through which light enters the body. Through another tube or camera for observation, some endoscopes even have micro integrated circuit sensors to feed back the observed information to the computer [1].

The use of light source is an important step in the development of endoscopes, making the examinations and surgeries via cystoscopy, hysteroscopy, colonoscopy, and laparoscopy, thoracoscopy, and even nasaloscopy routine procedures since sir Francis Cruise applied an external light source into the system, which was replaced by a small internal bulb decades later.

Hans Christian Jacobaeus has been recognized as the first physician to explore the abdominal and thoracic cavity in his publications of laparoscopy (1912) and thoracoscopy (1910) [2]. Actually, laparoscopy is a kind of endoscopy, which was used first to diagnose the diseases of liver and gallbladder by Heinz Kalk in the

1930s. Followed by the application of gaseous distention of the abdomen with CO_2, gastrointestinal, hepatobiliary, and gynecologic laparoscopy developed [3].

In the early part of last century, laparoscopic technologies have been developing vigorously and many groundbreaking events have taken place, such as performing the first laparoscopic procedure in dogs by Georg Kelling of Dresden, Germany, and performing the first laparoscopic operation in humans by Hans Christian Jacobaeus [4].

In the following decades, many physicians have further refined and popularized laparoscopic procedures. The emergence of television cameras based on computer chips is a groundbreaking event in the field of laparoscopy. This technological innovation simplifies the implementation of complex laparoscopic procedures by providing a magnified view of the surgical field onto the monitor and releasing the surgeon's hands.

In 1944, a gynecologic laparoscopic operation was performed by Raoul Palmer on a patient with artificial pneumoperitoneum in Trendelenburg position, resulting in the abdominal organs moving to the head and enhanced security of the procedure [5].

In the 1960s, the rod lens greatly improved the image quality of the endoscope, and Basil Hirschowitz invented a glass fiber with excellent light guiding properties to create a flexible endoscope. This innovation not only created the first practical medical endoscope, but also led to the evolution of endoscopes and to the era of fiberscopes (endoscopes where both light sources and images are transmitted by optical fibers and curved bodies).

Endoscopes with both inspection and surgical functions did not appear until the 1970s, and were only used for young, physically healthy patients. In the 1980s, laparoscopic tubal ligation and pelvic examination had become essential procedures for obstetricians and gynecologists.

Cuschieri started animal experiments for laparoscopic cholecystectomy in 1986. At the first World Congress of Surgical Endoscopy in 1988, he reported a successful laparoscopic cholecystectomy for experimental animals. It was applied in clinics in February 1989. French surgeon Philipe Mouret, who had carried out a successful laparoscopic cholecystectomy for the first time in humans, succeeded in performing laparoscopic cholecystectomy for the same patient in 1987, but it was not reported.

In 1988, Dubois in Paris also used this in clinical practice based on laparoscopic cholecystectomy in pigs. The results were first published in France and the surgery was screened at the annual meeting of the American Society of Gastroenterologists in April 1989. The video hit the world in one fell swoop [6]. It first shocked the surgical community in the United States, and a surge in laparoscopic cholecystectomy was initiated in the United States, which enabled laparoscopic cholecystectomy to progress from animal experiments and clinical exploration to clinical developments.

After this century, laparoscopy began to be applied in various kinds of surgeries from laparoscopic gastrectomy and colectomy, to laparoscopic liver resection, and even laparoscopic pancreaticoduodenectomy. Indeed, its safety has also been demonstrated by surgeons around the world, and it has shown its safety and perioperative mortality is no less than that of open surgery in high volume centers [7–9].

The first transatlantic surgery ever performed was a laparoscopic gallbladder removal in 2001. Remote surgeries and robotic surgeries have since become more common and are typically laparoscopic procedures. With the invention of the surgical robot arm, the physician can remotely control the robot arm for surgery. The first case of transatlantic surgery was called Lindbergh surgery.

2. ERAS and endoscopy

Endoscopic or laparoscopic procedures alleviate the pain and trauma from surgical treatments or examinations. Thus, enhanced recovery after surgery has been possible due to minimal invasion.

ERAS is the acronym for Enhanced Recovery After Surgery. The name was established by a group of surgeons from Northern Europe who formed a research group with the aim to explore the ultimate care pathway for patients undergoing colonic resections.

Henrik Kehlet had pioneered this work with his groundbreaking work on fast track surgery [10], showing that most patients had recovered enough to be discharged 2 days after open sigmoidectomy [11]. This was at a time when the length of postoperative stay for these operations was 10 days or more in most countries. These reports were met with skepticism but work within the group showed that this was possible, with the use of multimodal approach to recovery [12].

During the following years, the initial group published several reports showing that best practice as proposed by the scientific literature was not in use. In fact, care was very different in different countries [13]. Later work confirmed marked differences in outcomes between countries in Europe [14].

Since practice differed widely among the involved centers, it was decided to promote practice changes in all participating units based on guidelines produced by the study group. This proved to be more cumbersome than initially thought and was often done in steps with re-launches of protocol. However, as perioperative management improved, it became evident that the addition of several care management items was of importance rather than isolated protocol elements. Which elements of the enhanced recovery protocol were the most important depended on the starting point for each participating unit.

As these management measures were implemented, the group decided to record and assess the changes during the time when centers were changing their perioperative management practice. This proved to be very useful. It was very common to find that complete data collection of the process revealed in fact problems with unexpected areas of the protocol [15]. Of note, it was observed that the more items the protocol used in perioperative care, the better the outcomes [16]. This was initially shown in a single center and later in a multinational multicentric study across Europe and New Zealand as well [17]. In a larger trial with >2300 consecutive colorectal patients, all complications significantly decreased with better compliance, including major complications. Although increasing evidence suggested clear short-term benefits of the ERAS protocol [18], a follow-up in >900 colorectal cancer patients demonstrated a significant higher 5-year survival associated with higher compliance with the ERAS protocol. This may also be associated with the fact that patients with higher compliance to the protocol also had fewer complications, a factor shown to be strongly associated with poorer long-term outcomes [19].

The group grew over time with colleagues joining from several other countries. The Dutch group piloted the implementation of the first guidelines developed and reported dramatic improvements in recovery time [20]. Finding that the guidelines could be implemented in a structured way with prompt improvement in results, it was decided to make an effort to help spread the ERAS concepts more widely alongside further development of research. This formed the basis for the ERAS® Society that was created officially and registered in Sweden in 2010 (www.erassociety.org). This is an international nonprofit medical academic society with members from different professions involved in surgical care.

Although the group focused primarily on colorectal surgery, soon the principles were adapted for other major operations such as Hepato-Pancreatico-Biliary, upper gastrointestinal, urology, and gynecology, and today ERAS covers surgical specialties broadly. Since inception, a range of guidelines have been published and updated, authored by experts from around the world. The ERAS Society continues to develop guidelines addressing additional surgical specialties. The Society has published a manual on ERAS, in addition to running an annual international congress since 2012.

The ERAS implementation program is a structured systematic implementation program successfully employed internationally in >25 countries. In this program, hospital teams of surgeons, anesthetists, nurses, and allied health professionals come together in workshops over a period of 8–10 months and are coached while implementing ERAS in their own unit. The current ERAS Society implementation program was initiated in Sweden, then disseminated in the Netherlands, United Kingdom, and Switzerland and later to Canada, Australasia, and the United States. Further units were trained by Swedish and Swiss implementation teams in France, Spain, and Latin America. The work done by the Alberta Health Service in Canada is of particular note. The entire state is implementing ERAS protocols and clinical researchers have been very active in developing ERAS protocols for a range of surgical disciplines. More recently, in October 2016, an ERAS Society sister organization was started in the United States, ERAS (www.erasusa.org), to spread the mission of ERAS in the United States.

The ERAS implementation program introduces the use of the ERAS Interactive Audit System (EIAS) created and developed by the ERAS Society. This audit system provides real-time quality control, in addition to being a very powerful research tool. Data in the ERAS database are updated hourly and become available in the EIAS. This audit system helps teams to continuously keep track of outcomes and processes as well as benchmarking with other hospitals. This system also serves as a source and a platform for research for individual units as well as for the network involved with the ERAS Society.

Several reports from single centers have shown major savings for implementing ERAS into daily care. A report from Alberta, describing cost savings for ERAS in colorectal surgery statewide, showed return of investments of at least 240% [21]. Other publications have shown major cost saving in pancreas and in liver surgery [22, 23].

ERAS is a new type of multidisciplinary teamwork with readiness to make changes as better care is developed. For this reason, ERAS is not just a single, rigid protocol as protocols continuously change and improve as knowledge evolves. The ambition of the ERAS Society is to disseminate evidence-based principles for perioperative care and to support the development of new knowledge in perioperative medicine and surgical pathophysiology.

Physicians have been trying and experiencing ERAS appliance in Hepatopancreatobiliary (HPB) Surgery for more than 10 years. Many principles of Enhanced Recovery After Surgery management have been extracted from the ones in colorectal surgery. As a result, these principles may not be easily applied into HPB surgery. Consequently, the operations may be more complex and may require a longer postoperative stay. For example, there are differences in preoperative infusion. In the liver surgery, it is preferred to reduce the blood loss in the operation to the greatest extent via low central venous pressure, a relative hypovolemia and avoidance of excessive preoperative infusion.

In colorectal surgery, minimally invasive surgery is often used as part of ERP, although its positive effects have yet to be confirmed [24]. Laparoscopic hepatectomy is under study and is currently a hot topic of many reviews [25, 26]. It has been reported that patients with benign disease were hospitalized for 5 days after major

resection [27]. Laparoscopic minimally invasive surgery eliminates large upper abdominal incisions. Besides, anesthesia and analgesia in the perioperative surgical incision area, it shortens the postoperative hospital stay, and guarantees successful ERAS. In fact, laparoscopic resection has been challenged by open surgery during the initial stage of ERAS [28], and one of the RCTs for colon cancer surgery showed no difference in mortality, morbidity, readmission rate, or length of hospital stay [29].

Laparoscopic hepatobiliary and pancreatic surgery is still a concern due to its 8–15% open conversion rate secondary to major bleeding and 2% positive margin rate. There is also concern that pneumoperitoneum increases the risk of tumor spread and extra incisions required to remove large samples [30].

Although laparoscopic hepatectomy is widely used in most HPB centers, especially in atypical or wedge resection, laparoscopic techniques are not applied at the same speed in pancreatectomy. In particular, the application of laparoscopic surgery in complex operations such as pancreaticoduodenectomy, even in the leading institutions of robotic surgery, has not shown an improvement in length of hospitalization or morbidity, which needs further data to demonstrate [31, 32].

Among the indicators used to evaluate the effectiveness of ERAS, the length of hospital stay was considered to be more important. However, it may not best reflect the recovery of body function after surgery, and the incidence of complications may be a better quantitative indicator of safety. Therefore, we recommend the implementation of standardized multimodal approaches in HPB surgery to increase awareness of the goals of improving safety and clinical outcomes, which is of greater importance. Laparoscopic pancreaticoduodenectomy has been routinely carried out in our center. According to our own experience, gastrointestinal function of patients undergone LPD recovered quickly after surgery and intra-abdominal infection rate was reduced.

The illuminant of endoscope lights the cavity or tract of human body or organs, changes the managements of kinds of diseases, and benefits patients with minimally invasive approaches. Finally, I hope to introduce the appliance of endoscopic and laparoscopic procedures in digestive system via *endoscopy* and make the examinations and treatments more minimally invasive and effective [33–36].

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Section 2

Molecular Endoscopy

Chapter 2

Multimodal Optical Imaging by Microendoscope

Lin Huang and Zhen Qiu

Abstract

In the past decades, optical imaging field has been developing rapidly. Noninvasive imaging enabled by microendoscopes has become a promising tool for early cancer detection and imaging-guided surgery. In this chapter, we will mainly introduce most advances in the miniaturized microendoscope development, including photoacoustic, confocal fluorescence, multiphoton fluorescence, second-harmonic generation (SHG) label-free imaging, wide-field fluorescence, surface-enhanced Raman scattering (SERS) nanoparticle-based Raman spectroscopy. Enabled by the frontier micromachining techniques, micro-opto-electromechanical system (MOEMS)-based novel microendoscopes with various imaging modalities have been prototyped and further translated into clinics. The working principle of representative microendoscopes and optical imaging modalities will be introduced in detail.

Keywords: optical imaging, microendoscope, micromachining, micro-opto-electromechanical systems (MOEMS), confocal, multiphoton, wide-field, photoacoustic, Raman, surface-enhanced Raman scattering (SERS)

1. Introduction

Optical imaging is a key part of molecular imaging which allows the in vivo characterization and measurement of biological process at the cellular and molecular level [1–3]. It uses the interaction between light and tissue to probe tissue morphology and functions. Compared to other molecular imaging techniques, such as magnetic resonance imaging (MRI) [4], computed tomography (CT) [5], ultrasound (US) [6], single-photon emission computed tomography (SPECT) [7], and positron-emission tomography (PET) [8], optical imaging builds an interdisciplinary approach to noninvasively probe disease-specific morphology and functions with high resolution. Biochemically specific contrast from light absorption, scattering, and fluorescence are widely used in optical imaging approaches, providing precise information from the tissue morphology, anatomy, and physiology. Optical imaging has been applied in a variety of biological research and is very useful in the early-stage diagnosis of diseases and monitoring the treatment outcomes [9, 10].

Optical imaging has been undergoing explosive growth over the past few decades since it is not limited to specific image-capture methods but includes various modalities, such as confocal fluorescence [11], wide-field fluorescence [12], multiphoton fluorescence and SHG imaging [13–15], photoacoustic tomography (PAT) [16], and SERS nanoparticle-based Raman spectroscopy [17–19] which are the major techniques optimized for different target visualization. The summary and comparisons are listed in **Table 1**. Wide-field, confocal, SERS-based Raman

	Contrast mechanism	Contrast agent	Wavelength	FOV	Resolution
Confocal microendoscope [20]	Reflectance and fluorescence	Fluorescein and acriflavine	488 nm	500 × 500 μm	Lateral: 0.7 mm Axial: 7 mm
Wide-field fluorescence microendoscope [21]	Fluorescence	MMPSense 645	424, 480, and 642 nm	70–100 degrees (air)	12 μm
Multiphoton fluorescence and SHG microendoscope [22]	Fluorescence and SHG	Label-free	750 nm	120 × 120 μm	Lateral: 833 nm Axial: 6.11 μm
Photoacoustic microendoscope [23]	Absorption	Label-free	584 nm	7 × 7 mm	Lateral: 80 μm Axial: 55 μm
SERS based Raman microendoscope [24]	Raman scattering	SERS nanoparticles	785 nm	5 cm in 360 degree	N/A

Table 1.
A description and summary of various optical imaging modalities for in vivo endomicroscopy.

imaging needs staining by applying contrast agent. Multiphoton and photoacoustic techniques, on the contrary, are capable of label-free imaging. Confocal imaging and multiphoton imaging enable submicron (<1 μm) resolution and field of view (FOV) of 500 × 500 μm, while photoacoustic imaging has ~80 μm resolution and FOV of 7 × 7 mm. Generally, there is a trade-off between FOV and resolution in optical imaging methods. To sum up, optical imaging techniques are noninvasive, offer a very high resolution at the cellular level, and provide contrast with biochemical specificity from light absorption, scattering, and fluorescence, with conventional microscopy techniques. However, the list of biological processes that can be investigated by these techniques is limited due to the large benchtop microscopes.

To fully translate the powerful optical imaging techniques into the in vivo clinical usage, miniaturization of the microscopes is essential. Enabled by the frontier micromachining techniques, micro-opto-electromechanical system (MOEMS)-based novel microendoscopes with various imaging modalities have been prototyped and further translated into clinics [25]. Consequently, multimodal imaging enabled by microendoscopes has become a promising tool for clinical applications in vivo, such as early cancer detection and imaging-guided surgery [26]. The amount of microendoscopes with different optical imaging techniques can be puzzling to anyone new to the field. In this chapter, the working principle of representative microendoscopes and optical imaging modalities will be introduced in detail.

2. Confocal imaging

Confocal imaging allows high-contrast imaging of a small spot within an optically transparent or translucent tissue by blocking most of the out-of-focus light through a pinhole to a detector [11]. The illumination point source and the detection pinhole are in optically conjugate focal planes and thus named as "confocal." Compared to conventional optical microscopy, it provides better spatial resolution, controllable depth of field, and better image quality; and it is capable to collect optical sections of thick specimens. The contrasts provided by confocal imaging are generally reflectance [27] or fluorescence [28]. Promoted by the advances in fluorescence labeling, confocal microscopy has the capability of selectively imaging specific proteins at distinct cellular location [29]. However, the large microscope platform limits the application of confocal imaging within the laboratory.

Recently, a novel confocal microendoscope based on a single-mode fiber (SMF) acting as both the illumination point source and the detection pinhole was proposed by Kiesslich et al. [20]. Their laser colonoscope was integrated in the distal tip of a conventional videoendoscope, enabling endomicroscopically guided biopsies, shown in **Figure 1** [20]. The distal tip contained an air and water-jet nozzle, two light guides, an auxiliary water-jet channel (used for topical application of the contrast agent), and a 2.8-mm working channel. The diameters of the distal tip and the insertion tube were 13.4 and 12.8 mm, respectively. During laser endoscopy, a single-line laser delivered an excitation wavelength of 488 nm, and the maximum laser power output was ≤1 mW at the surface of the tissue. Confocal image data were collected at a scan rate of 0.8 frames per second (1024 by 512 pixels) or 1.6 frames per second (1024 by 1024 pixels). The optical slice thickness was 7 mm with a lateral resolution of 0.7 mm. The field of view was 500 by 500 mm. The range of the Z axis was 0–250 mm below the surface layer.

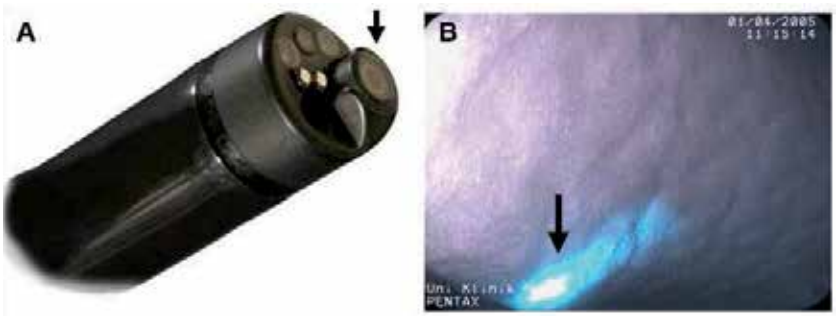

Figure 1.
(A) Confocal laser colonoscope. (B) The blue laser light is clearly visible in the endoscopic view. Used with permission.

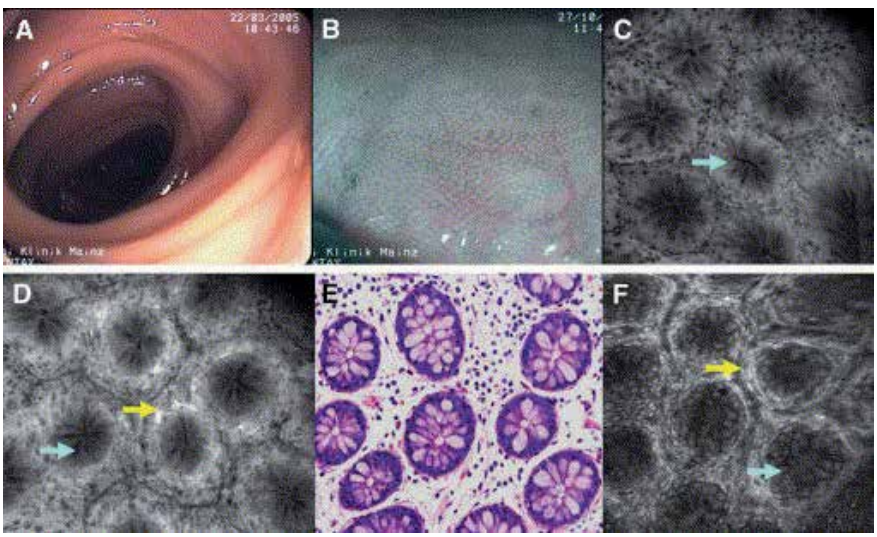

Figure 2.
Upper row: optical possibilities of confocal endomicroscopy. (A) Normal endoscopic view. (B) High-resolution or magnifying endoscopy image. (C) Confocal endomicroscopy image. Lower row: normal crypt architecture. (D) Confocal endomicroscopy with fluorescein intravenously given. (E) Conventional histology in horizontal sectioning of normal crypt architecture. (F) Confocal endomicroscopy after topical application of acriflavine. Used with permission.

To achieve high-resolution confocal imaging, exogenous fluorescence agents were applied. In human studies, fluorescein (10%; colon, esophagus, stomach) and topically applied acriflavine (0.2%; stomach, colon) were used most often. By using these exogenous fluorescence techniques, confocal images were acquired simultaneously with endoscopic images, making it possible to identify typical histological structures in the human gastrointestinal tract, shown in **Figure 2** [20]. This confocal microendoscope was further applied to detect cellular and vascular changes and distinguish different types of epithelial cell [30].

3. Wide-field fluorescence imaging

Wide-field fluorescence imaging allows rapid visualization of large surface areas in hollow organs, leading to disease localization and optical biopsy guidance [12]. With the advances in miniaturization of video charge-coupled device (CCD) chip, wide-field fluorescence imaging by microendoscope is involving rapidly [31]. By scanning a SMF in a spiral pattern through a tubular piezoelectric actuator, a scanning fiber endoscopy (SFE) was proposed to create an image with a large field of view (FOV) and high resolution [21, 32]. The SFE consisted of an ultrathin, highly flexible catheter that scans blue, green, and red laser beams (wavelengths are 424, 488, and 642 nm) in a spiral pattern on the tissue surface (**Figure 3A** and **B**) and collected reflectance and fluorescence through a ring of optical fibers (**Figure 3C–E**) [21]. The distal tip had an outer diameter of 3.17 mm and had a 11.5 cm rigid end. By combining reflectance

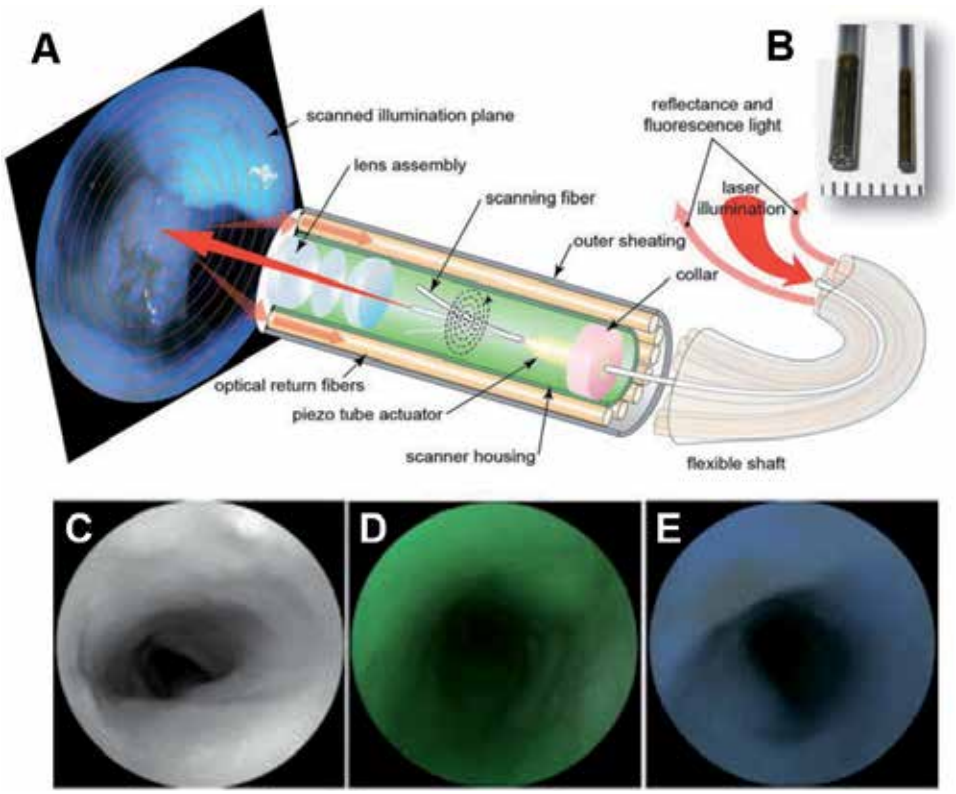

Figure 3.
The schematic of SFE (A) and a photo of the distal end (B). (C) White light endoscopic system image under reflectance mode. (D) Reflectance and laser-induced green fluorescence. (E) Reflectance and laser-induced blue fluorescence. Used with permission.

and laser-induced fluorescence of intrinsic fluorescent constituents in tissue, the SFE enabled video rate (30 frames/s) imaging to overcome motion artifacts in vivo.

This technique was initially proposed to detect fluorescence to visualize overexpressed molecular targets [33]. Recently, it was demonstrated as a multimodal laser-based angioscopy which is potentially a powerful platform for research, diagnosis, prognosis, and image-guided local therapy in atherosclerosis and cardiovascular disease [21]. The small size of the SFE allowed for collecting high-resolution images from the esophagus, stomach, and colon in the mouse models to perform in-depth imaging for study of molecular mechanisms of disease [34, 35]. The compact probe design based on spiral scanning of fiber instrument enabled a miniature package compatible with standard medical endoscopes.

4. Multiphoton fluorescence and SHG

Multiphoton fluorescence and second-harmonic generation (SHG) are nonlinear imaging techniques for noninvasive, high-resolution, real-time diagnostics of tissues at subcellular resolution. They are based on exciting and detecting nonlinear optical signals from biological tissues [13–15]. Femtosecond laser pulses are used to excite nonlinear signals such as two-photon-excited fluorescence (TPEF) and SHG from tissue [2]. Consequently, depth-resolved imaging is enabled because the excitation of nonlinear signals happens only within the focal volume of the laser beam. It is a functional imaging technique in which the contrasts from nicotinamide adenine dinucleotide hydrogen (NADH), flavin adenine dinucleotide (FAD), elastin, and collagen are biochemically specific. Therefore, they allow label-free imaging without any exogenous contrast agent. Currently, multiphoton fluorescence and SHG microscopy have mainly been carried out on a microscope stage on the laboratory bench [13–15]. For in vivo imaging and clinical applications, a fiber-optic-based microendoscope is needed where light can be delivered through a flexible fiber and images can be acquired using a miniature probe [36–38].

The Chris Xu group at Cornell University used piezoelectric actuators and a miniaturized high NA gradient-index (GRIN) lens to form a compact and flexible two-photon fluorescence (TPF)/SHG endoscope, which had an outside diameter of 3 mm and a rigid length of 4 cm, shown in **Figure 4** [37]. They achieved imaging at approximately a speed of 4.1 frames/s. GRIN lens has a small diameter and cylindrical geometry. However, it suffers from severe chromatic aberration and causes a considerable focal shift between the excitation wavelength (NIR) and the TPEF and SHG signal wavelength (visible).

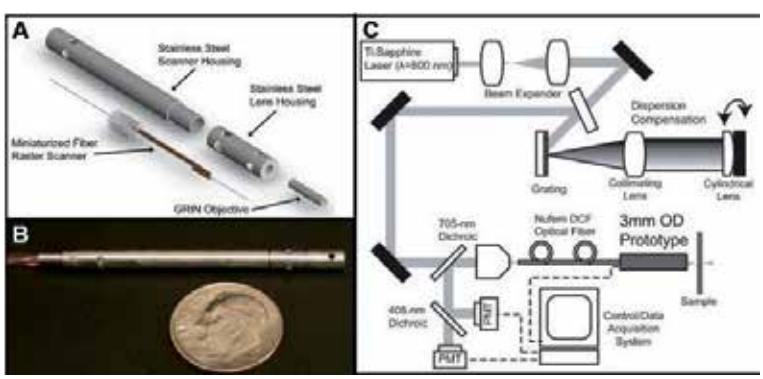

Figure 4.
System components and setup. (A) Mechanical assembly of the microendoscope. (B) Photograph of the prototype. (C) Imaging setup. Used with permission.

Ex vivo images of mouse tissue was acquired as shown in **Figure 5** [37]. In tissue, SHG contrast mainly comes from collagen, and thus it is especially useful for imaging cartilage, bone, tendon, the skin, and cornea where collagen is the most abundant extracellular matrix protein in the tissues [39]. TPEF signal derives from intrinsic autofluorescence sources, such as elastin, NADH, and flavins. The intrinsic TPEF signal can be observed from cells, collagen, and elastin fibers.

The rigid probe based on a GRIN lens is more desirable in laparoscopic applications or in interfacing with a biopsy probe. Currently, the Xingde Li group developed a handheld rigid probe with multiphoton fluorescence and SHG techniques for optical biopsy (**Figure 6A–C**) [22]. In the rigid probe, two functional parts are a handheld compact scanning box (3D) and a compound GRIN objective which was 15 cm long with an outer diameter of 1.75 mm. The probe could fit within a 14-gauge biopsy needle. The scanning box included a MEMS mirror for

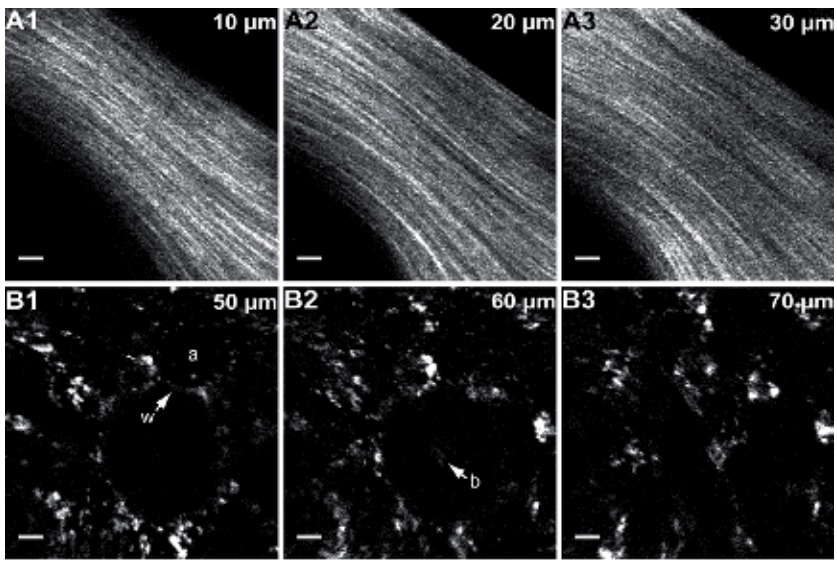

Figure 5.
TPEF/SHG images of ex vivo mouse tissue. (A) Unaveraged SHG images of mouse tail tendon at 10, 20, and 30 μm from the surface. (B) Unaveraged intrinsic fluorescence images of mouse lung at 50, 60, and 70 μm from the tissue surface. Used with permission.

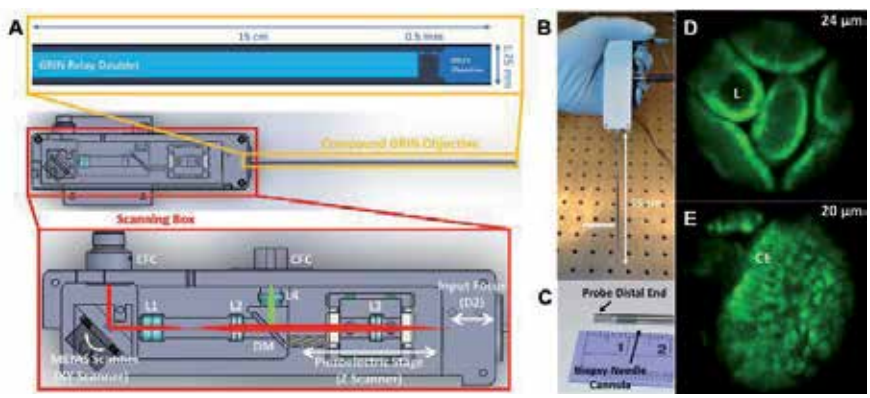

Figure 6.
Handheld rigid probe and TPEF images. (A) Handheld probe design schematic. (B) Photo of the handheld rigid probe. (C) Photo of the rigid probe inside a 14-gauge biopsy needle. In vivo TPEF images of the mouse kidney cortex (D) and mouse small intestinal mucosa (E). Scale bar, 20 μm. Used with permission.

two-dimensional (2D) raster beam scanning up to 10 frames/s and a piezoelectric stage for axial scanning. A SMF was used for delivery of femtosecond pulses, and a multimode fiber (MMF) with a large core diameter was used at the proximal end of the rigid probe to deliver the signal to a detector. In vivo images of the mouse kidney cortex and intestinal mucosa were acquired as shown in **Figure 6D** and **E**, with an imaging depth which was up to 24 μm [22].

5. Photoacoustic tomography

The drawback of pure optical imaging (both linear and nonlinear) in biological tissue is that the strong optical scattering causes shallow imaging depth (~1–2 mm). Photoacoustic tomography (PAT) is a relatively new technique that overcomes the limitations of existing pure optical imaging by detecting optical absorption contrast via the photoacoustic (PA) effect [16]. In PAT, a laser excites photoacoustic waves generated by rapid thermoelastic expansion through optical absorption of short laser pulse (PA effect), and ultrasound transducers detect the photoacoustic waves [40]. The major advantage of PAT is that it can image biological tissues in vivo with high spatial resolution for up to a few centimeters of penetration depth. Additionally, PAT allows label-free imaging with endogenous contrast. Thus, the PAT technique has been evolving rapidly with applications in various biological processes over the past decade.

A PAT microendoscope (**Figure 7A–D**) with simultaneous photoacoustic and ultrasonic imaging was implemented by the Lihong Wang group [41]. A rotating mirror acting as a scanner reflected the ultrasonic waves and laser pulses, and it was statically mounted with the associated illumination and ultrasonic pulse-generation detection units. The reflected ultrasonic and photoacoustic waves were detected and converted into electric signals via the ultrasonic transducer to a computer. By inserting the side-scanning 3.8-mm-diameter probe prototype into the esophagus, surrounding organs, such as the lung and trachea, were observed in both the photoacoustic and ultrasonic images (**Figure 7F–K**) [41]. However, only photoacoustic images showed their adjacent vasculatures. These experimental results demonstrated the deep imaging ability of the dual-mode microendoscope and the

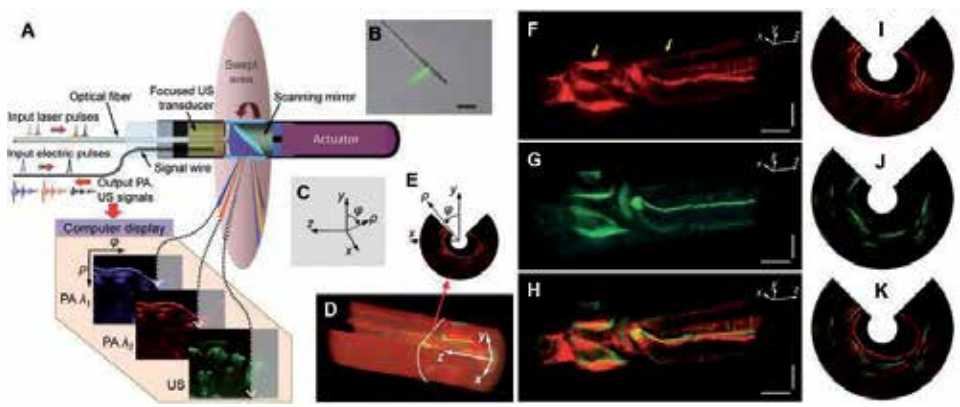

Figure 7.
Illustration of simultaneous, multiwavelength PA and ultrasonic endoscopy. (A) The endoscope design. (B) A photo shows the side-scanning 3.8-mm-diameter probe prototype. Scale bar, 2 cm. (C) Definition of Cartesian and cylindrical coordinate systems. (D) A volumetric image. (E) A representative cross section of d along the x-y plane. (F) Three-dimensionally rendered PA structural image. (G) Co-registered US structural image for the same volume of F. (H) An overlaid image of F and G. The horizontal and vertical scale bars are 2 cm and 5 mm, respectively. (I) A representative PA x-y cross-sectional image (18 mm diameter) near the lung. (J) Corresponding US cross-sectional image of I. (K) A combined image of I and J. Used with permission.

complementary contrast production. To further explore this microendoscope's potential, in vivo PA imaging of two rabbit esophagi was conducted, where high-resolution, three-dimensional microvasculature distribution in the esophagi walls and neighboring mediastinal regions was imaged [23].

6. SERS nanoparticle-based Raman spectroscopy

Surface-enhanced Raman scattering (SERS) is a plasmonic effect resulting enhanced Raman signals from molecules which have been attached to nanometer-sized metallic structures [17–19]. SERS nanoparticle-based Raman spectroscopy is a spectrally molecular imaging technique allowing for ultrahigh sensitivity and the unique ability to multiplex readouts from a variety of molecular targets using a single wavelength of excitation [42]. Based on SERS nanoparticles (~120 nm in diameter) in small animals, a Raman imaging instrument that enabled rapid, high-spatial resolution, spectroscopic imaging over a wide field of view (>6 cm^2) was proposed [43, 44]. In the Raman imaging system, the gold-based nanoparticles (S420, S421, S440, and S470 as shown in **Figure 8**) can dramatically increase the Raman scattered light emitted by small molecules adsorbed onto the surface [45, 46]. The advantage of multiplexing is that it simultaneously detects multiple biomarkers if each type of nanoparticles binds to a different protein target. Consequently, verity types of conjugated SERS nanoparticles with the tumor-targeting capabilities in preclinical animal models have been investigated [47–50].

To translate of this imaging approach to the clinic, a small, flexible, fiber-optic-based Raman imaging microendoscope, designed for GI tract (such as within the colon or esophagus) imaging, were proposed (**Figure 9A** and **D**) [24]. It utilized circumferential scanning to map of the signal from SERS nanoparticles located on a luminal surface (**Figure 9B** and **C**). The scan mirror was located between the collimating lens and the tissue and is angled at 50° to provide a radial projection of the illumination beam. As it rotated about its axis, the illumination beam swept around the device resulting in a 360° circumferential scan of the tissue. In vivo human study was conducted by using the imaging system packaged in the endoscopy suite, and the three-dimensional topography of the colon could is recreated (**Figure 9E–H**). These results provided an anatomic reference image on which the molecular data can be mapped. One advantage of SERS nanoparticle-based Raman microendoscope is that its noncontact feature allows the user to scan large, topologically complex surfaces much faster than devices requiring tissue contact [24]. Additionally, the enhanced Raman effect can occur within the entire plasmon

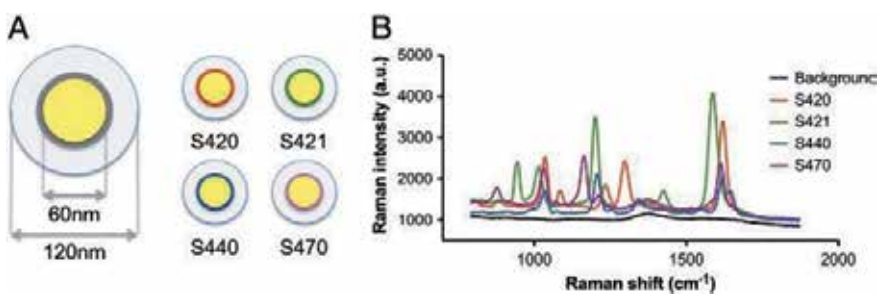

Figure 8.
Schematic representation of SERS nanoparticles and their Raman spectra. (A) Gold nanoparticles are covered with a layer of Raman active material and then a silica coating. (B) The spectral fingerprint of different Raman active materials with laser excitation at 785 nm. The background spectrum is acquired in the same experimental arrangement without nanoparticles. Used with permission.

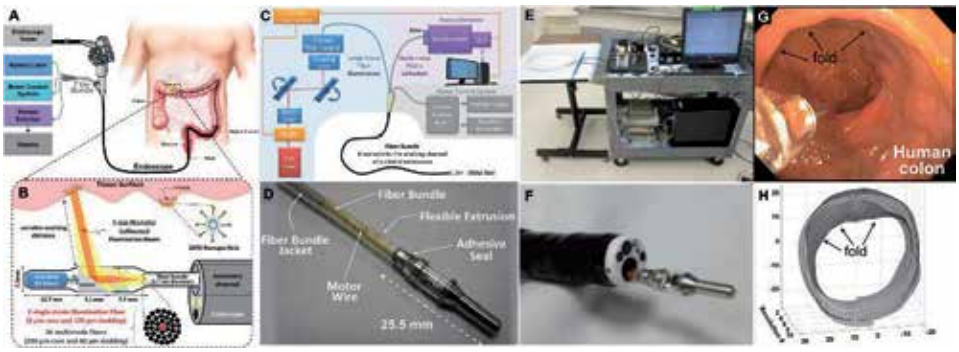

Figure 9.
Schematic of Raman imaging system and clinical application. (A) The device can be inserted through the colon. (B) Expanded schematic of the distal end. (C) System overview. (D) Close-up photograph of the distal end. (E) The imaging system in the endoscopy suite. (F) The device inserted and exiting from the distal end of a clinical endoscope. (G) The device being used in first human clinical study (C). (H) A three-dimensional reconstruction of the topography of the colon (D). Used with permission.

resonance spectrum of the nanoparticles, while fluorescein only happens at comparably narrow absorption peaks which vary with each fluorophore. Moreover, SERS nanoparticles do not suffer from photo bleaching, which is a limitation of fluorophore-based endoscopy.

7. Conclusions

Today, multimodal optical imaging by microendoscope has been evolving rapidly, leading to a diversity of exciting biological discoveries and clinical applications. It is an invaluable diagnostic approach allowing minimally invasive, real-time, subcellular access to tissues deep within the body, such as the oropharynx, esophagus, lung, stomach, colon, and rectum. Advanced endomicroscopes have been enabled by the advances in light sources, micro-optics, fiber optics, miniature scanner. Additionally, innovative target-specific nanoparticles could probe early disease detection before morphology changes occur. The miniature microendoscope system potentially allows for imaging beyond gross anatomical structures to appreciate biological function. In the future, directions toward more informative ways will include finer spatial resolution, shaper contrast, higher imaging speed, deeper penetration, and greater detection sensitivity. Further efforts lie in preclinical trial and clinical trail through the cross-disciplinary collaborations.

Conflict of interest

The authors have no financial interests or potential conflict of interest to disclose concerning this work.

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Section 3

Endoscopy for GI Diseases

Chapter 3

Laparoscopic Pancreatoduodenectomy

Michele Mazzola, Lorenzo Morini, Marianna Maspero, Camillo Leonardo Bertoglio, Sara Andreani, Carmelo Magistro, Paolo De Martini and Giovanni Ferrari

Abstract

In recent years, total laparoscopic pancreaticoduodenectomy (TLPD) has been introduced as a feasible alternative to open pancreaticoduodenectomy (OPD) when performed by experienced surgeons in laparoscopic and pancreatic surgery. Its application has been gradually increased, but its safety, reproducibility, and oncological outcomes are still debated due to its technical complexity and prolonged operating time. We performed a systematic analysis of the more relevant aspects of TLPD. In this chapter, we report a general overview of the different experiences present in the literature regarding indications, surgical techniques, postoperative outcomes, benefits and limitations of this approach, oncological results, learning curve, and costs. There is no standardized surgical technique for TLPD. Different techniques exist for both the demolitive stage and the reconstructive stage. We summarized the different aspects of the surgical technique based on the various experiences reported by different authors. Compared to OPD, TLPD provides the advantages of laparoscopy, i.e., reduced blood loss, decreased postoperative pain, and shorter length of hospital stay, without increasing the rate of postoperative complications or compromising oncological outcomes. An appropriate patient selection is crucial at the beginning of the learning curve. With increased experience, more challenging cases may also be approached with this technique, including those requiring major vascular resections or multi-visceral resections.

Keywords: mini-invasive pancreaticoduodenectomy, laparoscopic pancreaticoduodenectomy, advanced laparoscopic surgery, pancreatic surgery

1. Introduction

Minimally invasive techniques in pancreatic surgery were initially used only for diagnostic and stadiative purposes, palliative procedures, or the drainage of cysts and the enucleation of small solid lesions [1, 2]. In the last 10 years, with advances in technology and surgical techniques, there has been a growing application of minimally invasive surgery for the treatment of benign and malignant pancreatic neoplasms [3], and complex operations such as distal pancreatectomy (DP) and pancreaticoduodenectomy (PD) have started to be performed [2]. Laparoscopic distal pancreatectomy (LDP) does not require the execution of anastomosis, resulting in quite easy performance and achieving worldwide acceptance. On the other hand, the laparoscopic pancreaticoduodenectomy (LPD) has obtained a marginal acceptance until now, raising doubts about its safety and reproducibility, due to its technical complexity and prolonged operating time [3].

Although the first LPD was performed by Gagner and Pomp more than 20 years ago for the treatment of a chronic pancreatitis involving the pancreatic head [4], the procedure had a slow diffusion [5], especially in comparison to the other applications of minimally invasive surgery in the field of oncological treatment [3].

This slow diffusion can be explained by three main reasons.

The first one is the technical complexity of LPD, especially due to the retroperitoneal position of the pancreas and the proximity to the duodenum and surrounding vascular structures; the fashioning of the laparoscopic anastomoses; and the laparoscopic dissection of the uncinate process from the large vessels [6–8].

The second one is the high complication rate of PD, heavily affecting postoperative recovery; this represents a limit to the potential advantages of mini-invasiveness [9].

Finally, there is a lack of international consensus about the benefits regarding the feasibility and oncological efficacy of LPD [10].

However, in the last decade, the growing number of publications about laparoscopic pancreatic surgery seems to assess its feasibility and safety [3], especially if performed in highly experienced centers [11].

2. Indications

In all the cases where PD is indicated, laparoscopic approach can be theoretically applied:

- pancreatic adenocarcinoma
- symptomatic chronic pancreatitis
- neuroendocrine pancreatic tumors: functioning tumors, tumors with resectable metastases, tumors with diameters >2 cm, symptomatic nonfunctioning tumors, G3 with Ki67 > 20%, and neuroendocrine carcinoma
- cystic pancreatic tumors
- IPMN with high-risk stigmata (dilation of the Wirsung ≥10 mm, contrast-enhancing solid intracystic component ≥5 mm, causing obstructive jaundice, with positive cytology)
- malignant tumors of the distal common bile duct
- malignant tumors of the ampulla of Vater
- malignant tumors of the duodenum

Since the learning curve for LPD is long, patients should be adequately selected. As reported in the literature [12], it is preferable to start with patients with low BMI and small ampullary tumors, duodenal adenocarcinomas, or tumors of the distal biliary tract and avoid ductal pancreatic adenocarcinomas because of their infiltrative nature.

Accurate selection of patients is essential to decrease the rate of conversion and avoid unnecessary laparoscopic attempts, which would only increase the operative time and the risk of intraoperative complications.

Suggested contraindications to LPD are significant comorbidities [1, 2, 13–15], previous upper-mesocolic abdominal surgeries [1, 14, 16, 17], and high BMI [17, 18].

On the contrary, age does not seem to be a contraindication. A study by Buchs et al. [13] compared LPD in patients younger and older than 70 years: post-operative outcomes in the two groups were similar, showing that age alone may not be a selection criterion for LPD.

Current studies about LPD are subject to high selection bias, since most centers are still in the learning curve and selecting only ideal candidates for the procedures.

A recent review by Wang et al. [19] analyzed studies that evaluated inclusion and exclusion criteria for mini-invasive PD, reporting 14 studies that only mentioned inclusion criteria, 20 that only mentioned exclusion ones, and 13 that reported both. This review showed that patients selected for LPD had small periampullary tumors and low BMI. The most frequent contraindications were vascular invasion, previous upper-mesocolic procedures, and severe cardiovascular disease.

Indications and contraindications to LPD also depend on the experience of the surgical team [12]; with increased experience, it may also be performed for the treatment of tumors involving surrounding organs or vascular structures, and almost all contraindications to LPD may become relative. In this scenario, some pioneering groups have also started performing venous resections during LPDs [7, 8].

However, the majority of authors consider as exclusion criteria: large tumors [1, 16], chronic pancreatitis, tumors involving the superior mesenteric-portal vein confluence, the superior mesenteric artery or the hepatic artery [12, 13], and neoadjuvant radio-chemotherapy [20, 21], due to the local fibrosis caused by radiotherapy.

Many algorithms have been developed to help with LPD patient selection [22, 23].

3. Surgical technique

Currently, there is no consensus on the best surgical option for LPD, neither for the demolitive phase nor for the reconstructive one.

Differences in the surgical technique concern as follows:

- Preparatory phase: trocar placement, type of trocar used, access technique to peritoneum.
- Demolitive phase: surgical steps, devices and materials, pylorus preservation or not.
- Reconstructive phase: type of suture, anastomosis technique, surgical specimen extraction, drainages, stent placement in pancreatic duct to protect the pancreatico-jejunal anastomosis.

3.1 Preparatory phase

The number, type, and placement of trocars for LPD vary greatly throughout the literature. Most authors use 5 trocars (52.1%) [1, 24, 25]; some use 6 (30.4%) [26, 27]; more rarely, 4 [28, 29] or 7 [16] are used.

Pneumoperitoneum is usually induced using the "open" technique according to Hasson in periumbilical or supra-umbilical position [20, 24, 26, 28, 30], while rarely the "closed" technique with the Veress needle is used [1, 16, 27, 29].

Trocar placement varies between series, especially concerning the optic port and the port for the hepatic retractor. The optic port is more commonly placed in

the umbilical region (41.7%). The port for the hepatic retractor is, in many cases, placed along the midline in the subxiphoid region, while in some cases, it is placed along the right anterior axillary line, just under the hepatic ridge.

3.2 Demolitive phase

Boggi et al. [31] published a systematic review that analyzed various aspects of the demolitive phase. Their results are summarized in this section.

Concerning materials, the majority of authors used energy devices (678 patients, 90.8% of cases). Some authors used a single energy device (in 10 cases ultrasonic shears, in 4 cases radiofrequency), while 8 used a dual energy device (6 ultrasound and radiofrequency, 1 ultrasound and bipolar, 1 ultrasound and monopolar).

The section of the pancreatic neck can be done using the ultrasonic shears, the electrocautery (104 patients, 15.9%), the stapler or ultrasonic shears (100 patients, 15.3%), electrocautery or ultrasonic shears (65 patients, 9.9%), only stapler (12 patients 1.8%), or only radiofrequency (6 patients, 0.9%) (**Figures 1–3**).

The method used to section the gastroduodenal artery is another relevant technical aspect, since the arterial stump is a frequent site of bleeding in case of pancreatic fistula.

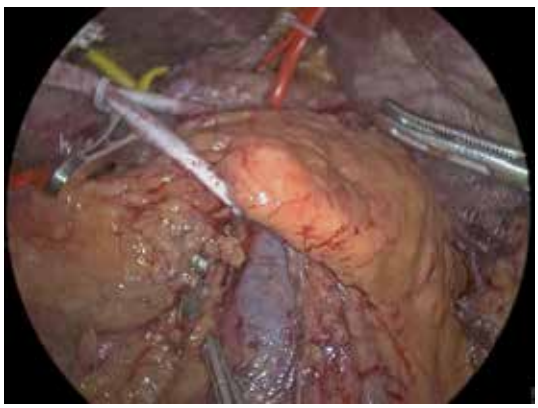

Figure 1.
Retropancreatic tunnel.

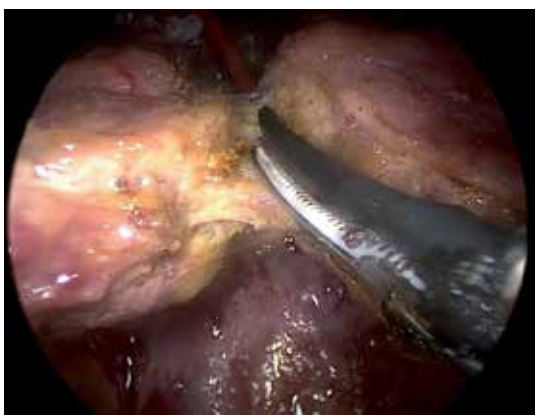

Figure 2.
Pancreatic neck section using ultrasonic shears.

In the majority of cases (274 patients, 54.5%), the use of clips was reported, while some authors (100 patients, 19.9%) reported only ligature. Other options are vascular stapler plus suture (1 article, 50 patients, 9.9%), clips plus suture (1 article, 35 patients, 6.9%), vascular stapler only (1 article, 24 patients, 2.7%), and radiofrequency only (1 article, 11 patients, 2.1%) (**Figures 4** and **5**).

The specimen is often extracted via an umbilical (42.2%), supra-pubic (15.7%), or subxiphoid (15%) mini-laparotomy; other sites for extraction are sub-umbilical (8.9%), the right inferior quadrant (8.8%), or supraumbilical (4.9%) one.

Finally, the surgeon must decide whether to preserve the pylorus (Traverso-Longmire intervention) or resect the gastric antrum (classic Whipple procedure).

Pylorus-preserving surgery is more commonly performed (55%) than gastric antrum resection among 21 authors (636 patients), 6 always preserve the pylorus (262 patients, 41.1%), 8 always section the gastric antrum (13 patients, 17.7%), while 7 used both techniques (261 patients, 41%).

Pylorus preservation in oncological cases is a controversial topic; it was compared with the Whipple technique without significant differences between the two techniques in terms of overall survival (p = 0.11), in-hospital mortality (p = 0.18) and morbidity (p = 0.69), incidence of postoperative pancreatic fistula (POPF; p = 0.63), biliary leakage (BL; p = 0.82), post-pancreatectomy hemorrage (PPH; p = 0.53), or delayed gastric emptying (DGE; p = 0.16) [32]. Pylorus-preservation

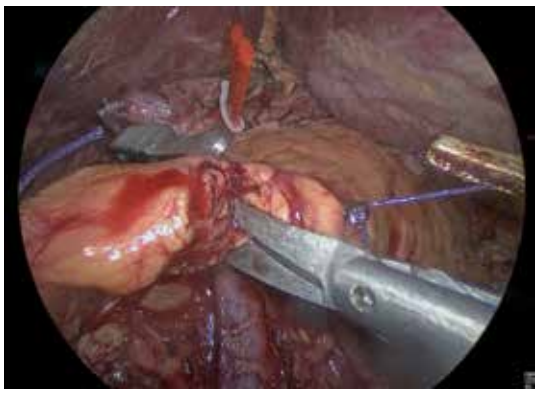

Figure 3.
Pancreatic neck section using ultrasonic scissors.

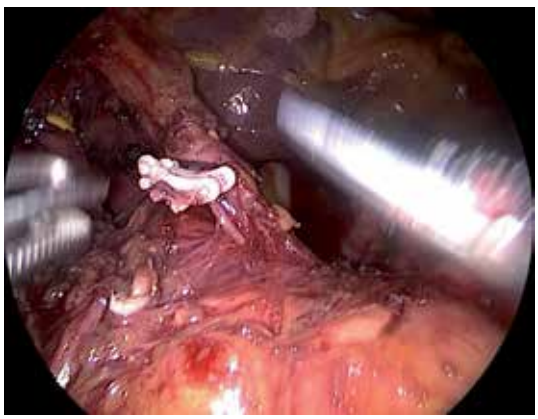

Figure 4.
Gastroduodenal artery closure using clips.

was associated with a shorter operative time (p = 0.0004) and a reduced intraoperative blood loss (p = 0.00001).

There is a lack of data about laparoscopic "artery first approach" to PD and total mesopancreas excision (TMpE), because no details about this important topics were reported in the literature.

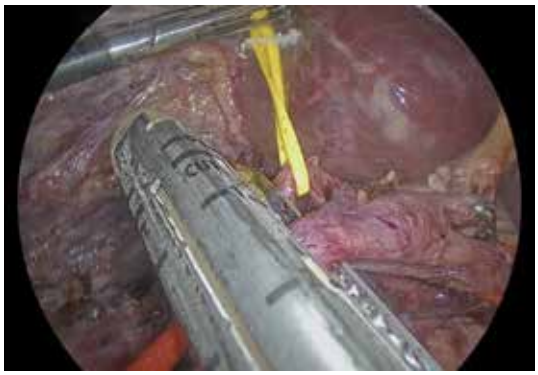

Figure 5.
Gastroduodenal artery closure using vascular stapler.

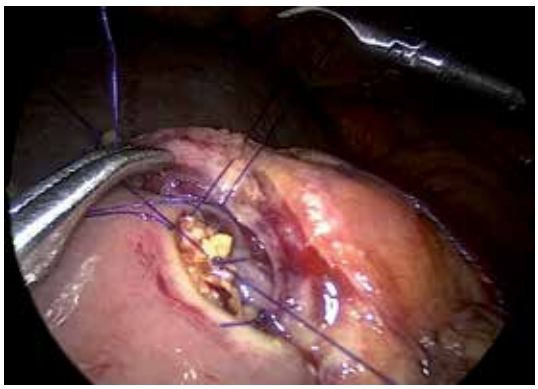

Figure 6.
Duct-to-mucosa anastomosis.

Figure 7.
Pancreato-jejunal anastomosis.

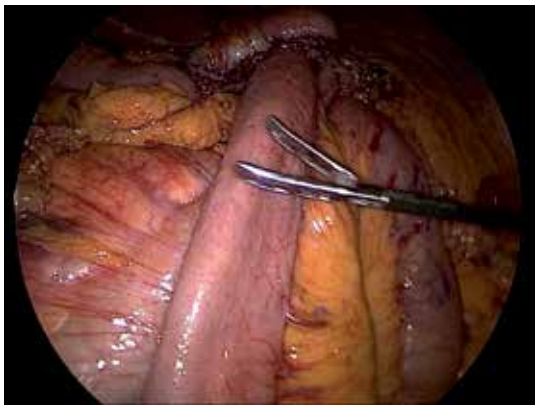

Figure 8.
Antecolic gastro-jejunal anastomosis.

3.3 Reconstructive phase

Great variability in the reconstructive phase is reported in the literature, both in materials (type of suture) and in fashioning anastomoses.

The management of the pancreatic stump represents one of the most important steps of the entire procedure [33, 34], especially when dealing with a soft gland, as it is one of the main risk factors for the development of a POPF [35, 36].

Pancreaticojejunostomy (PJ; 84% of cases; **Figures 6** and **7**) and pancreaticogastrostomy (PG; 9.8% of cases) are the most commonly performed anastomoses; on the other hand, the duct occlusion has mostly been abandoned (6.8% of cases) [31].

In order to reduce the risk of POPF, the majority of the authors (72.8%) positioned a stent in the Wirsung, either routinely or selectively; the pancreatic anastomosis was in most cases performed with a double layer (90.6%) and interrupted sutures (74.6%).

The gastro/duodenal-jejunal (GJ/DJ) anastomosis was antecolic in 76.3% of cases (**Figure 8**), retromesenteric in 13.4% of cases, and retrocolic in 10.2% of cases.

The majority of GJ and DJ anastomoses were handsewn (n = 491/566; 86.7%); mechanical anastomoses using stapler were performed in only 13.2% of cases and always to perform GJ anastomosis.

In a randomized multicentric study on 440 patients, Keck et al. [37] compared the outcomes of PG vs. PJ: although POPF rate was 20%, without significant differences between the two techniques, the rate of anastomotic bleeding was higher for PG.

Surprisingly in a meta-analysis [38] based on 676 patients underwent to PD, a significantly lower rate of POPF was found in favor of PG, while there were no differences in the incidence of BL, PPH, or DGE between the two anastomoses.

4. Postoperative outcomes

4.1 Short-term outcomes

Despite the technical and technological progress made in recent years, postoperative morbidity for PD remains high (30–50%) [39].

The most frequent postoperative complications for PD are DGE (19–23% of cases), POPF (9–18%), intra-abdominal abscess (9–10%), and intra-abdominal or GI bleeding (1–8%) [40].

Many authors questioned the possibility to improve postoperative outcomes through the use of mini-invasiveness.

Compared to open PD, LPD has been found to require longer operative time [30, 41–43] (**Tables 1** and **2**); however, it leads to

- reduce intraoperative blood loss and the need for transfusions [6, 26, 30, 41, 43–45]
- reduce postoperative pain [30]
- reduce intensive care unit (ICU) monitoring [42].
- reduce length of hospitals stay (LOS) [6, 30, 41–43, 45, 46] with differences varying between 2 and 5 days.
- reduce number of unscheduled readmissions [46].
- Thirty-day mortality and morbidity, including POPF, DGE, PPH, BL, and surgical site infection (SSI), are comparable between laparoscopic and open PD [30, 42–47].

4.2 Oncological outcomes

Regarding oncological radicality, laparoscopic PD appears to be at least noninferior to open PD.

Considering tumors of similar size and histological type, the number of harvested lymph nodes and the rate of negative resection margins have been found to be either comparable [20, 30, 45, 46, 48] between laparoscopic and open PD or superior in laparoscopic PD [6, 26, 41–43].

Author	Year	No of patients		Operative time (min)		Intraop blood loss (ml)		Postop LOS (days)		30-days mortality	
		VL	Op	VL	Op	VL	Op	VL	Op	VL	Op
Stauffer	2016	58	193	375	518	250	600	6	9	—	—
Sharpe	2015	384	4037	nr	nr	nr	nr	10	12	5.2	3.7
Song	2015	104	576	482	348	570	609	14	19	—	—
Speicher	2014	25	84	381	326	200	425	8	10	—	1.2
Dokmak	2014	46	46	342	264	368	293	23	25	2	—
Croome	2014	108	214	379	387	492	866	6	9	1	2
Mesleh	2013	75	nr	551	nr	nr	nr	7	nr	—	nr
Asbun	2012	53	215	541	401	195	1032	8	12	5.7	8.8

Abbreviations: N, number; min, minutes; Intraop, intraoperative; Postop, postoperative; VL, laparoscopic; Op, open.

Table 1.
Postoperative outcomes: comparison between laparoscopic and open PD.

Author	Year	Compl rate (CD > 3)		POPF rate		PPH rate		Median *n* of LNs harvested		R0 rate		Reop rate	
		VL	Op	VL	Op	VL	Op	VL	Op	VL	Op	VL	Op
Stauffer	2016	22	30	8	9	7	4	27	17	80	84	2	6
Sharpe	2015	nr	nr	nr	nr	nr	nr	16	18	80	74	nr	nr
Song	2015	7.5	5.4	6.5	6.5	nr	nr	15	16	72	81	nr	nr
Speicher	2014	nr	nr	16	22.6	nr	nr	14.5	12	83.3	78.6	8.7	10.7
Dokmak	2014	28	20	44	32	24	7	20	23	60	50	24	11
Croome	2014	6	14	11	12	7	6	21.4	20.1	77.8	76.6	nr	nr
Mesleh	2013	31	31	9	6	nr	nr	nr	nr	nr	nr	2	4
Asbun	2012	24.5	24.7	7.1	5.1	9.4	5.6	23.4	16.8	95	83	3.8	7

Abbreviations: Compl, complication; CD, Clavien-Dindo; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemorrage; LNs, lymph nodes; Reop, reoperation; VL, laparoscopic; Op, open.

Table 2.
Postoperative outcomes: comparison between laparoscopic and open PD.

Overall survival between laparoscopic and open PD is comparable [6, 30, 45]. However, the reduction in postoperative pain and physical impairment, paired with the reduced rate of surgical site complications, may allow for a broader access to adjuvant chemotherapy and an earlier start of treatment in patients who underwent laparoscopic PD [11, 49].

Current studies comparing laparoscopic PD vs. open PD have been criticized because they may suffer from selection bias, as many of them excluded patients with vascular involvement, high intraoperative risk, and multiple previous abdominal operations, all of which have higher chances of undergoing an open procedure.

However, the results from Croome et al. [6] and the review from Wang et al. [43] showed promising results also in complex cases, which required vascular resections.

5. Learning curve

The learning curve for LPD is particularly steep and represents an obstacle to a more widespread use of the procedure; it seems that learning curve can be shortened with specific training strategies, e.g., ex vivo training, proctoring, and simulation in loco.

The majority of studies about surgical learning curves define it as the number of procedures needed to achieve a decrease in operative time and blood loss and in the number of conversions.

With increased experience in those kinds of procedures, the surgeon is also able to deal laparoscopically with more technical complex situations, such as vascular resections (portal, mesenteric, and arterial), without increasing postoperative complications.

As shown in the review published by De Rooij et al. [12], there are three strategies to learn how to carry out PD completely laparoscopically (i.e., not only the demolitive phase, which is more commonly performed laparoscopically, but also the reconstructive one, which represents a considerable obstacle for some).

The first strategy consists of tutoring. The second one is a hybrid approach, i.e., performing the demolitive phase through laparoscopy and the reconstructive phase

through a service minilaparotomy. The third one is also a hybrid approach, but the reconstructive phase is carried out robotically.

Each strategy has its own learning curve and needs to be performed only in specialized centers with high volumes of pancreatic surgeries to avoid unnecessarily high rates of morbidity and mortality. Recent studies suggest that using hybrid techniques before performing the procedure completely laparoscopically might be useful. A cut off of 10 hybrid procedures is considered enough to start with full laparoscopy, although 50 hybrid procedures are required for significant improvements in operative outcomes to appear/significant improvements in operative outcomes appear after 50 hybrid procedures.

A study by Speicher et al. [41] shows that laparoscopic PD's learning curve goes through a slow and difficult initial phase (first 10 cases), a much faster improvement phase (10–20 cases), and finally a plateau with a slow but steady improvement with time (after 50 cases).

However, these considerations can only be applied to surgeons with great expertise in open PD and in advanced laparoscopic surgery; it is often difficult to satisfy both conditions, as many centers with high volumes of pancreatic surgeons do not have high volumes of laparoscopic surgery and vice versa.

Many years are required to overcome the learning curve and reach an adequate outcome level [50]. Pancreatic surgery should be centralized in dedicated centers, as this has been shown in many studies to improve outcomes [51, 52].

A review by Gumbs et al. [53] that analyzed 285 LPDs shows that the length of hospital stay and the operative time for the procedure decrease proportionally to the higher volume of cases of the center.

Different studies show that, as one moves along the learning curve, there is a decrease in operative time, blood loss, morbidity, and open conversions, resulting in a reduced length of hospital stay.

Kim et al. [24] analyzed 100 consecutive cases of pylorus-preserving LPD, of which all performed by the same surgeon and divided them in three time periods. With increased experience, operative time decreased from 9.8 hours in the first-time period to 6.6 in the third. Length of hospital stay went from 20.4 to 11.5 days. Morbidity, including pancreatic fistula, intraoperative bleeding, delayed gastric emptying, and ileus, decreased from 33.3 to 17.6%.

Similar results, demonstrating an improvement in the surgical outomes increasing the learning curve, also reported by Speicher et al. [41], with diminished operative time and blood loss with increased experience, and Song et al. [30].

Song et al. divided LPD's cases into two cohorts (the first 47 consecutive cases vs. the next 50 cases). The second cohort had decreased operative time (399.4 vs. 566.5 minutes, $p < 0.0001$), decreased intraoperative blood loss (503 vs. 685 cc, $p = 0.018$), and decreased length of hospitals stay (11.2 days vs. 17.3, $p < 0.001$).

Another cohort study shows that rates of postoperative pancreatic fistulas diminished from 36 to 18% after only 11 LPDs [1]. Other study also confirmed that morbidity is inversely proportional to the number of procedures performed in a single center [9, 20, 30].

Mortality also decreased with an increase in experience [54]; analyzing a national database with over 7000 patients who underwent PD from 2010 to 2011, higher 30-day mortality with LPD than with open PD was found. However, this result only applied to those centers with less than 10 LPDs in 2 years, where 30-day mortality was twice that of open PD. In centers with more than 10 LPDs, 30-day mortality was similar in laparoscopic and open procedures.

The dramatic improvement shown by these authors as they progress along the learning curve is encouraging and may bring much more surgeons to perform PD laparoscopically.

6. Costs

Most of the financial benefit of laparoscopic vs. open PD is attributed to the reduced length of hospital stay [15, 17, 20, 30]. However, laparoscopy significantly increases operative time (usually by 2 hours) [30] and requires expensive materials with an increase in cost of 35%, $p < 0.0001$, both of which lead to increased costs [30].

Speicher et al. and Mesleh et al. compared open vs. laparoscopic PD costs [41, 44]. They concluded that total costs were comparable. According to Speicher et al. [41], laparoscopic PD costs 24,590 dollars vs. 19,720 dollars in open technique ($p = 0.19$).

According to Mesleh et al. [44], laparoscopic PD is significantly more expensive ($p < 0.0001$) than open PD, due to the cost of the surgical material and the increased operative time (551 vs. 355 minutes).

Morbidity and postoperative length of hospital stay were comparable and did not influence the overall cost. However, the post-operative management for open PD is slightly more expensive than laparoscopic PD when single categories are taken into account (expenses for nursing, anaesthesia, drugs, labs, and imaging).

As recovery expenses represent 65–70% of the overall cost, the decreased postoperative cost of laparoscopic PD balances out its increased intra-operative cost when compared to open PD.

7. Conclusions

LPD is a safe, standardizable, and oncologically adequate surgical technique, but only if performed by surgeons with extensive experience both in pancreatic surgery and in laparoscopy and, at least at the beginning of the learning curve, on appropriately selected cases.

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Chapter 4

Endoscopic Management of Leaks and Fistula in Gastrointestinal Tract

Mahesh Kumar Goenka, Gajanan Ashokrao Rodge and Usha Goenka

Abstract

Leak, perforation, and fistula are the three main types of transmural defects in the gastrointestinal (GI) tract. Evolution of interventional endoscopic\ techniques as well as widespread use of laparoscopic and bariatric surgical procedures has contributed to the rising incidence of GI defects. The basic principle for management of leaks and fistula is to provide a barricade to the flow of luminal contents across the defect. This can be achieved either by a surgical or endoscopic method. Minimally invasive closure techniques such as clipping, stenting, suturing, and endoscopic vacuum therapy have revolutionized the management of GI defects. This chapter deals with endoscopic techniques and their present status in the management of luminal GI leaks and fistula.

Keywords: leaks, fistula, endoscopic management, through-the-scope clip, over-the-scope clip, suture, sealants, stents

1. Introduction

Leak, perforation, and fistula are the three main types of transmural defects in the gastrointestinal (GI) tract. Evolution of interventional endoscopic techniques as well as widespread use of laparoscopic and bariatric surgical procedures has contributed to the rising incidence of GI defects [1–3]. Some of these defects may be serious and life-threatening and require emergency interventions. Successful endoscopic closure of gastrointestinal (GI) leaks and fistulae has shifted the management from surgery to a more conservative endoscopic approach.

Minimally invasive closure techniques such as clipping, stenting, suturing, and endoscopic vacuum therapy have revolutionized the management of GI defects [4–6]. These techniques provide a more affordable alternative to surgery with less morbidity and hospital stay. Innovations in interventional endoscopy like over-the-scope clips (OTSCs) have shown promising results in closing GI defects with good safety and efficacy [7]. This chapter deals with endoscopic techniques and their present status in the management of luminal GI leaks and fistula. Pancreatic and biliary leaks, which have somewhat different approaches, are not covered in this review.

- Iatrogenic:
  - Diagnostic endoscopy
  - EVL
  - Dilatation
  - ESD/EMR
  - POEM
  - Trauma
  - PEG and feeding tubes
  - Post-stenting
  - Postsurgical anastomotic dehiscence
- Spontaneous
  - Boerhaave's
- Foreign body
- Tuberculosis
- Crohn's
- Malignancy

EVL: endoscopic variceal ligation; ESD: endoscopic submucosal dissection; EMR: endoscopic mucosal resection; POEM: peroral endoscopic myotomy; PEG: percutaneous endoscopic gastrostomy.

Table 1.
Etiology of GI leaks and fistula.

2. Definitions and etiology

While the terms perforation, leak, and fistula are often used interchangeably, they in strict terms can be defined as follows:

Perforation—Acute full thickness defect in GI tract [8].
Leak—Disruption at a surgical anastomosis resulting in a fluid collection [9].
Fistula—Abnormal communication between two epithelialized surfaces [9].

Perforation occurs spontaneously or more commonly after an injury, iatrogenic or traumatic [8]. GI leaks are most commonly seen at the site of surgical anastomosis and depending on the site of anastomosis can be either intra-peritoneal or extra-peritoneal. GI fistula can be internal (between GI organs) or external (between GI tract and body surface). **Table 1** enumerates the various etiologies of GI leaks and fistula [10–18].

3. Approach to management

The basic principle for management of leaks and fistula is to provide a barricade to the flow of luminal contents across the defect. This can be achieved either by a surgical or endoscopic method. Regardless of the chosen technique, the management requires a multi-disciplinary approach. The general measures which must be involved include: bowel rest, intravenous fluid as clinically indicated, appropriate antibiotic coverage, maintenance of nutrition, drainage of associated collection, and close hemodynamic monitoring. Proton pump inhibitors should be added in upper GI tract leaks. Contrast radiological studies help in defining and delineating the site of leak. European Society of Gastrointestinal Endoscopy (ESGE) position statement [19] recommends that endoscopic closure should be considered depending on the type of perforation, its size, and the endoscopist expertise available at the center.

Different techniques are combined together for successful closure of leaks and fistulae in many cases. For example, an esophagogastric fistula may be initially

Diversion	Closure
• Luminal stents - Covered self-expandable stents - Plastic stents	• Endoclips - Through-the-scope clips - Over-the-scope clips
	• Injection of fibrin glue/cyanoacrylate
	• Suture devices

Table 2.
Endoscopic modalities for management of leaks/fistula.

managed with fibrin glue injection and endoscopic clip closure. An esophageal stent should be placed across the fistula site following the closure for diversion of the luminal stream. **Table 2** (adapted [20]) lists the different modalities which can be used for endoscopic management of GI leaks and fistula.

3.1 Luminal stenting

Stent placement for managing leaks and fistulae has been commonly used in the upper GI tract. The basic purpose of stenting is to cover the luminal disruption and divert the GI secretions/GI content away from the point of defect. This provides a temporary barricade to the region and prevents influx of enzymatic fluid through the opening. Therefore, preferred stents are the covered one's (at least partially covered) which can be removed once the defect is sealed. **Figure 1** (adapted [20]) shows the different stents available to close GI defects.

All of these stents are self-expanding metallic stent except for a single design of plastic stent (Polyflex, Boston, MA, USA). Fully covered stents are generally preferred in benign conditions as they can be removed easily later on. **Figure 2** (adapted [20]) shows a patient with leak following gastrojejunostomy managed successfully with a covered stent placed across the leak [20].

Table 3 compares the different studies on esophageal stent placement for management of leaks/fistulae [21–23]. The overall stent migration rate was between 28 and 33% and is one of the major issues with use of covered stent for closing of the GI defects. Large diameter stents (Mega stents by Niti or Danis stents by Ella;

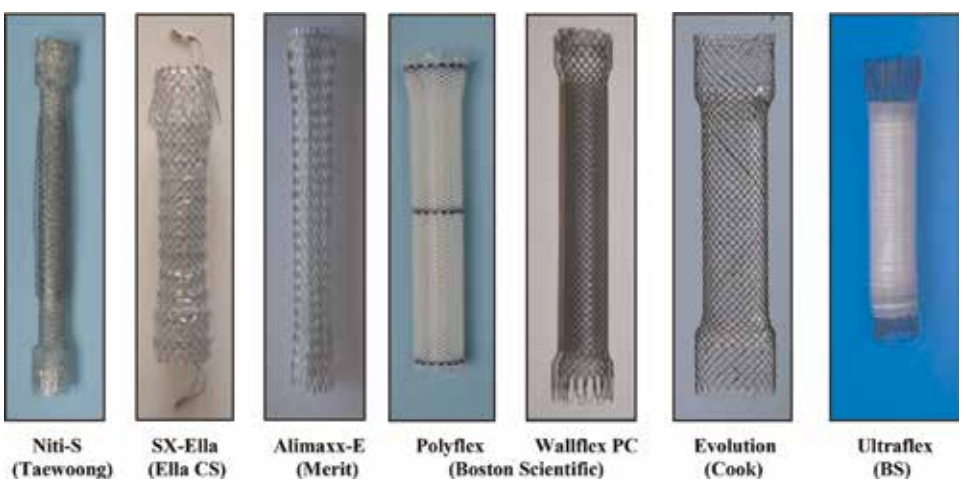

Figure 1.
Stents for GI leaks and fistula.

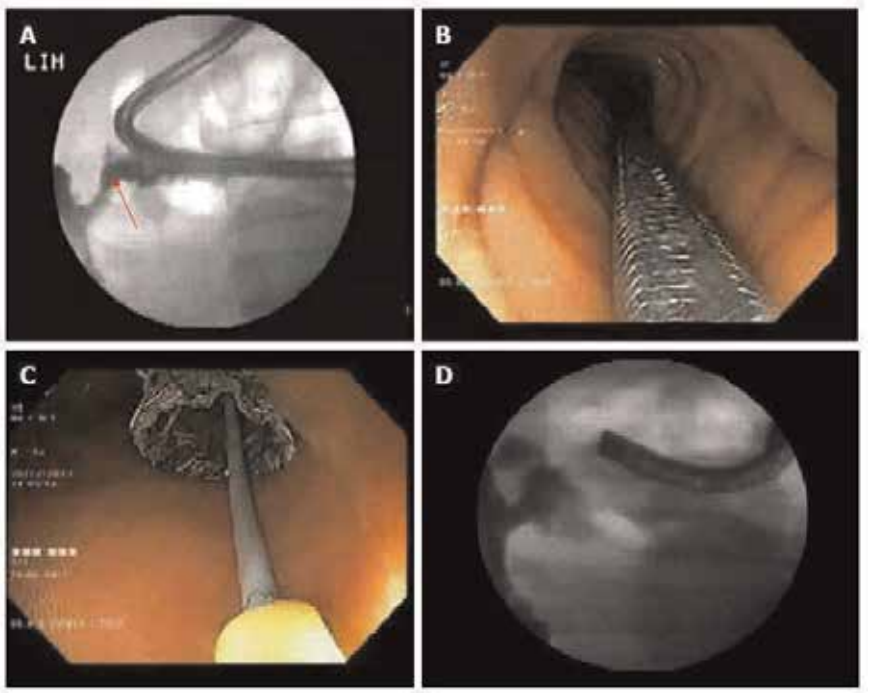

Figure 2.
(A) Contrast introduced through the surgical drain site shows site of the leak (arrow); (B and C) fully covered stent being deployed; (D) post-stenting contrast showing closure of the leak.

	Eloubeidi et al. [21]	Buscaglia et al. [22]	El Hajj et al. [23]
Total patients included	35	31	54
Patients with leaks/fistulae	12	15	44
Stent type(s) used	AliMaxx-E FCSEMS	Wallflex FCSEMS	SEPS, PCSEMS, FCSEMS
Overall technical success rate (%)	100	100	100
Closure of leak/fistula (%)	44	80 (short-term closure)	83
Overall stent migration rate (%)	33	33	28

FCSEMS: fully covered self-expandable metal stents; SEPS: self-expandable plastic stents; PCSEMS: partially covered self-expandable metal stents.

Table 3.
Comparison of studies on esophageal stent placement for management of leaks/fistulae.

Figure 3) and the modified stent designs (**Figure 4**) (adapted [20]) reduce the chances of stent migration [20].

3.2 Endoclip closure

Endoclips, which are more commonly used for controlling GI bleed, can also be used for closing the GI wall disruptions [24]. For the first time in 1993, endoclips were used successfully for closure of a GI perforation after endoscopic removal of gastric leiomyoma [25]. Endoclips are of two types, through-the-scope clips (TTSCs) and over-the-scope clips (OTSCs). In TTSCs, the clip is loaded on the clip applicator which is introduced through the biopsy channel of the endoscope. TTSCs have been

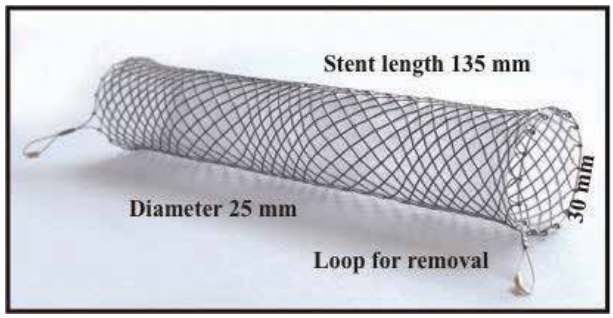

Figure 3.
Danis stent; length—135 mm; end diameter—30 mm; mid diameter—25 mm; provided with a loop at the end for removal.

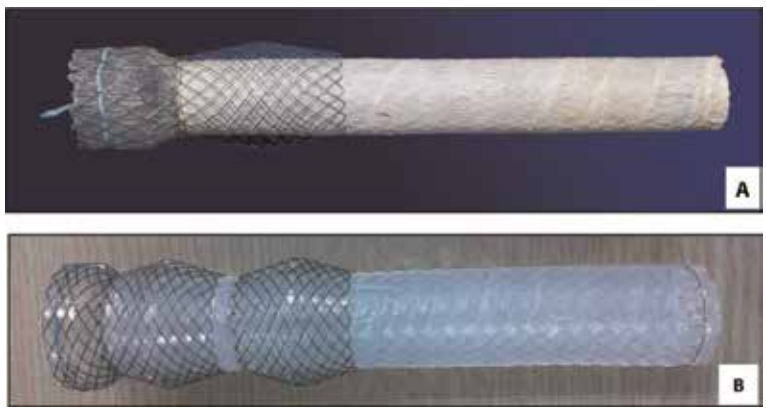

Figure 4.
Modified stent design with extra covering or dumb-bell shape.

used successfully to close leaks following endoscopic mucosal resection (EMR) [26] and endoscopic submucosal dissection (ESD) [27]. TTSCs are usually less effective for defects of >1 cm, where another technique should be combined with TTSC. The TTSCs available from different manufacturers differ in size and mechanical properties. The most commonly used TTSCs (**Figure 5**) (adapted [20]) are the Quick clip (Olympus, America Inc., Center Valley, PA, USA), Instinct clip (Cook Medical Inc., Bloomington, IN, USA), and Resolution clip (Boston Scientific Inc., Natick, MA, USA). Most of the recent versions of TTSC are re-operable and rotatable; these properties allow the clips to be placed accurately and improve the clinical success.

The recently introduced OTSCs can close full thickness GI defects up to 2–3 cm in diameter. The design of OTSC is different and is mounted over-the-scope tip on a

Figure 5.
Through-the-scope clips from different manufacturers.

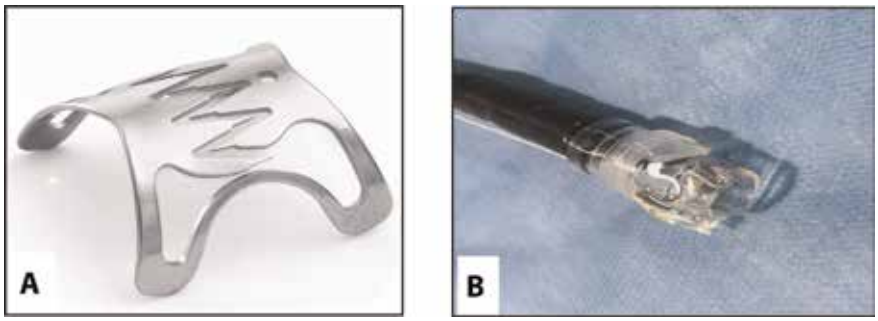

Figure 6.
(A) Ovesco clip and (B) ovesco loaded on tip of endoscope.

transparent cylinder somewhat akin to variceal band ligator device. OTSCs (**Figure 6A** and **B**) from Ovesco Endoscopy (Tübingen, Germany) are nitinol, biocompatible clips with teeth ends designed in the shape of a bear trap which can produce a full thickness closure. OTSCs have a greater tissue capture and compressive strength which gives it advantage over TTSCs to close chronic leaks and fistulae even in the case of inflamed or fibrotic tissue surrounding the defect. Accessories like anchor and twin grasper, which can pull the defective mucosa into the OTS cylinder or reduce the gap of the defect, can be used for larger defects. In a large muticenter study by Chavez et al. [28], 188 patients with GI leaks and fistula were treated with OTSCs. OTS was used as primary treatment in 97 patients and as rescue therapy in 64 patients (27 patients were lost on follow-up). The success rate was 75% in first group and 47% in second group with an overall success rate of 64%.

Padlock clip (Aponos Medical Corp., Kingston, NH, USA) is a recently introduced OTSC which uses somewhat different technique and design than Ovesco (**Figure 7A**). The six needles on the inner aspect point toward each other help in circumferential tissue approximation at 360° due to its radial compression technology. The Padlock clip is preassembled in an open position over the tip of endoscope and is deployed by its Lock-It delivery system with a trigger wire located parallel to the scope connected to a handle (**Figure 7B**). Recent studies have shown Padlock clip to be safe and effective in closing GI wall defects [29, 30]. However, data regarding its clinical use is still limited.

3.3 Sealants

Sealants have been used for a long time to close GI leaks and fistula, however the results are mixed with limited data. The most commonly used tissue sealants are cyanoacrylate and fibrin glue [31, 32]. The frequent sites of application include

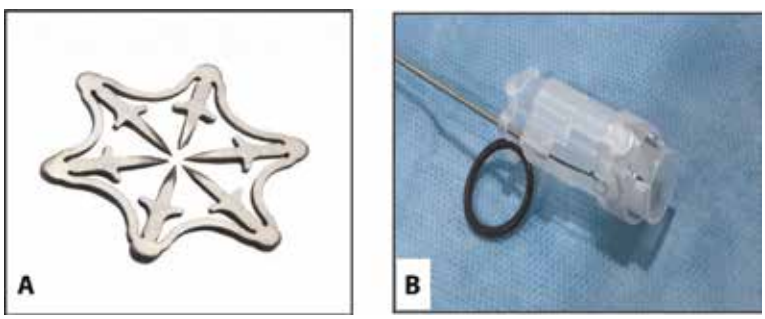

Figure 7.
(A) Padlock clip and (B) preassembled padlock clip.

endoscopically accessible areas of anastomotic leakage after esophagectomy and gastrectomy or after bariatric surgical procedures. The glue is applied via a double lumen catheter after removal of secretions or pus so that the targeted area becomes dry and it helps to form a fibrin clot. The underlying epithelium around the opening of the fistula is denuded with the aim of development of reactive inflammatory response around the opening. After application, the glue polymerizes on contact with moisture, causing tissue necrosis and an inflammatory response. Kotzampassi et al. used endoscopic tissue sealants (fibrin and cyanoacrylate glue) for anastomotic leakage after gastrointestinal operation and the success rate was 96.8% [33]. However, repeated sessions and large volumes of sealants may be necessary in many cases.

3.4 Sutures

Endoscopic suturing can be used for stent fixation and closure of larger defects including fistula and perforations, although the technique is more demanding and requires expertise. The Apollo Overstitch (Apollo Endosurgery, Austin, TX, USA) is US Food and Drug Administration (FDA) approved endoscopic suture device which offers full thickness plication. It is a single unit disposable device allowing continuous or intermittent suturing with a cinching device. The device is front loaded onto a double channel endoscope (**Figure 8**). The major advantage of Apollo Overstitch is that it can be reloaded inside the body without any need of removing it between stitches and allows one endoscopic channel to be free. In a large multicenter retrospective study by Sharaiha et al., endoscopic suturing used for management of GI defects and/or stent anchorage was found to be safe and efficacious [34]. The technical and clinical success rates achieved were 97 and 79%, respectively. Clinical success was high for perforations (93%) and fistulas (83%), however the results were disappointing for closure of anastomotic leaks (27%) [34]. Overstitch has also been used successfully in closure of iatrogenic esophageal perforations [35], endoscopic submucosal dissection (ESD) [36], and mucosal defect after Peroral Endoscopic Myotomy (POEM) [37] and stoma reduction post-bariatric surgery [38, 39].

3.5 Other techniques

Vacuum-assisted closure (VAC) device is a widely used treatment modality for management of cutaneous wounds [40]. It applies negative pressure to the wound through a vacuum-sealed sponge and helps in drainage of wound secretion which

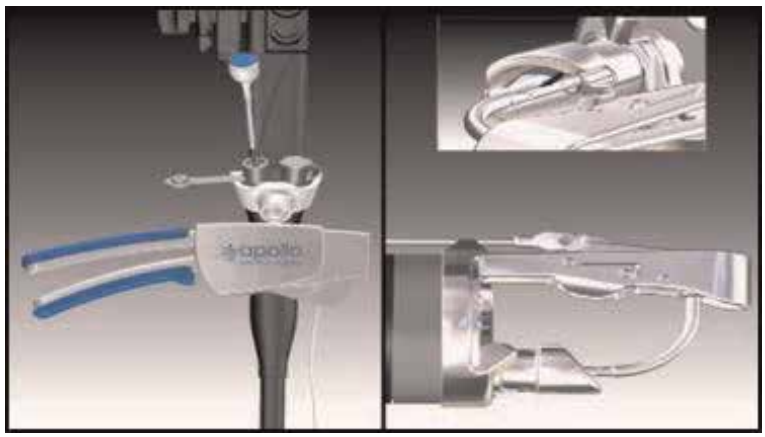

Figure 8.
Apollo overstitch device (Apollo Endosurgery, Austin, TX, USA).

promotes wound healing by increasing tissue vascularity and fresh granulation tissue. Endoscopic vacuum-assisted closure (EVAC) is a minimally invasive method which is mainly used in management of anastomotic leakage post-surgery [41, 42]. The sponge allows drainage of the leak by providing a gentle, continuous suction over tissue in contact with the sponge surface leading to a gradual reduction in the size of the wound cavity [43].

Atrial septal occluders (ASO) developed for the closure of atrial septal defects have been shown in case reports to be effective in treating GI fistulas including TEF [44, 45]. It consists of two self-expandable disks which are covered by polyester fabric and attached by a short connector that has various diameters. The other endoscopic methods used in management of GI leaks and fistula include fistula plugs [46], surgisis soft tissue grafts [47], and biodegradable stents [48]. However, more experience and data are required with these modalities to be included in routine clinical practice.

3.6 Limitations

The main limitations of endoscopic management are in situations with large perforation, difficult or inaccessible endoscopic location, fibrosis at the margins of the defect, presence of abscess or fecal contamination, etc. [49]. In these conditions,

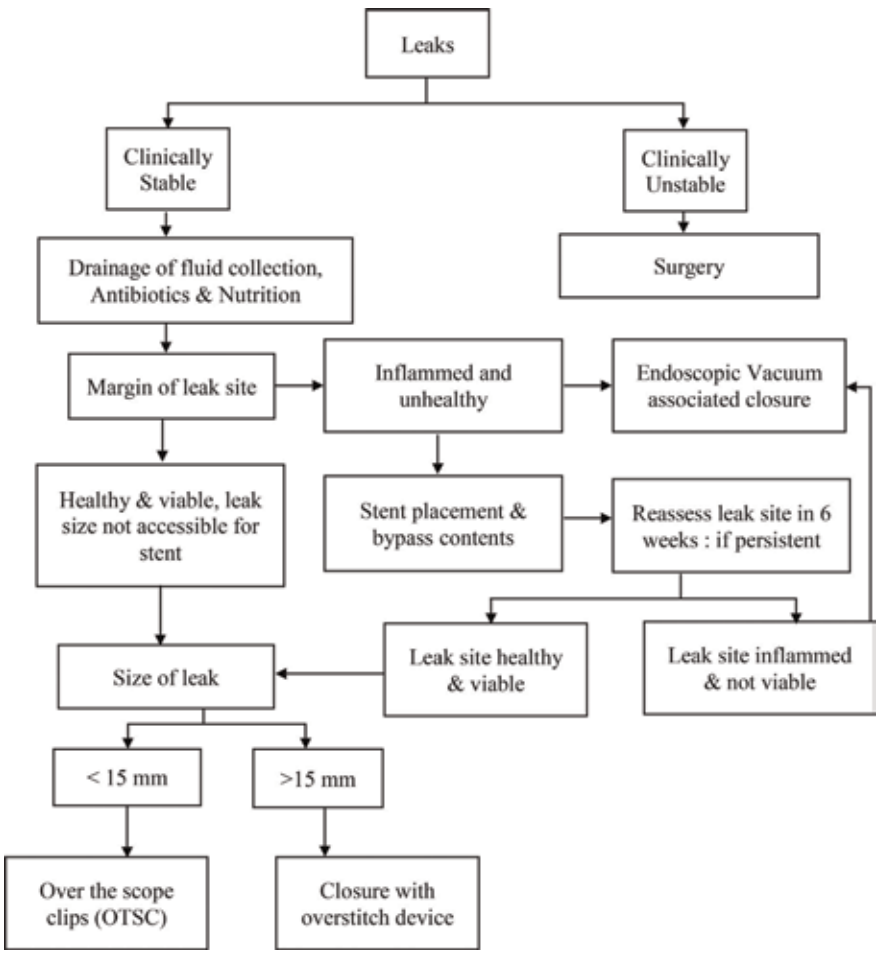

Figure 9.
Algorithm for management of leaks.

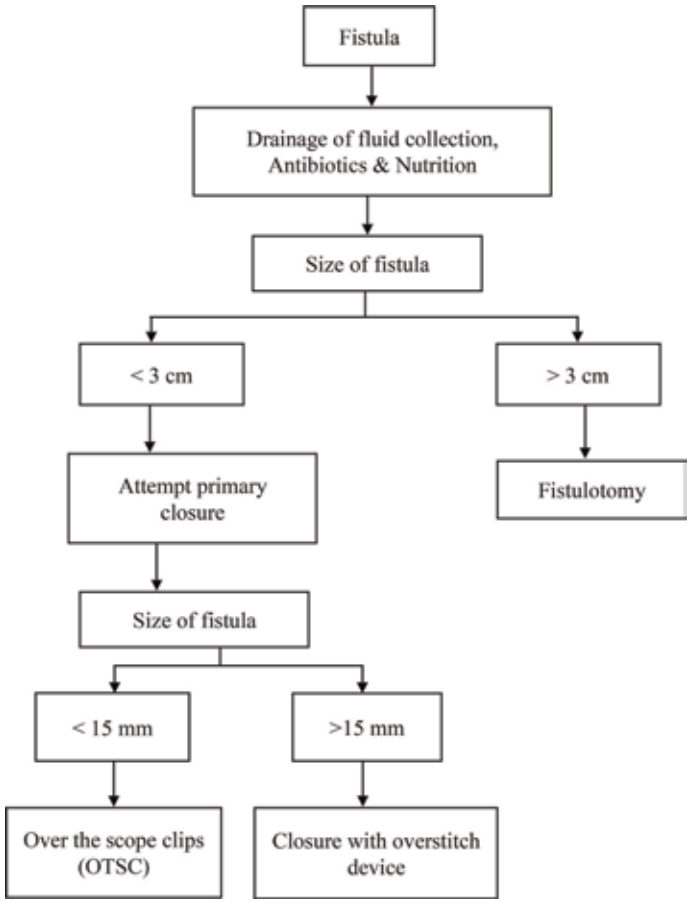

Figure 10.
Algorithm for management of fistula.

an additional procedure or surgical alternative should be considered. In cases with technical failure, where clip closure is unsuccessful, surgical intervention should be immediately considered to avoid sepsis [50]. Other complications such as perforation and bleeding are known with the endoscopic modalities.

3.7 Algorithm for management of leaks and fistula

Figures 9 and **10** (adapted [51]) give a systematic approach toward management of leaks and fistula.

4. Conclusion

The incidence of leaks and fistula involving the GI tract has increased in our routine practice. Only a small group of patient will respond to conservative management, while most of them will require either surgery or endoscopic management. Endoclips (TTSC and OTSC) and covered stents are the preferred endotherapy modalities to treat GI leaks and fistula. The small leaks (<10 mm) can be managed by traditional TTSCs, while the larger leaks require covered stents or OTSCs. In general, if the leak is located in proximal esophagus, distal-most esophagus, stomach, or in the right colon, clips are preferred over stents [52]. Results of

Endovac, Plugs and Grafts, and Biodegradable stents are promising. However, larger clinical studies are required before they can be used in routine clinical practice.

In view of availability of multiple endoscopic techniques, management according to the algorithm guides the endoscopist to select the best modality based on the location, size, and associated features.

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Chapter 5

EUS-Guided Biliary Drainage

Takeshi Ogura and Kazuhide Higuchi

Abstract

Endoscopic ultrasound-guided biliary drainage (EUS-BD) has been developed as an alternative method for failed endoscopic retrograde cholangiopancreatography (ERCP). EUS-BD can be divided into two main approach routes, such as transgastric or transduodenal approach. Also, EUS-guided hepaticogastrostomy, choledochoduodenostomy (CDS), and gallbladder drainage (GBD) have been reported. In this chapter, we described technical tips for each basic technique, including literature review. As advanced technique of EUS-BD, antegrade stone removal has been reported. More recently, electrohydraulic lithotripsy for bile duct stones under transluminal cholangioscopy guidance, hepaticojejunostomy stricture dilation through EUS-hepaticogastrostomy (HGS) route, or EUS-guided gastrojejunostomy has been reported. Although EUS-BD has various potential as treatment technique, treatment method should be selected for each patient's conditions.

Keywords: EUS-guided biliary drainage, EUS-BD, EUS, endoscopic ultrasound-guided biliary drainage, ERCP, endoscopic retrograde cholangiopancreatography, PTBD, percutaneous transhepatic biliary drainage

1. Introduction

Biliary drainage under endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard and is an established technique for malignant biliary obstruction. However, successful selective biliary cannulation is not always obtained. In addition, if the case is complicated by malignant gastroduodenal obstruction or surgically altered anatomy preventing advance of the endoscope into the ampulla of Vater, ERCP itself may not be indicated. As an alternative biliary drainage technique, percutaneous transhepatic biliary drainage (PTBD) is another established technique. However, this alternative may also be contraindicated for patients with massive ascites and shows several disadvantages such as risk of self-tube removal or cosmetic problems. Endoscopic ultrasound (EUS)-guided biliary drainage (BD) has recently been developed as a novel alternative biliary drainage technique. EUS-BD can be divided into two main approach routes: transgastric and transduodenal. In addition, EUS-guided hepaticogastrostomy (HGS), choledochoduodenostomy (CDS), and gallbladder drainage (GBD) have been reported. In this chapter, we provide technical tips for each basic technique and review the associated literature.

2. EUS-guided biliary drainage

2.1 EUS-guided CDS

2.1.1 Indications

EUS-CDS is mainly attempted for patients with failed endoscopic balloon dilation (EBD) excluded prospective clinical trial, as previously described [1, 2]. This procedure can be performed for obstructions in the middle and lower bile duct. This indicates that pancreatobiliary carcinoma is the main indication for EUS-CDS. EUS-CDS is contraindicated in patients with surgically altered anatomy, such as a Roux-en-Y anastomosis or tumor invasion-associated duodenal obstruction through which an endoscope cannot be passed. In such cases, EUS-guided hepaticogastrostomy may be indicated. However, if the duodenal bulb is not involved, EUS-CDS can be performed in combination with duodenal stenting. Optimal indications regarding EUS-CDS versus ERCP for benign disease have not been defined, completely. Prospective randomized controlled studies between ERCP and EUS-CDS are therefore needed to assess the clinical efficacy of the procedure. Indications for EUS-CDS are the following: (1) failed EBD including inaccessibility of the Vater, such as that caused by malignant duodenal obstruction, (2) contraindications for percutaneous transhepatic cholangiography drainage (PTCD), and (3) middle or lower bile duct obstruction. EUS-CDS has recently been attempted as a first-line drainage technique. According to randomized controlled trials [3, 4], EUS-CDS offers similar safety to ERCP. In addition, EUS-CDS may result in fewer cases of tumor ingrowth but may also be associated with greater frequencies of food impaction or stent migration. Further high-quality randomized trials are needed.

2.1.2 Technical tips

The EUS scope is introduced into the duodenum, turned slightly to the left, and angled downward to identify the common bile duct (CBD) on EUS. To avoid any intervening vessels, the CBD should be punctured using a 19-G needle under color Doppler guidance. Then, bile juice is aspirated to be ensure the biliary tract, and the contrast medium is injected to obtain image of the CBD. During this step, avoiding puncture of the duodenal mucosa [5, 6] and cystic duct is important. When a double duodenal mucosal line is visualized on EUS, the CBD should not be punctured to avoid puncture and stenting through the double duodenal mucosa. To prevent this adverse event, a water-filling technique may be impactful [5]. After guidewire insertion, to insert the stent delivery system, dilation for the duodenal and CBD wall is sometimes needed. Various devices have been described for dilatation of the fistula after puncturing the CBD. The most common devices for transmural tract dilation are the dilator (6 to 10 Fr), balloon catheter (4–8 mm), and needle knife. Park et al. described that the overall complication rate for EUS-CDS and EUS-HGS was 27% (15/55) [7]. As risk factor for complication associated with EUS-BD ($P = 0.01$, HR 12.4, 95%CI, 1.83–83.5), the use of a needle knife for fistula dilation is identified. Because of the acute angulation of the scope, following deployment of the catheter at the duodenum, the needle knife points tangentially when deployed. This can lead to accidental incision with a chance of pneumoperitoneum or bleeding. Therefore, the author's conclusion is that fistula dilation should be avoided to prevent procedural complication. The next step is stent deployment (**Figures 1**–**3**).

Endoscopist can select both plastic and metallic stents during EUS-CDS as drainage device. Plastic stents with diameters ranging from 5 to 10 Fr were commonly used according to previous reports. A 7- or 8.5-Fr plastic stent is used,

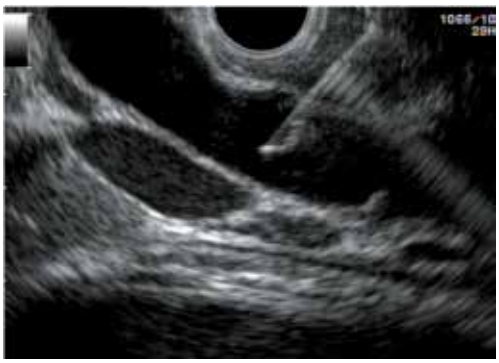

Figure 1.
The common bile duct is punctured using 19-G needle from the duodenal bulb.

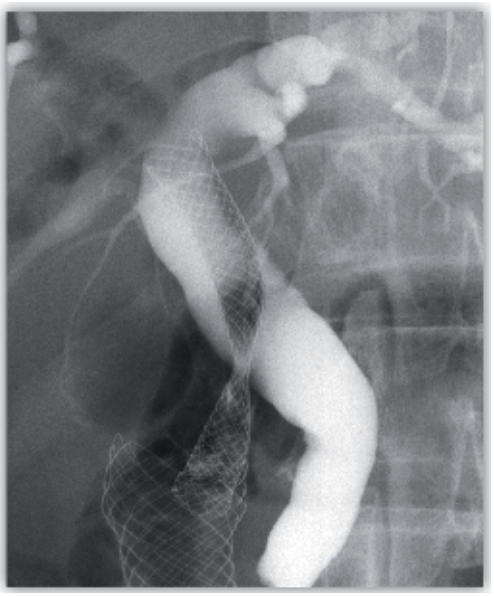

Figure 2.
The covered metal stent deployment is performed from the common bile duct to the duodenum.

because the diameter of the working channel is 3.7 mm. However, bile leakage can occur with plastic stent placement (**Figure 6**). This patient experienced high fever and abdominal pain for up to 3 days after EUS-CDS, and bile leakage was seen according to computed tomography and duodenoscopy. If a large fistula is created before stent deployment, bile leakage from the gap between fistula and the stent is likely to occur because plastic stent is fine gauge compared with metal stent. On the other hand, although no comparative studies appear to have been conducted, metallic stents are expected to offer several clinical benefits. First, because of their large diameter, metallic stents tend to remain in the patent longer than plastic stents.

Second, bile leakage is less likely because of the close proximity between the metallic stent and duodenal and bile duct wall. If an uncovered metallic stent is used, however, bile leakage can easily occur, which sometimes proves fatal. Therefore, covered self-expandable metal stents (SEMSs) should be used. However, although SEMSs can prevent bile leakage, the side branch of biliary tract may be occluded. This suggests that if the distance between the puncture site and hepatic

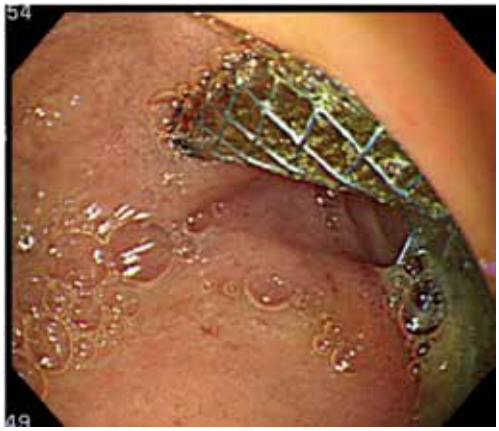

Figure 3.
Metal stent is placed in the duodenum bulb.

hilar portion is short, a partially covered SEMS should be selected to prevent occlusion of the intrahepatic bile duct. However, if EUS-CDS is performed using by a partially covered SEMS, bile leakage can occur from the uncovered site, particularly between the bile duct and duodenum. A challenging complication is stent migration during EUS-BD. In the use of a standard metallic stent in EUS-CDS, some authors have found that a double-pigtail plastic stent should be placed inside the metal stent to prevent stent migration. To prevent stent migration, standard SEMSs with a wide flange should be used, and stent shortening to a length of 60 mm may be preferable. Recently, a novel SEMS has been available. The lumen-apposing metal stent (LAMS) (NAGI Stent; Taewoong Medical Co., Seoul, Korea) is a 10.5-Fr delivery system and consists of a fully covered, 20-mm-long, 16-mm-diameter stent. The hot AXIOS stent (Xlumena, Inc., Mountain View, CA, USA) is a fully covered, 10-mm-diameter delivery system, with 10-mm-long braided stent with bilateral 20-mm-diameter anchor flanges. These novel SEMSs are mainly used for EUS-guided pseudocystic drainage and EUS-guided cholecystogastrostomy [8–10]. These SEMSs also seem useful for EUS-CDS, although clinical trials are needed to confirm their utility.

2.1.3 Clinical results

According to a recent meta-analysis including 572 patients [11], the pooled rate of all adverse events was 0.136 (95% CI, 0.097–0.188; P = 0.01) with moderate heterogeneity (I = 56.9), and pooled rates were 4.2% for cholangitis, 4.1% for bleeding, 3.7% for bile leakage, and 2.9% for perforation. On subgroup analysis, the pooled rate of adverse events with the use of lumen-apposing metal stents was 9.3% (95%CI, 4.8–17.3%). On the other hand, the rate of adverse events such as cholangitis, bleeding, and bile leakage was 13.4%.

2.2 EUS-guided HGS

2.2.1 Indications

EUS-HGS should be indicated for failed ERCP due to surgical anatomy or inaccessible ampulla of Vater, because adverse events such as stent migration can sometimes prove fatal. However, although EUS-CDS cannot be attempted in patients complicated with surgical anatomy, such as Roux-en-Y anastomosis or

malignant duodenal obstruction, EUS-HGS can be attempted because the access route of EUS-HGS is the stomach. Regarding biliary stricture sites, EUS-HGS may be challenging in case of hepatic hilum stricture because stent deployment is performed from the left intrahepatic bile duct. Therefore, the right hepatic bile duct cannot drain. As expanding indication, EUS-BD for right hepatic bile duct obstruction has been developed [12, 13]. Park et al. [12] reported that EUS-guided biliary access is successfully performed in antegrade bypass stenting (n = 2), antegrade transanastomotic stenting (n = 1), antegrade transanastomotic balloon dilation (n = 1), and the use of the cholangiogram as a roadmap (n = 1) among six patients with isolated right hepatic bile duct obstruction. We also conducted that EUS-BD was successfully performed using bridging method (n = 7) and locking stent method (n = 4) among 11 patients with right hepatic bile duct obstruction [13]. No severe adverse events were identified in either study. EUS-HGS has potential as indication for hepatic hilar stricture. However, because it is technically challenging, the right hepatic approach under EUS guidance should be performed for selected patients. Recently, Khashab et al. [14] reported a comparative evaluation of PTCD and EUS-BD in patients who were complicated with distal malignant biliary obstruction. According to this study, although the technical success rate was higher in the PTCD than in EUS-BD (100% vs. 86.4%, P = 0.007), clinical success and stent patency were not different. Rates of adverse event (70.6% vs. 18.2%, P < 0.001) and total charges were significantly higher in the PTCD ($9.072 ± 3.817 vs. $18.261 ± 16.021, P = 0.003). Therefore, their conclusion is that EUS-BD might be preferred if EUS-BD can be performed by experienced endoscopists. However, there are several limitations such as small number of patients, a single-center study, and a single operator. Therefore, to determine whether EUS-HGS or PTCD should be performed in a multicenter, prospective randomized controlled study is needed. The current indications for EUS-HGS are the following: (1) failed ERCP, (2) inaccessibility of the Vater due to surgical anatomy or duodenal obstruction caused by the tumor, and (3) contraindications for PTCD due to massive ascites and risk of self-tube removal. Compared with PTCD, metallic stent placement can be used in EUS-HGS in primary session. Therefore, EUS-HGS may be indicated even if a small amount of ascites is present in the access route. However, if massive ascites is present, preventing the formation of fistula between the stomach and liver, EUS-HGS is not indicated. The contraindications for EUS-HGS are the following: (1) massive ascites between the stomach and liver and (2) unresectable gastric cancer.

2.2.2 Technical tips

The EUS device is introduced into the stomach. Then, using counterclockwise rotation, the left hepatic lobe can be identified. A 19-G FNA needle may be better than a 22-G. A stiffer guidewire is inserted into the biliary tract through the EUS-fine needle aspiration (FNA) needle because fistula dilation is an important point to insert the stent delivery system compared with EUS-CDS. If segment 2 (B2) is punctured, because devices can be passed across the mediastinum, when puncturing from the esophagus, severe adverse events such as mediastinitis or pneumomediastinum may occur. Therefore, segment 3 (B3) should be initially punctured. There are two important points regarding the intrahepatic bile duct puncture. The first point is the angle of the bile duct, and the second point is the volume of the liver parenchyma. The bile duct that runs from the upper left to the lower right based on EUS imaging should be punctured to advance the guidewire toward the hepatic hilum. Furthermore, avoiding stent migration into the abdominal cavity requires a sufficient volume of liver parenchyma to obtain anchoring function, like PTCD procedure**.** Therefore, B3 is better as puncturing site. The next

step is guidewire insertion. During EUS-HGS, one of the most important procedures is the guidewire insertion. If the guidewire is introduced into the peripheral biliary tract, the next step may not be attempted. The biliary tract running from the upper left to the lower right on EUS imaging should be punctured to successfully advance the guidewire toward the hepatic hilum, as described in the above section. If the guidewire is advanced into the periphery of the biliary tract, the guidewire should be pulled, and then advance of the guidewire into the hepatic hilum should be attempted. However, during this procedure, the guidewire is sometimes kinked with the FNA needle. To avoid this adverse event, the liver impaction method appears clinically impactful [15]. Various types of guidewire are available. A 0.025-inch guidewire with a highly flexible tip, sufficient stiffness, and easy seeking ability is preferable for EUS-guided procedures. After the guidewire is inserted along with other devices, continued visualization of the other devices on EUS imaging is important during various EUS-guided procedures to fit the alignment. To perform stent deployment, the bile duct and stomach wall must be dilated. Various techniques for dilating a fistula have been reported to date [16–20]. A graded dilation technique using a dilator or a 4-mm balloon catheter is used by many authors according to previous studies. The mechanical dilator (6 to 10 Fr), balloon catheter (4–8 mm), and needle knife are mainly selected by many authors. Park et al. [16] described that, among the total of 57 patients who underwent EUS-BD, post-procedural adverse events such as bile peritonitis (n = 2), mild bleeding (n = 2), and self-limited pneumoperitoneum (n = 7) were observed. According to multivariate analysis, the use of a needle knife was the only risk factor for post-procedure adverse events of EUS-BD (P = 0.01, HR 12.4, 95%CI, 1.83–83.5). Therefore, their conclusion is that a needle knife should not be selected as a dilation device. To avoid this risk, an electrocautery dilator, which was coaxial with the guidewire, has been developed. Although this device is clinically useful as a dilation device, this device has disadvantages such as burning effect. When the bile duct is punctured while avoiding small vessels using color Doppler, bleeding can occur due to the burning effect of the electrocautery dilator. To reduce burning effects, a novel electrocautery dilator has become available in Japan (Fine 025; Medico's Hirata Inc., Japan, Osaka) [17]. Further study is needed to evaluate this device. On the other hand, a graded dilation technique using a balloon or mechanical dilator may be safe because burning effect does not occur. Park et al. [18] reported that graded dilation using a 4-Fr catheter and 6- or 7-Fr bougie dilator device is safe. In this study, technical success rate of EUS-CDS was high, with a low rate of adverse events. According to our previous report [19], we reported successful EUS-HGS using an ERCP catheter and a 4-mm balloon catheter without using electrocautery devices. This technique may be associated with a lower frequency of bleeding caused by the burning, although bile leakage might easily occur during graded dilation because procedure time is longer. Recently, novel techniques and dilation devices for EUS-BD have been reported. Paik et al. [20] reported a simplified fistula dilation technique. After the biliary tract was punctured using a 19-G FNA needle, direct insertion using a 4-mm balloon catheter was performed. In 28 patients, the technical success rate was 96% (27/28). In addition, early adverse events were not seen in any patients. We also described a simplified fistula dilation technique using a fine-gauge balloon catheter [21, 22]. As an even more novel technique, a one-step stent placement technique has been described [23]. According to this study, 32 patients, who were complicated with malignant biliary stricture, were enrolled. EUS-BD was performed using a novel metallic stent. The introducer for this novel stent has only a 3-Fr-tip-4-Fr tapered. The technical success rate of one-step stent deployment was 88% (14/16). In addition, the procedure time was short in the one-step stent placement group. The risk of bile

leakage may be increased, if procedure time is longer. In fact, in their reports, although significant differences were not seen, early adverse events were uncommon in the one-step dilation group compared with the graded dilation group (31.3% vs. 6.3%, P = 0.172). Although randomized, clinical trials and additional cases are needed to clarify which dilation technique or devices are more suitable in EUS-HGS, these techniques have potentials of decreasing the frequency of adverse events such as bile leakage. The final step is stent deployment. A fully covered self-expanding metal stent (FCSEMS) with strong radial force may be suitable for EUS-HGS compared with a plastic stent for the following reasons: (1) if a large fistula is created before inserting the stent delivery system, bile leakage from the gap between the stent and fistula the fistula is less likely; (2) longer stent patency may be obtained due to large diameter compared with plastic stent; and (3) a tamponade effect of stent expansion may occur if bleeding from the stomach wall is present. However, the following disadvantages are seen for FCSEMS: (1) the stent is expensive; (2) stent shortening must be considered during stent deployment, especially in the luminal portion to prevent stent migration into the abdominal cavity; and (3) side branches may be obstructed by covered site of the metal stent [24]. A novel metallic stent and several efforts to prevent stent migration have been recently reported. Some authors have described that a double-pigtail plastic stent can be placed inside the metal stent, when standard metallic stents are used. Prevention of stent dislocation requires sufficient stent length. We have also described that EUS-HGS can be safely performed using a partially covered metallic stent with long length [25]. More recently, Song et al. [26] described a preliminary study on a newly hybrid metal stent in EUS-BD procedure. The distal portion of this stent, which is 3.5-mm long, comprises silicone-covered nitinol wire to prevent bile leakage through the mesh. Also, anti-migration flaps are present proximal and distal to the covered site to prevent stent migration into the abdominal cavity. This novel stent, on the proximal site, has the uncovered site. This uncovered site is 1.5- to 5.5-mm long. This fact can prevent bile duct branch obstruction. In their study using this novel hybrid stent, EUS-HGS was successfully attempted for all 10 patients. In addition, no bile leakage or stent migration was seen in any patients. On the other hand, EUS-HGS using a newly designed plastic stent has been described by Umeda and Itoi et al. [27] that report using an 8-Fr single-pigtail plastic stent, which is a push-type stent that is usually not possible to retract (total length, 20 cm; effective length, 15 cm; four flanges). Also, the proximal end has a pigtail structure, and the distal end is strongly tapered. EUS-HGS using this plastic stent was successfully attempted in all 23 patients. Although bleeding or abdominal pain was seen in four patients (17.4%), no severe adverse events such as stent migration into the abdominal cavity or stent dislocation were observed during follow-up (median 5.0 months). Median stent patency was 4.0 months, and therefore, this result was clinically encouraging. However, as the author described in this report, additional long-term studies with a larger number of cases are needed to clarify the clinical benefit of using this stent for EUS-HGS. To prevent stent migration, technical tips for stent deployment are also extremely important. One of the consensus techniques in Japan is the intra-scope channel release technique [28]. The following steps were followed for stent release under the intra-scope channel technique. The stent delivery system was inserted into the confluence of B2 and B3. Next, stent release was performed from the intrahepatic bile duct to the hepatic parenchyma. Thereafter, the EUS scope was stabilized until the stent was deployed up to 1 cm within the EUS scope. The EUS scope was then withdrawn slightly while simultaneously pushing the stent delivery system. In that procedure, stent release was performed completely under endoscopic guidance (**Figures 4–6**).

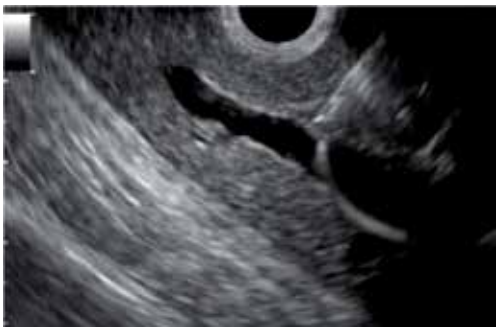

Figure 4.
The intrahepatic bile duct is punctured using 19-G needle from the stomach.

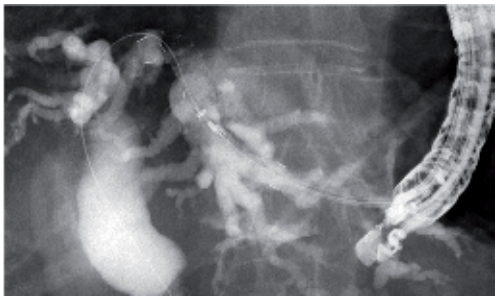

Figure 5.
The covered metal stent deployment is performed from the intrahepatic bile duct to the stomach.

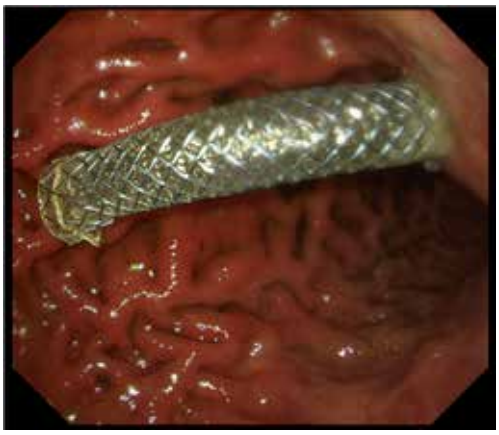

Figure 6.
The metal stent is placed in the stomach.

2.2.3 Clinical results

According to a recent meta-analysis of 686 patients [29], overall clinical success and technical success rates were, respectively, 84% (95%CI 80–88%) and 96% (95%CI, 93–98%) for EUS-HGS. On the other hand, in terms of technical results for EUS-HGS conducted by non-expert hands, the technical success rate was only 64.7% (22/34) [30]. This technique should therefore be performed in expert-assisted situations, and improvement of devices is warranted. The rate of adverse events including bile leakage, stent migration, bleeding, and peritonitis was relatively high (29%).

2.3 EUS-guided gallbladder drainage (GBD)

2.3.1 Indications

Compared with percutaneous transhepatic gallbladder drainage (PTGBD), one of the advantages of EUS-GBD is internal drainage. In addition, the procedure is technically simple compared with endoscopic retrograde gallbladder drainage (ETGBD). However, the results of long-term follow-up remain unclear, and there is still insufficient evidence on the performance of EUS-GBD as the first-line drainage technique. Current indications for EUS-GBD are thus as follows: (1) nonsurgical candidates with/without stone extraction, (2) as a bridge to surgical cholecystectomy, (3) conversion from PTGBD to EUS-GBD, (4) alternative to failed PTGBD/ETGBD, and (5) alternative to failed EUS-guided biliary drainage such as EUS-CDS or HGS [31].

2.3.2 Technical tips

The EUS probe is advanced into the stomach or duodenum to identify the gallbladder. The gallbladder neck is normally detected from the duodenal bulb, and the body or tail of the gallbladder is also detected via the stomach. No evidence of clinical differences between the use of these two sites has been found in previous reports. Tyberg et al. conducted a clinical study of differences between transgastric and transduodenal approaches regarding EUS-GBD [32]. In this study including a total of 42 patients, technical success was achieved in 92.6% (25/27) in transgastric approach group and in 100% in the transduodenal approach group. Adverse events were observed in four patients in the transgastric approach group (14.8%) and in five patients in the transduodenal approach group (33%). Therefore, they concluded that stent location was not a significant predictor of clinical failure ($P = 0.432$) or adverse events ($P = 0.289$). Also, Teoh et al. performed a comparative analysis of EUS-GBD from the antrum route or duodenum route [31]. Among a total of 59 patients, technical and clinical success rates were 94.4% (34/36) and 91.2% (31/34), respectively, among patients who underwent EUS-GBD from the antrum and 100% (23/23) and 95.7% (22/23) among patients who underwent EUS-GBD from the duodenum ($P = 0.52$ and 0.39). Overall adverse events also showed no significant difference between the two groups ($P = 0.64$). Endoscopists are thus free to select the site preferred for puncture. However, the duodenum may have less mobility compared with the stomach. This may result in less technically challenging and lower risks of both early and late stent migration with the transduodenal route. In addition, the frequency of food reflux into the gallbladder through the EUS-GBD stent may be lower when puncture is attempted via the duodenum compared with the stomach [33, 34]. On the other hand, EUS-GBD from the stomach may have several benefits. First, because the lumen is normally larger in the gallbladder body than in the gallbladder neck, puncturing the gallbladder through the stomach may be easy. In particular, the gallbladder body allows a greater lumen area to accommodate the internal flanges of the LAMS. Second, if serious complications such as perforation or stent migration occur, the consequences may be less serious because subsequent surgery is easier in patients who have undergone EUS-GBD from the stomach compared with from the duodenum. Endoscopists should thus be mindful of the characteristics of each site before performing EUS-GBD (**Figures 7** and **8**).

The next step is fistula dilation. According to previous reports [33, 35–42], a 6- or 7-Fr bougie, tapered catheter, and 4-mm balloon were the most commonly used devices for dilatation prior to insertion of drainage devices. If some resistance to passage of the stent delivery system is present, electrocautery dilation may be useful

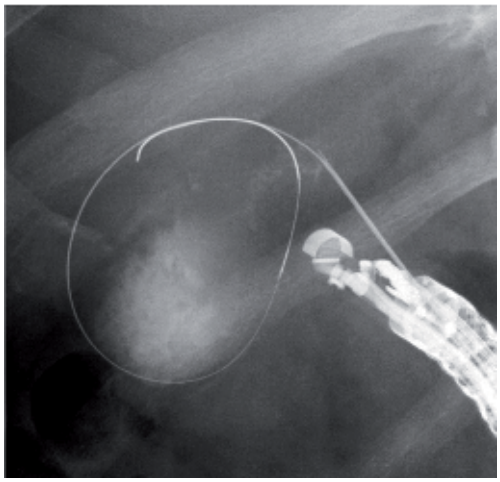

Figure 7.
The gallbladder is punctured using 19-G needle from the duodenum.

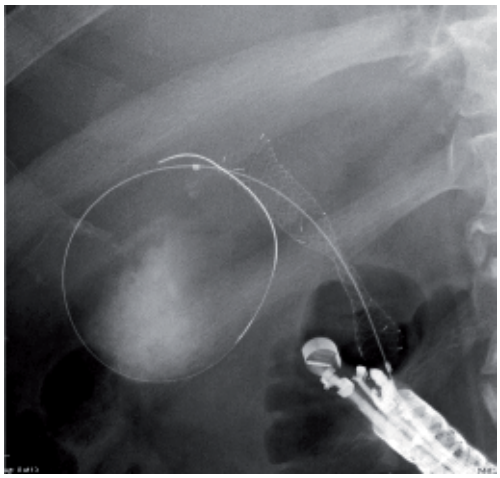

Figure 8.
The covered metal stent deployment is performed from the gallbladder to the duodenum.

according to previous reports. Bile leakage may occur as with other EUS-BD procedures, after this step and prior to stent deployment. In fact, the risk of bile leakage is frequently observed compared with EUS-HGS, because of the lack of a tamponade effect from the liver. As a result, dilation with one-step process may be preferred. Electrocautery dilation can certainly be performed regarding dilation of the fistula; however, it carries a risk of burns, which can in turn lead to bleeding. A dilation technique using a fine-gauge balloon catheter may be suitable from the perspective of preventing adverse events. However, since no evidence suggests which dilation devices should be used, a randomized controlled study among various dilation devices should be attempted.

Recently, the hot AXIOS stent with electrocautery-enhanced delivery system (Boston Scientific, Marlborough, MA, USA) has been developed. This stent is a through-the-scope LAMS mounted on a stent delivery system with an electrocautery wire at the distal tip. The electrocautery tip allows passage of the catheter into the gallbladder without the need for prior dilation of the tract by application of a pure cutting current. This fact may have clinical benefits, such as shortening of

the procedure time, reduced bile leakage during fistula dilation, and an improved technical success rate due to the single-step nature of the procedure. However, a previous retrospective study [31] showed no significant differences in technical success rates between hot and cold AXIOS [100% (10/10) vs. 95.9% (47/49), respectively; P = 1.00]. In addition, rates of adverse events were not significantly different [20% (2/10) vs. 34.7% (17/49), respectively; P = 0.48]. Since electrocautery dilation procedures may carry a risk of bleeding due to the potential for burns, a randomized controlled trial is needed to determine the superiority of hot AXIOS.

The next step is stent deployment. EUS-GBD has been performed using plastic stents. However, because stent deployment in EUS-GBD is performed from the gallbladder to the stomach or duodenum through the abdominal cavity, no tamponade effect arises such as due to the hepatic parenchyma, as seen with EUS-HGS. Bile leakage can therefore occur due to the gap between the fistula and plastic stent. In addition, stent patency is shorter compared with the covered SEMS (cSEMS). Jang et al. reported a comparative trial between EUS-GBD and PTGBD for acute cholecystitis [38]. In a study including 29 patients, who underwent EUS-GBD, laparoscopic cholecystectomy was performed in 23 patients (79.3%). None of the patients initially underwent open cholecystectomy, although 2 of the 23 patients (8.7%) in the EUS-GBD group and 3 of 26 patients (11.5%) in the PTGBD group required conversion to open cholecystectomy (P = 0.99). They also described that EUS-GBD did not cause severe inflammation or adhesions to the tissues surrounding the gallbladder and laparoscopic cholecystectomy could be safely attempted following EUS-GBD using plastic stents or endoscopic naso-gallbladder drainage (ENGBD) without an increase in technical difficulty as compared with PTGBD. Therefore, the use of a plastic stent should first be considered, if the patient is likely to undergo cholecystectomy in the future. Recently, cSEMS has been used as the drainage device for EUS-GBD instead of plastic stents in patients who are not good candidates for surgery due to other severe organ failure or the presence of advanced malignancy. The cSEMS is useful as compared with plastic stents, since self-expanding stents prevent bile leakage and are associated with longer stent patency. However, because of weak flanges, the standard tubular cSEMS has a risk of stent migration after stent deployment. As a method to prevent stent migration, several authors have described combination usage of a double-pigtail plastic stent or ENGBD and cSEMS [33, 39, 40, 42]. Indeed, stent migration has not been observed in EUS-GBD cases using this technique. And if the cSEMS migrates, the pigtail plastic stent remains in place from the gallbladder to the gastrointestinal lumen. This maintains fistula patency, allowing re-intervention.

Khan et al. undertook a systematic review of endoscopic gallbladder drainage [43]. In this review, subgroup analysis was attempted regarding the kinds of stent in the EUS-GBD. According to their results, EUS-GBD using SEMS is less likely to cause adverse events than EUS-GBD using a plastic stent or ENGBD. Therefore, if the patient is unlikely to undergo future cholecystectomy, EUS-GBD using SEMS might be preferable to prevent adverse events.

LAMS deployment has been reported in EUS-guided transluminal interventions, including EUS-guided pancreatic fluid collection [44], EUS-guided bile duct drainage [45], and EUS-guided gastroenterostomy [46]. LAMS has several benefits compared with SEMS. LAMS has a larger inner diameter, allowing better drainage. Also, the unique design such as the form of anchoring flanges may play an important role in preventing stent migration into both abdominal and luminal portions. Finally, a standard endoscope can be passed into the gallbladder lumen through the LAMS after LAMS deployment. In cases requiring EUS-guided intervention for walled-off necrosis [47], the use of SEMS or LAMS is superior to plastic stents in terms of overall treatment efficacy. The number of procedures required was

significantly lower with LAMS compared with SEMS or plastic stent placement. However, since high-quality evidence is lacking regarding the use of LAMS in EUS-GBD procedures, comparative studies between LAMS and other drainage devices for EUS-GBD are needed.

Finally, this chapter referred to our previous papers [48–50].

3. Conclusions

EUS-guided biliary drainage has clinical impact as alternative drainage technique. If more evidences are available, indications of this technique will be spread.

Conflict of interest

The authors declare no conflict of interest.

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Chapter 6

Stents in Gastrointestinal Diseases

Eduardo Aimore Bonin, Bruno Verschoor, Fernanda Hoffmann Silva, Kelly Cristina Vieira and Susan Kakitani Takata

Abstract

Stent is a medical device originally designed for recanalization and/or sealing of any obstructing or leaking lesion. In gastroenterology, it has a major role in recanalization of gastrointestinal (GI) tumors and postoperative leak sealing. Among several materials and models used in stent manufacturing, self-expandable metallic stents (SEMS) are the most common used stents. Over the years, SEMS has evolved into a standard of care medical device in several oncological conditions, such as advanced esophageal cancer. Other potential applications are drug-eluting devices, scar tissue modeling for benign conditions, and GI tract drainage/anastomosis. The aim of this chapter is to review the most common GI stent models and its indications in gastrointestinal diseases.

Keywords: stent, gastroenterology, endoscopy

1. Introduction

Stent is an artificial tube graft defined as "a short narrow metal or plastic tube often in the form of a mesh that is inserted into the lumen of an anatomical vessel (such as an artery or a bile duct) especially to keep a previously blocked passageway open" [1]. Stenting is a medical procedure for placing a stent. It should be differentiated from shunting, when a tube conduit is used for allowing flow between two previous unconnected structures. Splint refers to a rod- or a cast-like shell device placed outside any desired organ to make it stable. An **endoprosthesis** refers to a stent inserted into the lumen (endoluminal), which can be inside the gastrointestinal (GI) visceral tract (esophagus, stomach, duodenum, intestinal, colorectal), or into a blood or biliary vessel (endovascular or endobiliary, respectively).

The term stent is an eponym of a British dentist, Charles T. Stent (1807–1885), who developed a compound originally used for dental impressions [2]. He developed a formula made of gutta-percha, a natural latex produced from tropical trees native to Southeast Asia and Northern Australia. The etymological origin of "stent" as a term in surgery started with Dr. Johannes F. Esser in 1917, which used Stent's dental compound as a mold for bridging skin grafts [2]. The term stent became popular among surgeons for such applications and was then later used to define any surgical mold for bridging tissues until a healing process has taken place, as in 1954, when a polyethylene tube was described by Drs. Remine and Grindlay as "to act as a stent for the anastomosis" in experimental biliary surgery [2].

In gastroenterology, **gastrointestinal stents** have been originally used to treat obstructed cancer in the GI tract. From early modern medicine in the nineteenth century until nowadays, GI tract cancer or luminal palliation has always been a huge challenge for surgeons and physicians. In esophageal cancer, for example, nonsurgical attempts to relieve dysphagia and starvation from the early to mid-1800s were esophageal dilatation or placement of an esophageal gumlike, rubber-made tube. The esophageal tube was passed through the mouth or nose across the tumor, acting as a feeding tube, with no effect on dysphagia [3]. These early esophageal tubes ultimately gave place to flexible polyethylene or silicone nasogastric feeding tubes used today. It was a matter of time for physicians to come out with a solution involving an artificial tube that could fit across the tumor and relieve dysphagia. **The first successful esophageal stenting procedure** has been credited to Sir Charters James Symonds in 1885 [4], who developed an esophageal semirigid tube with a funnel attached to a silk suture to treat malignant esophageal tumors. This tube was orally and blindly inserted, and the suture was brought out from the mouth and attached to the patient's ear. Later in the 1920s–1930s, a stent introducer over a guide-wire technique was developed to increase safety and facilitate stent insertion. After further technical developments with the aid of a flexible endoscope, several materials were used to increase softness. Gumlike or black rubber tubes gave place to tubes made of latex or silicone (the Celestin or Atkinson esophageal tube) or also polyvinyl, which all became popular in the 1960s–1980s [5]. Although being the best palliation measure at that time, avoiding surgery, these tubes were associated to high-risk complications, such as esophageal perforation. As they were semirigid, their passage through a narrow friable lumen required prior dilatation. To overcome this problem, a self-expandable tube would be the solution. **The first self-expandable metal stent (SEMS) models** were stainless steel coil springs [5]. Their design was similar to endovascular stent models produced in the 1980s. For being developed for gastrointestinal (GI) tract use, they were inserted orally using an introducer and a fixation thread to tie them down into a compressed shape around an introducer or a gastroscope. Once positioned across the tumor, the stent was released to expand to its original shape using a novel feature that is producing significantly more radial force expansion instead of mostly axial. These stents became popular compared to their rigid plastic stent counterparts, especially after a first randomized study favoring SEMS over semirigid plastic stents for esophageal cancer [6]. Although being more expensive, they resulted in a higher cost-effectiveness due to their lower complication rates, lower hospitalization rate, and lower mortality. These stents gained significant improvement in design over time: a mesh-like stent to increase flexibility, while retaining a good radial expansion, a longer body, and a proximal flare at its end to prevent migration, and a synthetic covering film to prevent tumor ingrowth.

The third-generation SEMS were made of nitinol (an acronym for nickel titanium Naval Ordnance Laboratories) [5], a so-called memory-shape alloy; once deformed it returns to its pre-deformed shape when heated. This results in a more flexible stent that can fit into a reduced caliber introducer/delivery system. Their first models had a higher foreshortening (25–40%) and a lower radial expansion compared to prior stainless steel models. As they gained later refinements in stent design and metal alloy, these stents are capable of being passed through a working channel of an endoscope to reach deeper parts of the gastrointestinal tract, reaching, for example, the proximal biliary tree, pancreatic duct, and proximal colon. Apart from other models made of self-expandable plastic or biodegradable material, nowadays SEMS remains the standard of care in most gastrointestinal stent applications.

2. Stent types

There are several different gastrointestinal stent shapes and materials (**Figure 1**), and there is no ideal stent type to date to fit all expectations.

Each distinguished shape and material have several physical properties, which enable a distinct function, ultimately influencing clinical outcome and stent choice (**Figure 2**) [7].

A **laser-cut stent** is a seamless metal tube (i.e., nitinol) being cut into several mesh stent patterns, which differs from a **handmade woven, wire-braided or**

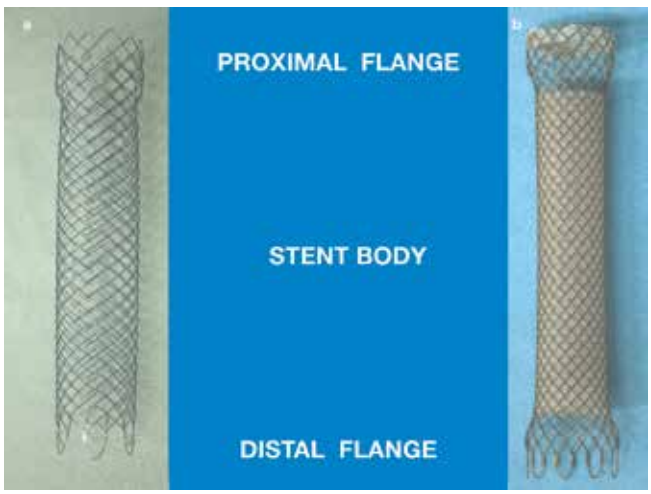

Figure 1.
A typical self-expandable metal stent. One is an uncovered colonic enteral stent (a) and another is a partially covered (silicone covering) esophageal stent (b). Its proximal flange has a larger caliber than its body, to ensure anchoring and prevent migration. Also, a curved wire flange instead of sharp struts is designed to prevent stent piercing into tissue. Picture from Eduardo A. Bonin.

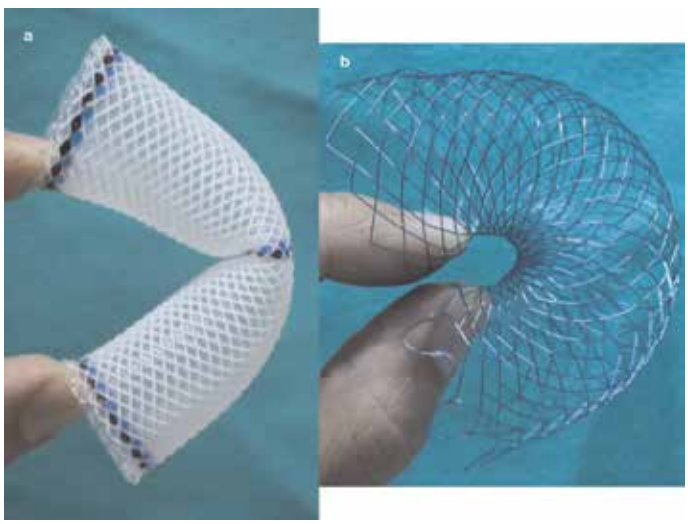

Figure 2.
Self-expandable stents, one totally made of plastic (silicone) (a), no longer commercially available for the gastrointestinal tract. The other is a multi-wire braided-type metal (nitinol), uncovered stent (b). Note the "kinking effect" of the plastic stent when compressed (a), where the metal stent remains patent, with some foreshortening. Picture from Eduardo A. Bonin.

knitted stent configuration (**Figure 2**). A laser-cut stent has higher radial force and a lower foreshortening property, thus being more predictable when deployed. This can be useful in a straight narrow short lumen such as the biliary tree, a coronary vessel, or the bronchial tree [8]. They also have a higher radial force and higher longitudinal force. For some laser-cut stents with pointed struts at its distal end, longitudinal force might induce tissue reaction from direct piercing [8]. Wire-braided or knitted stents are more flexible and have a greater conformability (less "kinking effect") when deployed (**Figure 2**). They also allow placing another stent across its mesh, as required in some specific anatomic structures such as the biliary tree.

The most common stent types used in gastroenterology are made of semi-rigid, plastic tubes (polyethylene) or SEMS (nitinol or stainless steel mesh). Semirigid plastic tube stents are currently being used exclusively in the biliary tree and the pancreas [9]. They are commonly made of polyethylene, a softer plastic with a better molding capability compared to polyurethane. They remain a first-line and cost-effective method compared to fully covered SEMS in most biliopancreatic benign conditions (biliary stricture, fistula) with a lower migration rate, however having higher occlusion rates. Fully covered SEMS are currently being investigated for refractory benign biliary strictures (**Table 5**). Semirigid, plastic tubes are no longer used in the gastrointestinal tract (esophagus, stomach, or colorectal).

A typical **SEMS** design has a cylinder-shape body part, which is used to cover or seal the desired area, and a flare (funnel-like shape) at one or both extremities (**Figure 1**). Self-expandable plastic stents (SEPS) are another version of SEMS in terms of material used. SEMS can be found as uncovered or partially and totally covered using a synthetic covering film such as polyethylene or silicone (**Figure 1**).

Biodegradable stents and drug-eluting stents are other models under investigation. **Biodegradable stents** are made of biodegradable material (i.e., polyesters, polycarbonates, bacterial-derived polymers, and corrodible metals), mostly used in coronary artery disease. In gastroenterology, these stents are particularly useful in benign conditions, where a metallic stent would be incorporated to tissue over time, becoming very difficult to remove once achieving a stable luminal patency. Several models have been tested in clinical trials, and none has proved a consistent clinical result in terms of luminal patency. **Drug-eluting stents** are capable of maintaining patency not only from radial expansion but also from drug delivery directly to tissue, reducing its occlusion rates. These stents are very popular in cardiology, where they are superior to traditional bare stents to prevent coronary artery re-occlusion from endothelial intimal proliferation. In gastroenterology, they have been used in malignant disease to prevent tumor ingrowth and overgrowth. Despite the use of covered SEMS, its synthetic covering membrane is destroyed over time by hydrolysis and oxidation from gastrointestinal contents. Chemotherapeutic antitumoral agents, such as paclitaxel, have been initially tested with no proven benefit over the standard fully covered SEMS. For hydrophilic agents such as gemcitabine, a slow-release surface-stabilizing substance pullulan acetate has been added to increase optimal local drug release. Five-fluorouracil (5-FU) has also being tested as an antiproliferative agent for local tumor control in esophageal and biliopancreatic cancer [10]. Although promising, most of these stents are still in the experimental field, with scarce clinical experience. One major concern about these stents is local drug delivery causing injury to adjacent tissue and distant organ toxicity due to systemic exposure. Setting an appropriate drug concentration and release will enable an optimal local drug distribution to reach the desired effect.

3. A typical SEMS placement procedure in the gastrointestinal tract

A gastrointestinal stenting procedure usually requires the aid of an endoscope under radiological (fluoroscopy) guidance or at least one of these techniques. The procedure can be performed even in high-risk patients, with or without general anesthesia. Stent placement requires a special training and is reserved for interventional radiologists or interventional endoscopy gastroenterologists or surgeons. For SEMS placement there is an introducer system, in which the stent is compressed against a guiding catheter using an outer catheter sheath (**Figure 3**) or a thread suture (older models).

The procedure always requires a guide wire, with stiffness enough to avoid kinking, especially for passing a bulky fully covered large SEMS. For such stents a dilation procedure may be required using the smallest caliber dilation possible to avoid perforation. Fortunately, introducer systems are becoming thinner over time to facilitate insertion. Those are commonly used for intestinal and biliary stents. The stent and introducer system (**Figure 3**) is advanced over the guide wire and placed across the desired area. The stent is then deployed pulling back the outer catheter sheath (or advancing the outer catheter sheath, for a few models), under endoscopic or radiological guidance. The over-the-wire (OTW) technique refers to placing a stent over a guide wire having an endoscope alongside to ensure proper placement, with or without radiological guidance. The through-the-scope (TTS) technique refers to placing the stent over a guide wire using the working channel of an endoscope (**Figure 3**). Alternatively, one may compress the stent over an endoscope using sutures and release it at difficult-to-reach proximal portions of the gastrointestinal tract (over-the-scope technique) [11]. Technical issues can be related to a poor preclinical evaluation, lack of patient information consent, wrong stent choice, and lack of accessories/logistics [12].

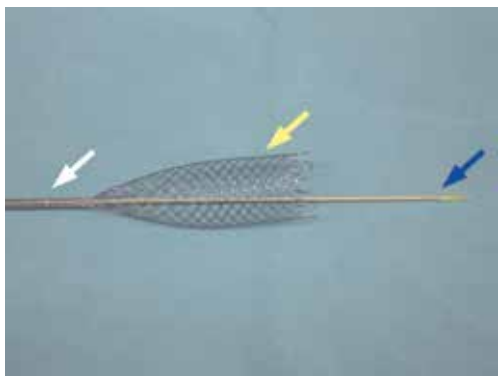

Figure 3.
A typical catheter-based self-expandable metal stent (SEMS) delivery system. The outer catheter has been pulled back to open the stent (white arrow). This can be done under radiological or endoscopic guidance. Note the SEMS being partially deployed (yellow arrow). The blue arrow depicts the proximal part of the delivery system, which is facing the distal flange of the SEMS (for duodenal and esophageal models). Note some foreshortening of the SEMS while being deployed (distance between the yellow and blue arrows). For biliary and colonic stents, the proximal flange is facing the proximal part of the catheter delivery system. Picture from Eduardo A. Bonin.

4. Stent-related issues

Nowadays, a huge effort in stent design is to overcome the most common stent-related issues: migration, stent-related perforation, and stent occlusion.

Anchoring measures to prevent stent migration: the most popular anchoring measure is having a flange at its proximal end to anchor it against a more elastic, healthy GI tract wall proximal to the tumor. Using a barbed proximal end, similar as found in plastic tube stents, has the same principle. An **uncovered stent** (**Figure 1**) has a lower migration rate compared to a covered stent because it becomes fixed and embedded to tissue over time due to pressure necrosis. However, this poses a special problem for removing it, which is required in benign conditions. **Partially covered stents** (**Figure 1**) are stents covered only at the body of the stent, leaving its proximal end to embed into tissue. They are very popular for malignant esophageal and biliopancreatic cancer, but again, there is a problem in removing the stent when used in benign conditions. Other measures are stent fixation using an endoscopic clip (**Figure 5**) or using an endoscopic suturing device [13] or passing a temporary suture thread at its proximal end, coming out from a nostril and fixated at the ear (**Figure 4**). A double-layer stent (a fully covered stent with an outer uncovered mesh layer) has also been proposed (**Figure 4**). Lumen-apposing stents are fully covered SEMS with a larger flange that allows transluminal drainage procedures (**Figure 8**).

Stent-related perforation occurs due to gastrointestinal wall pressure necrosis due to stent compression, usually occurring at the stent's distal end. Perforation can be devastating and is more likely to occur when there is more angulation (surgically altered anatomy or the colon). More flexible and longer stents are less likely to have this issue, having in mind to avoid placing a short and/or more rigid or self-expandable plastic stent at any sharp angulation.

Stent occlusion may occur from tumor ingrowth or overgrowth and/or accumulation of debris and bacterial biofilm deposit. Tumor overgrowth corresponds to

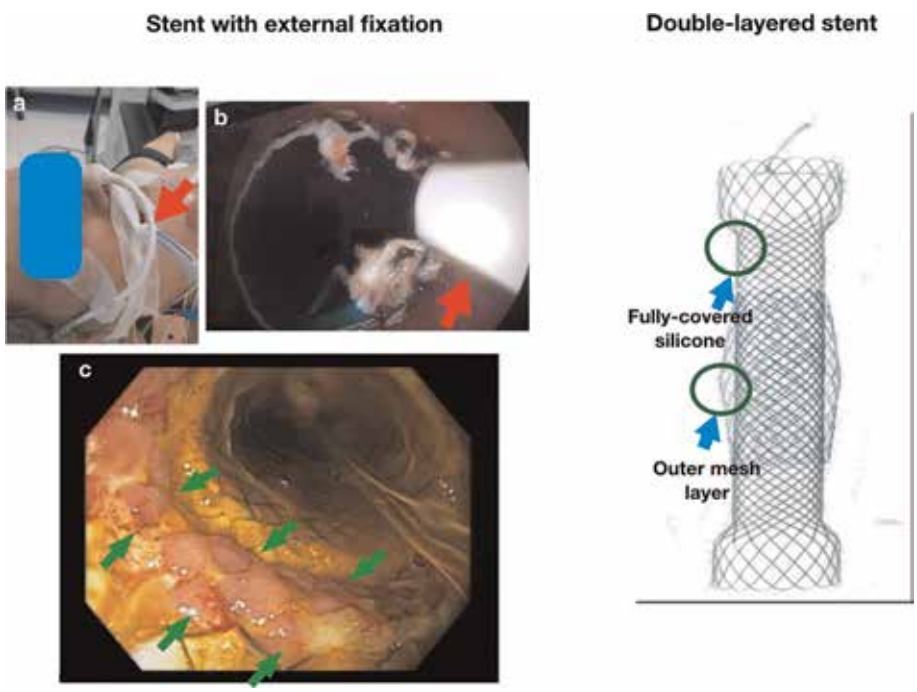

Figure 4.
Anchoring methods for stenting. A suture thread passed at the proximal flange can be used to anchor the stent at the level of the nostril (a, b, c, red arrows). Using a near-fully covered stent with a short uncovered line at the proximal flange allows ingrowth of granulating tissue to prevent migration (c, green arrows). A double-layer stent is a fully covered stent with an outer mesh layer to prevent migration (picture modified from www.stent.net.com).

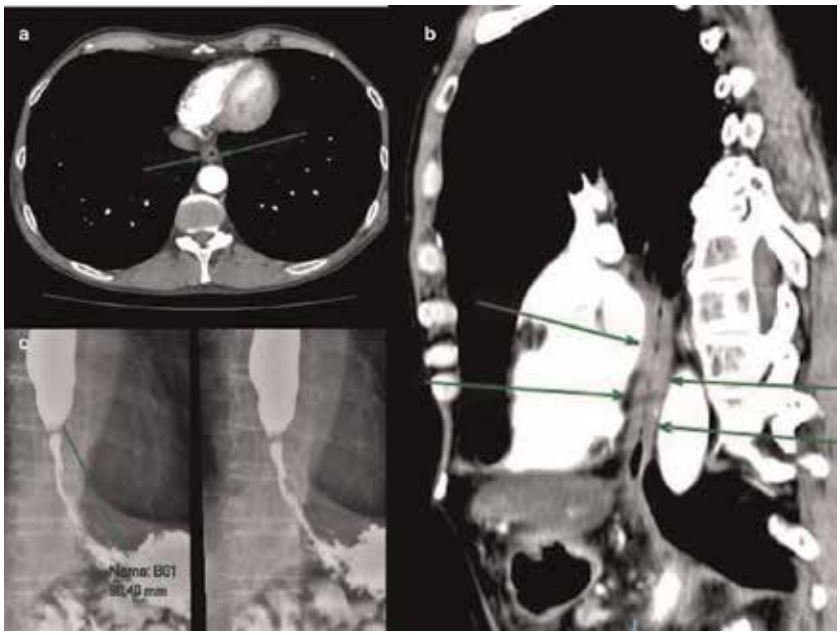

Figure 5.
A 65-year-old male with advanced mid-distal esophageal cancer treated with chemoradiation. He developed a liver metastasis and an extensive esophageal stenosis (a–c), refractory to dilatation. Because of dysphagia and an ongoing, non-curable disease, it was decided for esophageal stenting. Picture from Eduardo A. Bonin.

tumor growth at any of both ends of a stent. This is avoided by covering the tumor at least 2 cm away from any of both ends. Tumor ingrowth corresponds to tumor growing within the stent mesh. This has been largely supervened using a covering film (silicone, polyethylene, polyvinyl). Larger caliber stents and stents with a good radius force expansion are associated to a larger fluid flow, thus a lower risk of occlusion.

5. Stents in gastrointestinal diseases

In clinical practice, stents are being used for **gastrointestinal tract tumor palliation** (luminal patency maintenance, luminal recanalization, tunneling), **gastrointestinal bleeding** (luminal vessel compression), **gastrointestinal perforation or leak sealing** (gastrointestinal fistula sealing), and **gastrointestinal bypass or anastomosis** (gastrointestinal transluminal drainage).

For each stent application, there are several technical and clinical issues to be assessed. **Technical success** refers to a successful stent deployment across the GI tract for a specific function (tumor palliation, compression, or anastomosis). Generally speaking, a successfully deployed stent should remain in the desired position and ideally expanded to its full radial force until up to 48 hours after deployment. **Clinical success** refers to achieving a desired clinical endpoint (i.e., relief of dysphagia, biliary decompression, fistula sealing) from the first 3–30 days (early) or 3 months and beyond (later) after stent deployment. A **bridging stent** refers to a stent used as a temporary measure for GI tract decompression, as in obstructed colon cancer patients to avoid colostomy. Since stents are commonly used for palliation of end-of-life cancer patients, **quality of life** is also a major concern. **Cost-effectiveness** refers to evaluation of cost of the device and procedure, complication, hospitalization, and mortality rates compared to other available

Level of evidence	
A. High-quality evidence	Further research is unlikely to change our confidence in the estimate of effect. Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies
B. Moderate-quality evidence	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or very strong evidence from observational studies
C. Low-quality evidence	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws, indirect evidence, or expert consensus
Strength of recommendation	
1. Strong recommendation	Recommendation can apply to most patients in most circumstances.
2. Weak recommendation	The best action may differ depending on the circumstances or patient or society values. Other alternatives may be equally reasonable

RCT, randomized controlled trial.

Table 1.
Level of evidence and strength of recommendation (extracted from [14]).

techniques in terms of clinical success and quality of life. SEMS are often more cost-effective than traditional or laparoscopic surgery for palliation of cancer in high-risk patients.

GI stenting is one of many nonsurgical methods to achieve palliation of gastrointestinal cancer. Stents are more popular compared to other technologies for upper GI luminal recanalization/tunneling-ablation such as Nd:YAG laser ablation, argon plasma coagulation, or brachytherapy because it is the first-line recommended method [14] and it is an affordable single device with high technical success rates (approaching 90%) and no need for specific or expensive, dedicated equipment. For its widespread use, it is the most common nonsurgical palliation technique used for GI tract cancer worldwide. There are several recommendation guidelines for GI stenting from Western and Eastern surgical and gastrointestinal endoscopy societies based on evidence medicine (**Table 1**) [14]. For this present chapter, we have selected the most recently published guidelines.

6. Indications

6.1 Gastrointestinal cancer

Stenting is a first-line approach to esophageal cancer palliation [15] (**Table 2**, **Figures 5** and **6**).

Initial historical attempts to relieve dysphagia and alleviate starvation were esophageal dilatation and the use of an esophageal catheter-like tube. This first measure is temporary, unsuccessful over time due to tumor growth and associated to high risk of perforation. It can be still used as an initial approach in areas with no access to more advanced resources. The main, absolute indication for esophageal stenting is tracheoesophageal cancer fistula. Esophageal dysphagia is another major indication; however, it has been balanced with esophageal brachytherapy, when available. Esophageal stenting leads to a better quality of life mainly because of

1. Placement of partially or fully covered self-expandable metal stents (SEMS) is recommended for palliative treatment of malignant dysphagia over laser therapy, photodynamic therapy, and esophageal bypass (strong recommendation, high-quality evidence)
2. For patients with longer life expectancy, brachytherapy is recommended as a valid alternative or in addition to stenting in esophageal cancer patients with malignant dysphagia. Brachytherapy may provide a survival advantage and possibly a better quality of life compared to SEMS placement alone (strong recommendation, high-quality evidence)
3. SEMS placement is recommended as the preferred treatment for sealing malignant tracheoesophageal or bronchoesophageal fistula (strong recommendation, low-quality evidence)
4. The use of concurrent external radiotherapy and esophageal stent treatment is not recommended. SEMS placement is also not recommended as a bridge to surgery or prior to preoperative chemoradiotherapy. It is associated with a high incidence of adverse events, and alternative satisfactory options such as placement of a feeding tube are available (strong recommendation, low-quality evidence)

Table 2.
Recommendations for stenting in esophageal cancer (modified from [15]).

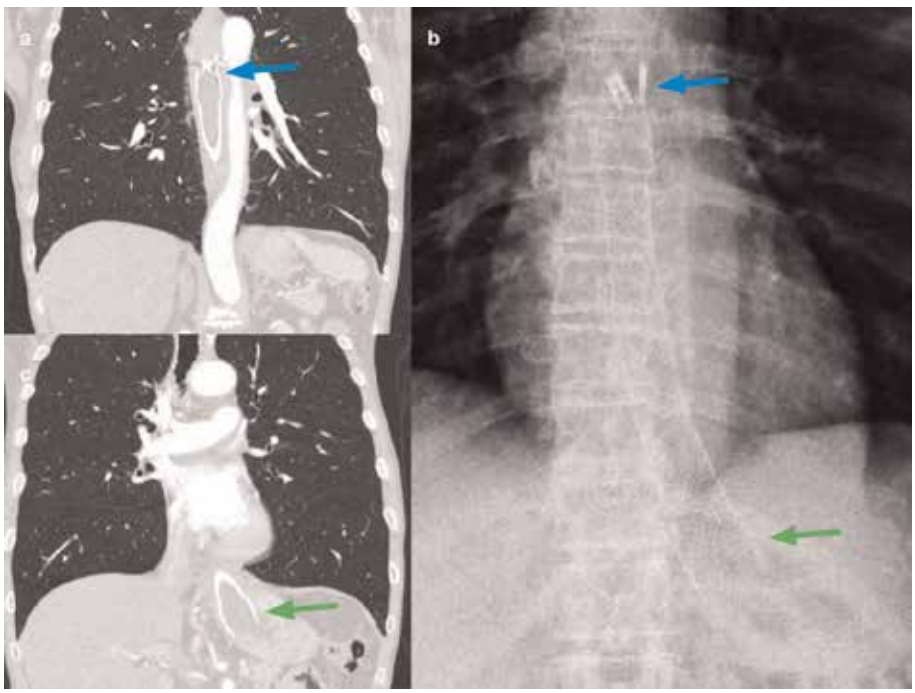

Figure 6.
The same patient as in ***Figure 5****. A 23 mm/12 cm partially covered self-expandable metal stent was placed covering the stenosis. The stent migrated distally 2 days after the procedure, which required repositioning. The stent was then fixed with clips at its proximal end (a, b, blue arrows). The patient resumed oral diet, and the stent remained in place, with its distal end at the level of the cardia (b, c, green arrows). Picture from Eduardo A. Bonin.*

relief of dysphagia. It also helps in patient's nutritional condition, but this should not be highly expected. The clinical success rates for dysphagia are 80–95%, with a median duration of esophageal stent patency being reported as 94% at 4 weeks, 78% at 3 months, and 67% at 6 months [16]. Recurrent obstruction occurs in 30% of patients, and migration rate is more common for covered stents (10–25%) than uncovered stents (2–5%). Stent placement can be considered as a temporary/bridge measure for those who have severe dysphagia before radio- or chemotherapy (neoadjuvant therapy). However, the stent has to be removed after a few weeks,

and a high migration risk is expected once the tumor responds and reduces its size from treatment. Thus, the cost-benefit of a bridging stent for esophageal cancer remains controversial. Several **anti-reflux in-stent valve mechanisms** have been used for preventing gastroesophageal reflux in distal esophageal tumors; however, it seems not to add any advantage over standard esophageal SEMS [17].

Chemotherapy and radiotherapy have evolved over the years into better quality of life scores in palliation of esophageal cancer patients, since many of them are spared from dysphagia for several months on the course of disease. The correct timing for esophageal stent insertion is crucial for a better clinical outcome. It is usually considered when there is an ongoing disease and dysphagia despite optimal previous chemotherapy and radiotherapy treatment. Esophageal stenting with SEMS is superior to any other surgical palliation method for any given patient. It is also superior to gastrostomy for nutritional therapy in advanced cancer patients. Combinations of brachytherapy with SEMS are an interesting approach due to a reduced requirement for re-interventions [18].

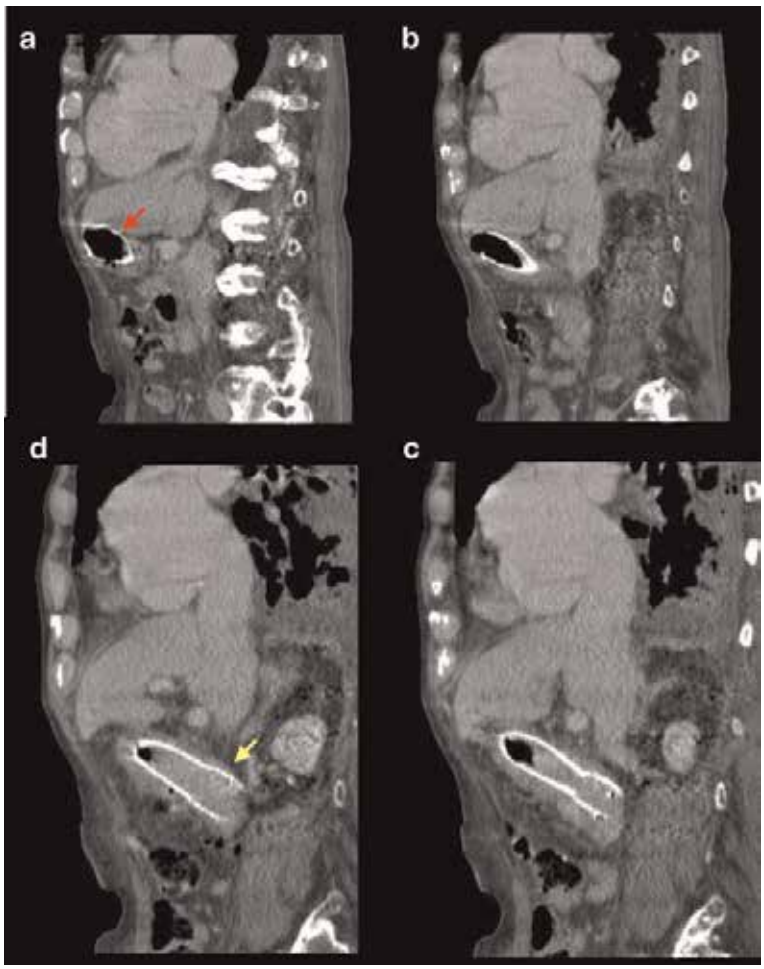

Figure 7.
A 90-year-old male with gastric outlet obstruction due to advanced gastric (antral) cancer. He was not clinically fit for a surgical intervention. A duodenal stent was inserted endoscopically. He was able to eat per mouth until he deceased 6 months later because of advanced cancer and pneumonia. The red arrow depicts the proximal flange, located at the antrum (a, b). The distal flange is at the duodenum (c, d, yellow arrow). Picture from Eduardo A. Bonin.

Gastroduodenal outlet obstruction (GOO) may rise from a locally advanced gastric, duodenal, or pancreatic cancer. It occurs in up to 20% of pancreatic cancer patients and is associated to recurrent vomiting, severe weight loss, and malnutrition. This condition is associated to a poor prognosis, with a 3–4 month average life expectancy. Stent placement should be considered for palliation of such patients, especially those who are not fit for surgery or have metastatic cancer (**Figure 7**).

Patients with pancreatic cancer and a larger life expectancy have always the option for a surgical bypass, which nowadays is achieved using minimally invasive laparoscopic techniques. Surgical bypass appears to offer a longer luminal patency compared to stents for patients with GOO with a life expectation of more than 2 months [19]. Patients with locally advanced gastric cancer who are fit for surgery can be considered for gastric resection (partial gastrectomy) as a palliation method [20], since it treats the obstruction and also reduces the chance of tumor bleeding. Although peritoneal disease (carcinomatosis) is considered a relative contraindication to SEMS placement for GOO given the risk of multifocal obstruction, this procedure seems reasonable in such advanced gastric cancer patients [21].

For malignant biliopancreatic diseases, SEMS are preferred over traditional plastic tube stents due to its better cost-effectiveness (lower occlusion rates) [22]. This applies to biliary obstruction in pancreatic cancer and biliary tract cancer. Apart from some evidence-based recommendations [23] (**Table 3**), there are several other clinical aspects in biliary and pancreatic stenting that are beyond the scope of this book chapter.

In **colorectal cancer, acute colonic obstruction** represents a major complication, since it requires prompt intervention because of the risk of colonic necrosis and perforation. It is the primary symptom for 10–30% of patients with colorectal cancer. Others may develop colonic obstruction under their course of any nonsurgical adjuvant therapy. Emergency surgery for an acute obstructed colonic cancer is associated with a morbidity rate of 32–64% and mortality rate of 15–34% [24].

1. Routine preoperative biliary drainage is not recommended in patients with malignant extrahepatic biliary obstruction; preoperative biliary drainage should be reserved for patients with cholangitis, severe symptomatic jaundice (e.g., intense pruritus), or delayed surgery or before neoadjuvant chemotherapy in jaundiced patients (strong recommendation, moderate-quality evidence)
2. Endoscopic placement of a 10 mm diameter self-expandable metal stent (SEMS) is recommended for preoperative biliary drainage of malignant extrahepatic biliary obstruction (strong recommendation, moderate-quality evidence)
3. SEMS insertion is recommended for palliative drainage of extrahepatic malignant biliary obstruction (strong recommendation, high-quality evidence)
4. Insertion of uncovered SEMS is not recommended for the drainage of extrahepatic biliary obstruction of unconfirmed etiology (strong recommendation, low-quality evidence)
5. Routine preoperative biliary drainage is not recommended in patients with malignant hilar obstruction (weak recommendation, low-quality evidence)
6. Uncovered SEMS is recommended for palliative drainage of malignant hilar obstruction (strong recommendation, moderate-quality evidence)
7. Temporary insertion of multiple plastic stents or of a fully covered SEMS is recommended for treatment of benign biliary strictures (strong recommendation, moderate-quality evidence)
8. Endoscopic placement of plastic stent(s) is recommended to treat bile duct leaks that are not due to transection of the common bile duct or common hepatic duct (strong recommendation, moderate-quality evidence)

Table 3.
Recommendations for stenting in biliopancreatic diseases (modified from [23]).

1. Prophylactic colonic stent placement is not recommended. Colonic stenting should be reserved for patients with clinical symptoms and imaging evidence of malignant large-bowel obstruction, without signs of perforation (strong recommendation, low-quality evidence)
2. Colonic SEMS placement as a bridge to elective surgery is not recommended as a standard treatment of symptomatic left-sided malignant colonic obstruction (strong recommendation, high-quality evidence)
3. For patients with potentially curable but obstructing left-sided colonic cancer, stent placement may be considered as an alternative to emergency surgery in those who have an increased risk of postoperative mortality, i.e., American Society of Anesthesiologists (ASA) physical status ≥ III and/or age > 70 years (weak recommendation, low-quality evidence)
4. SEMS placement is recommended as the preferred treatment for palliation of malignant colonic obstruction (strong recommendation, high-quality evidence), except in patients treated or considered for treatment with antiangiogenic drugs (e.g., bevacizumab) (strong recommendation, low-quality evidence)

Table 4.
Recommendations for stenting in colorectal cancer (modified from [26]).

Stenting of obstructed colon cancer is mainly used for palliation in advanced left-sided high-risk colonic cancer patients (**Table 4**) [25, 26], since it avoids a definitive stoma, with a potential increase in quality of life. It can also be used as an alternative temporary decompression measure as a bridge before surgical resection, as it may prevent the need of a stoma (colostomy) in 30–40% of cases. However, there are some concerns regarding its safety and long-term oncological issues [27]. Colonic stenting is associated to technical and clinical success rate approaching 90%. It has an overall adverse event rate of up to 25% (perforation, migration, colonic decompression failure as major events, pain as minor event). Patients at higher risk of major events have strictures longer than 4 cm and complete obstruction. A colonic decompression failure may require urgent surgery. Perforation is another feared complication, with an estimated rate of 9.5%. Stent migration usually occurs within a week after placement at a rate of 10% of patients when used as a bridge to surgery, whereas stent occlusion occurs in 10% of palliative patients [27], usually 3–6 months after placement (tumor growth). Covered stents are solely used in benign conditions, with a migration rate reaching up to 90% within 1–3 weeks after placement [25].

7. Benign gastrointestinal tract conditions

7.1 Gastrointestinal strictures, fistulas, and bleeding tamponade

Benign GI tract strictures usually occur from previous surgery (anastomotic) or post-radiotherapy. Caustic chemically induced esophageal strictures are fortunately becoming more rare due to chemical commercial restrictions. Recalcitrant gastrointestinal strictures remain a huge clinical challenge, since results are not consistent and no single therapy has been proven uniformly efficacious. Gastrointestinal stenting has emerged as an alternative therapy for benign stricture treatment, and a fully covered SEMS has been regarded the stent of choice, preferably using a fixation method (**Table 5**) [28].

Gastrointestinal perforation and fistula management have evolved dramatically over the last 15 years toward a noninvasive endoscopic treatment. Gastrointestinal perforation or laceration usually refers to any gastrointestinal full-thickness wall opening that can occur during a therapeutic endoscopic procedure [29] or spontaneously from intense vomiting (Boerhaave syndrome) or gut wall necrosis

1. SEMS is not recommended as first-line therapy for the management of benign esophageal strictures because of the potential for adverse events, the availability of alternative therapies, and costs (strong recommendation, low-quality evidence)
2. Temporary placement of SEMS should be considered as therapy for refractory benign esophageal strictures (weak recommendation, moderate-quality evidence). Stents should usually be removed at a maximum of 3 months (strong recommendation, low-quality evidence)
3. Fully covered SEMS are preferred over partially covered SEMS for the treatment of refractory benign esophageal strictures, because of their lack of embedment and ease of removability (weak recommendation, low-quality evidence)
4. For the removal of partially covered esophageal SEMS that are embedded, the stent-in-stent technique is recommended (strong recommendation, low-quality evidence)
5. Temporary stent placement can be considered for treating esophageal leaks, fistulas, and perforations. The optimal stenting duration remains unclear and should be individualized (strong recommendation, low-quality evidence)
6. Placement of a SEMS is recommended for the treatment of esophageal variceal bleeding refractory to medical, endoscopic, and/or radiological therapy or as initial therapy for patients with massive esophageal variceal bleeding (strong recommendation, moderate-quality evidence)

Table 5.
Recommendations for stenting for benign disease (modified from [15]).

following an intense inflammatory process [30]. Gastrointestinal leakage may also occur postoperatively after a given gastrointestinal anastomosis. Any of these situations may lead to gastrointestinal fluid leak/extravasation and consequent abdominal cavity contamination, leading to an established communication (fistula) of the afflicted organ to the abdominal cavity or to other GI tract compartments or the skin. Gastrointestinal stenting may aid as a sealing procedure to avoid gastrointestinal content leakage and also to maintain luminal patency, reducing any pressure from an unexpected gastrointestinal anastomotic stricture (**Table 5**).

Gastroesophageal varices are mostly found in cirrhotic patients. Other causes include **Schistosoma** infection and portal vein thrombosis from other causes excluding cirrhosis. They may lead to massive bleeding with a high-rate mortality. Variceal band ligation and endoscopic injection therapy are the treatment of choice for ongoing acute variceal bleeding despite medical management. However, patients with massive refractory bleeding and coagulation impairment (usually due to cirrhosis) may require a life-saving tamponade measure, usually done using an esophagogastric balloon device (Sengstaken-Blakemore tube). This device requires a highly compromised team to take care of the balloon device tube and is very uncomfortable for an awaken patient. It also leads to complications such as mucosal ischemic injury. Stenting has emerged as an alternative effective temporary tamponade measure for such bleeding cases until a definitive treatment can be applied (**Table 5**).

8. Other indications

8.1 Gastrointestinal bypass/drainage/anastomosis

Transgastric pancreatic fluid collection drainage (cystogastrostomy drainage) has been for at least 20 years the most popular representative of a typical transmural endoscopic drainage procedure (**Figure 8**). Until 5 years ago, no one would assume a gastrointestinal anastomosis being performed totally under endoscopic technique in the clinical setting, until a novel lumen-apposing self-expandable metal stent (LAMS) has been developed.

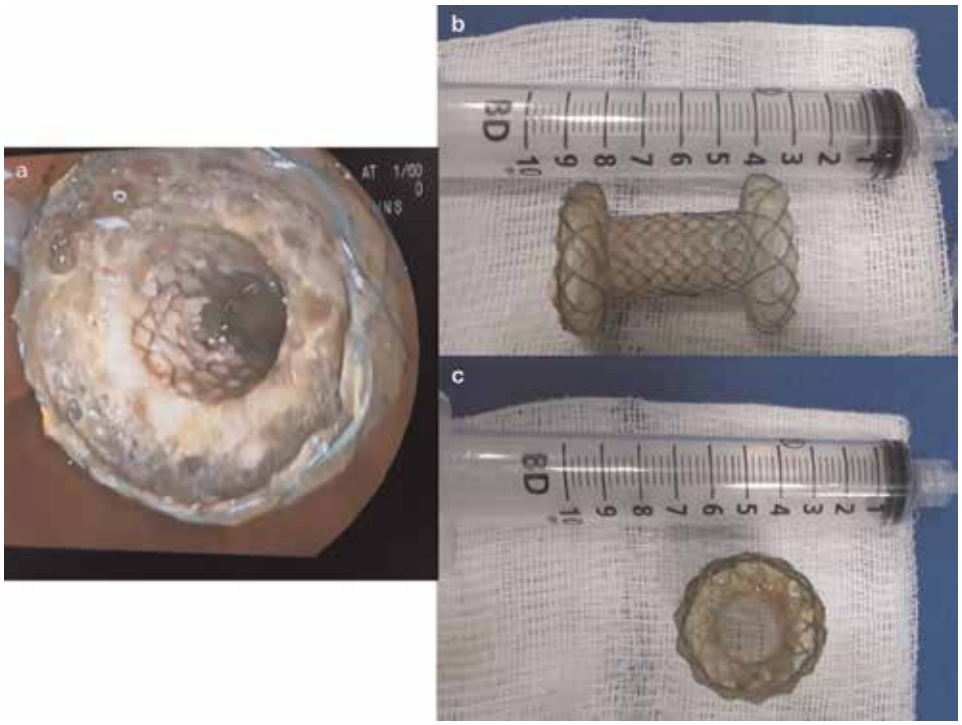

Figure 8.
Lumen-apposing self-expandable metal stent used for transgastric drainage of a walled of pancreatic necrosis. (a) Four weeks after transgastric endoscopic necrosectomy, the resulting cavity has been replaced by granulating tissue. The stent was then removed. The stent has large flanges to avoid migration (b) and a 14 mm lumen to allow endoscope insertion (c). Picture from Eduardo A. Bonin.

This totally covered, dumbbell-shape self-expandable metal stent has been used for gastroenteral (gastrojejunal) and bilioenteric (cholecysto-gastric, choledoco-duodenal) anastomosis in clinical practice with promising results [31]. A recent case control retrospective trial has demonstrated its role compared to traditional endoscopic stenting in managing gastric outlet obstruction from malignant and benign conditions [32].

9. Summary

Gastrointestinal stenting is a procedure associated to a high safety and technical success profile, and its clinical indications have surpassed its original use, esophageal cancer. Self-expandable metal stent placement is the preferred nonsurgical method for biliopancreatic and upper and lower gastrointestinal tract cancer palliation. Stenting is also being used for several other indications, such as benign gastrointestinal stricture treatment, gastrointestinal fistula management, variceal bleeding arrest, and gastrointestinal bypass or drainage. Several efforts have been made to overcome its three remaining clinical major issues: stent occlusion, stent migration, and stent-related perforation.

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With the rapid development of modern medical technology, endoscopic technology has also achieved unprecedented development. Its fields cover examination, treatment, surgery, and even molecular imaging diagnosis. Endoscopy technology brings a minimally invasive diagnosis and treatment experience to patients. Invasive treatment and examination of digestive surgery has changed from large incisions to several Trocar holes, from surgery to endoscopic treatment, and from laparotomy to endoscopy or laparoscopy, which has changed the diagnosis treatment and management of digestive surgery, enhanced the recovery after surgery, and benefited the patients needing to undergo surgical procedures. It is for this reason that we plan to introduce the development of endoscopic and laparoscopic surgery in digestive surgery and enhanced rehabilitation medicine.

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