The SAGES Manual Operating Through the Endoscope

Matthew Kroh
Salvatore Docimo Jr.
Sofiane El Djouzi
Amber Shada
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Editors

Second Edition

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Editors
Matthew Kroh
Digestive Disease Inst, A100
Cleveland Clinic
Cleveland, OH, USA

Sofiane El Djouzi
BariJuve Surgical
Hoffman Estates, IL, USA

Kevin M. Reavis
Center for Advanced Surgery
The Oregon Clinic
Portland, OR, USA

Salvatore Docimo Jr.
Department of Surgery
University of South Florida
Tampa, FL, USA

Amber Shada
Department of Surgery
University of Wisconsin Health
Madison, WI, USA

ISBN 978-3-031-21043-3 ISBN 978-3-031-21044-0 (eBook)
https://doi.org/10.1007/978-3-031-21044-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To my mother and father, Aggie and Gordon Kroh, for their endless support and positive encouragement.

– Matthew Kroh

To Aisa for your support and patience, which allows me to take on these projects. To Massimo and Luna, always striving to make you proud. To all my mentors over the years, your guidance never waivers, and thank you for always picking up the phone.... and thanks mom and dad for everything!!

– Docimo JR. Salvatore

I would like to dedicate this book to those who motivated me to pick up an endoscope and use it every chance I could. To Dr. Chip Foley and Dr. Bruce Schirmer, who instilled a love for flexible endoscopy early on in my training. To Dr. Lee Swanstrom, who taught me to have no fear in what I can accomplish with this tool. To my colleagues and partners, who support my ideas and help care for my patients.

And for the fellows, residents, and students I have had the opportunity to teach. As long as my own curiosity and eagerness for learning mirrors yours, my professional development will never cease and my patients will benefit. Thank you.

– Amber Shada

This book is dedicated to my wife, Chanez, who has been a constant source of support and encouragement during my career and life challenges. I am truly thankful for having you in my life. This work is also dedicated to my parents, Aomar and Yamina, who have always loved me unconditionally and whose good examples have taught me to work hard for the things that I aspire to achieve.

– Sofiane El Djouzi

To my wife Kelly, our sons Nathan and Andrew, and to my dedicated partners and SAGES family whose collective support allowed this book to become a reality.

– Kevin M. Reavis, MD FACS

Preface

Flexible endoscopy is playing an increasingly important and more complex role in the diagnosis and treatment of disorders of the gastrointestinal tract. This manual arose from the rapidly expanding procedures and techniques that have developed and evolved over the past several years. Our goal was to create a cutting-edge and wide-ranging resource that endoscopists can review cataloging therapeutic interventions in the gastrointestinal tract. Key topics should be of interest to gastroenterologists, surgeons, internists, and trainees alike, looking to advance their knowledge in these critical domains.

Chapters cover major topics of foregut, colorectal, and bariatric diseases, with techniques of luminal endoscopy, third space endoscopy, trans-luminal approaches, management of surgical complications, and adjunctive endoscopy with traditional laparoscopy. The text includes dynamic images and key clinical data, in addition to technical pearls to performing these procedures. Equipment needed, set-up, and periprocedural outcomes are also discussed.

Our intended audience is the clinician at any level who wishes to become educated and proficient in the latest endoscopic approaches to treating gastrointestinal disease. Though this is a rapidly advancing field, we hope this text can serve as a comprehensive source for these procedures and continue to

advance the overall field. We welcome out readers' feedback and suggestions for continuous improvement to this second edition book.

Cleveland, OH, USA	Matthew Kroh
Tampa, FL, USA	Salvatore Docimo Jr.
Hoffman Estates, IL, USA	Sofiane El Djouzi
Madison, WI, USA	Amber Shada
Portland, OR, USA	Kevin M. Reavis

Acknowledgments

As editor-in-chief, I would like to offer my gratitude to the co-editors: Drs. Kevin Reavis, Amber Shada, Sofiane El Djouzi, and Salvatore Docimo. It was a pleasure working with each of you and I look forward to our continued collaborations to advance this exciting field of surgical endoscopy.

Contents

Chapter 1
The Interface Between Therapeutic Gastrointestinal Endoscopy and Endoscopic Gastrointestinal Surgery

Jeffrey L. Ponsky

Modern gastrointestinal endoscopy commenced with the development of flexible fiberoptic endoscopes in the 1950s [1]. Techniques soon developed which employed these instruments in the diagnostic evaluation of the upper and lower gastrointestinal tract. Flexible biopsy forceps were developed to permit the sampling of tissue. Originally these methods were performed by a single individual looking through the eyepiece of the endoscope. Soon after, fiberoptic teaching attachments were developed which attached to the instrument's eyepiece and permitted a second individual to observe the procedure simultaneously.

J. L. Ponsky (✉)
Emeritus of Surgery, Case Western Reserve University, Cleveland, OH, USA

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_1

The appreciation of abnormal tissue, particularly polyps in the colon, prompted the desire to develop a method for safely removing lesions. With the innovation of electrified metallic wire loops (snares), the technique of endoscopic polypectomy was born and began the era of therapeutic gastrointestinal endoscopy [2]. At the same time, creative endoscopists designed electrified wire probes to cauterize bleeding ulcers and injection needles to introduce sclerosants into esophageal varices. These same needles were used to introduce epinephrine to slow or stop bleeding lesions in the stomach and duodenum.

A major advance involved the development of the ability to access the papilla of Vater in the duodenum, thus adding an advanced means of evaluating biliary and pancreatic disease, endoscopic retrograde cholangiopancreatography (ERCP) [3]. In 1974, a therapeutic dimension was added to ERCP with the innovation of endoscopic sphincterotomy [4]. Now, with access to the bile duct, stones could be removed, tumors sampled, and stents inserted to relieve the obstruction. Similar interventions permitted access to the pancreatic duct.

In the esophagus, methods were developed to dilate strictures, stent tumors, and ablate Barrett's esophagus. More advanced techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) permitted resection of premalignant and early malignant lesions.

The application of techniques used to treat hemorrhoidal veins was applied to the treatment of esophageal varices. This included the first injection of sclerosant solutions and then the use of band ligation [5]. The latter has become the standard methodology for eradicating varices and is easy to perform, safe, and effective.

An early minimally invasive surgical approach to obtaining enteral access for feeding was the development of a percutaneous endoscopic method (PEG) to establish a gastrostomy [6]. This approach was the first to cross the abdominal and intestinal walls to complement endoscopic therapy.

Endoscopic tools, though primitive, have been developed to treat gastroesophageal reflux; these have included injection techniques, suturing devices, and stapling machines. Thermal probes utilizing radiofrequency energy have been proven the best therapy for ablating dysplastic Barrett's mucosa [7].

In the early twenty-first century, innovative endoscopists conceptualized a technique that would permit intra-abdominal surgical procedures to be performed by means of translumenal access endoscopically via the stomach or colon [8]. Originally performed in animal models, the procedure was soon performed to remove the appendix in a human patient. The excitement generated was enormous and prompted the formation of a joint committee of surgeons and gastroenterologists, which was named NOSCAR (Natural Orifice Surgery Consortium for Assessment and Research), which would define parameters for research and practice of this innovation. The method itself was called NOTES, Natural Orifice Translumenal Endoscopic Surgery.

Under rigorous institutional review board (IRB) protocols, a number of procedures were studied, including transgastric cholecystectomy and appendectomy and a number of trans-colonic procedures. Unfortunately, due to a lack of effective instrumentation and failure to achieve economic parity with traditional techniques, the method was sidelined. There have been numerous outgrowths and clinical advancements because of this episode in endoscopic history, including the conceptualization and development of the intramural procedures such as POEM and POP, as well as full-thickness resection methods.

Evolving from curiosity and then a crucial diagnostic technology, endoscopic ultrasound (EUS) has become a major force in therapeutic endoscopy. Originally utilizing radial ultrasound, EUS was helpful in identifying abnormalities in the gut wall and adjacent structures. With the addition of linear ultrasound probes, endoscopists were able to perform therapy such as drainage of pseudocysts and pancreatic necrosis, as well as performing nerve blocks for palliation of pain.

More recently, with the advancement of stent technology permitting apposition of adjacent visceral walls, ultrasound technology has been used to drain obstructed gallbladders via the stomach or duodenum, debride large peri-pancreatic collections, and access the excluded stomach after Roux-en-Y bariatric surgery in order to perform ERCP [9].

More recently, directly as a result of work done to improve the NOTES procedures was the development of intramural surgery. In working to develop a tunneling method in the esophagus as an access method to the peritoneal cavity, investigators were able to visualize the esophageal musculature and conceived of a method to divide these muscles to treat achalasia [10]. First performed in animals, the method was initially performed in humans in Japan [11]. Termed Peroral Endoscopic Myotomy, POEM, the procedure rapidly gained popularity, was widely evaluated, and adopted worldwide. It has been shown to be effective in the treatment of achalasia and other muscular disorders of the esophagus. It has also led the way to other endoscopic maneuvers in this submucosal space, such as removal of benign tumors including leiomyomas and division of the cricopharyngeus muscle to treat Zenker's diverticulum. A further application of this intramural surgery has been the division of the pyloric muscle to treat gastroparesis. This method, termed peroral pyloromyotomy (POP) or G-POEM, involves the creation of a submucosal tunnel proximal to the pyloric ring, division of the ring with electrocautery, and clip closure of the mucosotomy [12].

It is clear that gastrointestinal endoscopy has evolved from a purely diagnostic technique, through the stage of endoscopic therapy for maladies of the intestinal lumen, to an access tool for the performance of surgical procedures on the gastrointestinal tract and adjacent organs.

Since the earliest days of flexible endoscopy, there has been debate over who should most appropriately perform these procedures. Gastroenterologists have argued that they are most appropriately suited to own this specialty, owing to their knowledge and capability to treat gastrointestinal dis-

eases. Certainly, the great majority of endoscopic procedures, predominantly upper and lower endoscopy and ERCP, are performed by gastroenterologists. Surgeons have argued that they have been instrumental in the development of most of the major therapeutic innovations in the field and, therefore should be involved in the performance of the procedures. Both are correct. To eliminate either group would diminish the field. Each specialty adds specific knowledge and perspective to the performance and development of endoscopy.

A review of the advances and refinements in gastrointestinal endoscopy will reveal the greatest progress has been achieved when both groups are involved and working cooperatively. Great efforts should be made to integrate training and research to achieve optimal quality of practice and advancement of innovation.

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Chapter 2
Endoscopic Tools: Instruments

Richard Johnson and Vimal Narula

Introduction

As any craftsman or artist knows, in order to become proficient with one's task it is vitally important to have a thorough knowledge of the tools available. This chapter will serve as an overview of the various endoscopic instruments to give the endoscopist a foundation to develop their skills moving forward. This chapter will help to serve as a bedrock from which the endoscopist can build as they develop a practice. This chapter is not meant to serve as a comprehensive review of all endoscopic instruments, as that is both constantly evolving and beyond the scope of a single chapter. Each instrument will come with a short description of both the device itself and its application. Images are provided to supplement these descriptions.

R. Johnson (✉) · V. Narula
Ohio State University, Columbus, OH, USA
e-mail: richard.johnson@osumc.edu; Raaja.narula@osumc.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_2

Endoscope

The endoscope itself is described elsewhere in this book, but it is important in this chapter to review the channel sizes of endoscopes as the vast majority of instruments will be passed through the channels in order to get to the area of interest of the endoscopist. For the most part, smaller endoscopes will have smaller working channels and larger endoscopes will have larger channels. The working channel diameter on choledochoscopes is 1.2 mm. Colonoscopes have working channel diameters that range from 2.8 mm to 4.2 mm. Duodenoscopes have a working channel diameter of 2.0 mm to 4.8 mm. Finally, endoscope working channel diameters range from 2.2 mm to 3.8 mm [1, 2]. It is important that the endoscopist is familiar with the size channel on the types of endoscopes used at his or her institution.

Standard Instruments

Forceps

One of the earliest and still most commonly used devices is the forceps. This device has been utilized for various tasks and specialized for some specific jobs by device makers. The basic design is similar throughout. The device has a jaw on the end of it that is passed through the working channel through the endoscope. The endoscopist then is able to open or close the jaw with a handle device. This will allow for biopsy, manipulation, or removal of tissue (Figs. 2.1, 2.2 and 2.3). Some forceps will have two articulating jaws, others will have just one. The addition of a spike between the jaws will allow for multiple bites with just one insertion of the device. The jaws also come in various sizes.

When removing tissue, the endoscopist can apply electrosurgical energy (hot biopsy) or not (cold biopsy). With cold biopsies one will either rely on the body tissue to provide hemostasis or will subsequently apply hemostasis with another device. By avoiding electrosurgical energy use, the

FIGURE 2.1 The handle portion of an endoscopic forceps

risk of perforation is reduced. This can be very useful in thin-walled areas such as the cecum. It is also important to remember that electrosurgery may distort the specimen as in a colonic polyp when it will be important for the pathologist to be able to provide microscopic examination.

FIGURE 2.2 The distal end of an endoscopic forceps in the closed position

FIGURE 2.3 The distal end of an endoscopic forceps in the open position

Snare

The snare is an instrument that has a metal wire that has a single or multiple loops at its end. It is used for removal or biopsy of tissue. It can also be used with electrosurgery for hemostasis. The wire loops are encased in a protective plastic sheath and passed through the endoscope channel. The

snares come in a variety of sizes and can be monofilaments or braided. The handle mechanism that allows for opening and closing of the snare can also allow for connection to an electrosurgical energy source (Figs. 2.4, 2.5 and 2.6) [2].

Snares are commonly used in the pull type percutaneous endoscopic gastrostomy tube insertion as well as removal of foreign bodies. In these instances, no electrosurgical energy is needed. Similar to forceps snares can be used to remove lesions with or without electrosurgery. When no energy source is used such as in smaller lesions or flat lesions a sepa-

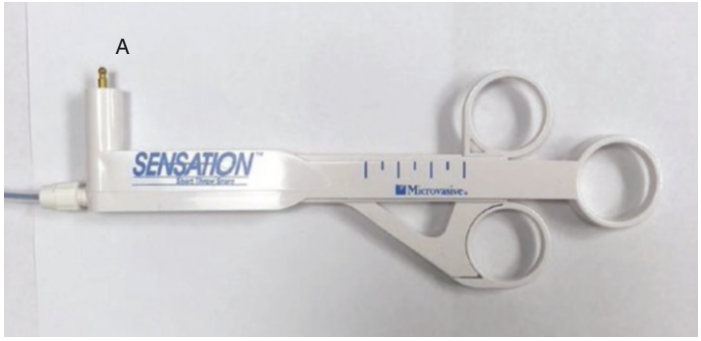

FIGURE 2.4 The handle of an endoscopic snare. (A) The attachment site for electrosurgical energy

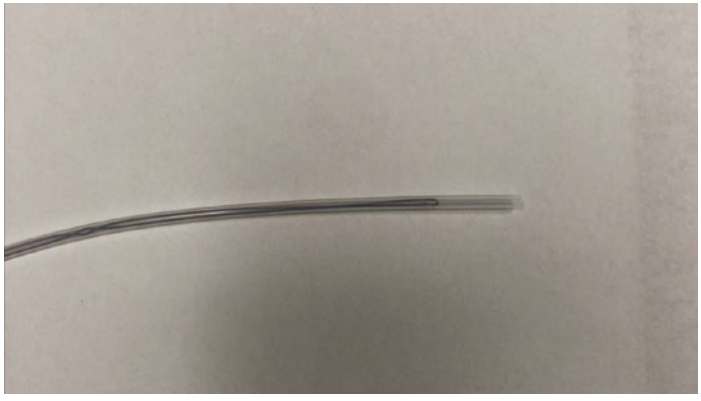

FIGURE 2.5 The distal end of an endoscopic snare in the closed position

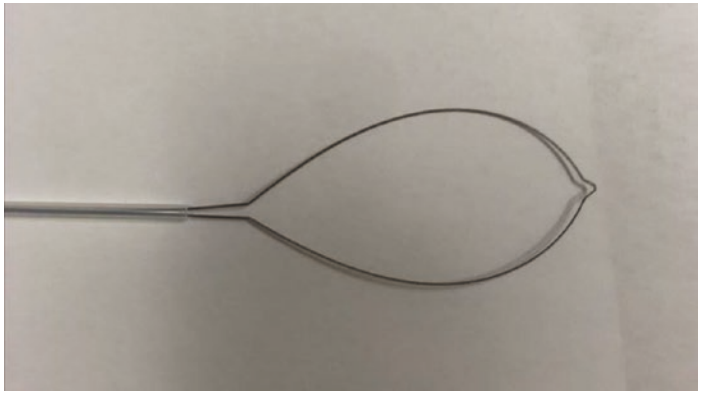

Figure 2.6 The distal end of an endoscopic snare in the open position

rate device is often used for hemostasis. For larger lesions or some pedunculated lesions, coagulation of the base of the lesions can be achieved by closing the snare while applying electrosurgical energy. For some of the larger flat lesions, a submucosal lift with injection of saline will allow for a safer application of energy by creating a buffer between the site of the energy application and the deeper layers of the intestinal wall to decrease the chance of a perforation. After resection, the endoscopist will still need to retrieve the lesion. This can be done by suctioning smaller lesions into a specimen trap or for larger lesions using the snare itself, suctioning the lesion onto the scope tip, or using a mesh net to retrieve the lesion. Obviously, the techniques for the larger lesion will require removal of the entire endoscope to retrieve the lesion.

Injection Catheter

The injection catheter can be used in multiple ways. As described above it can be used for a submucosal lift prior to hot snare excision of a mucosal lesion. The device consists of an outer protective plastic sheath encasing a needle that is passed through the endoscope channel [2]. The outer handle

controls the deployment of the needle. There is a wide array of material that can then be injected through the needle including hemostatic agents, tattoo agents, or simple saline. Of note, the submucosal lift technique is used as part of both endoscopic mucosal resections, per oral endoscopic myotomies, and per oral pyloromyotomy (Figs. 2.7, 2.8 and 2.9).

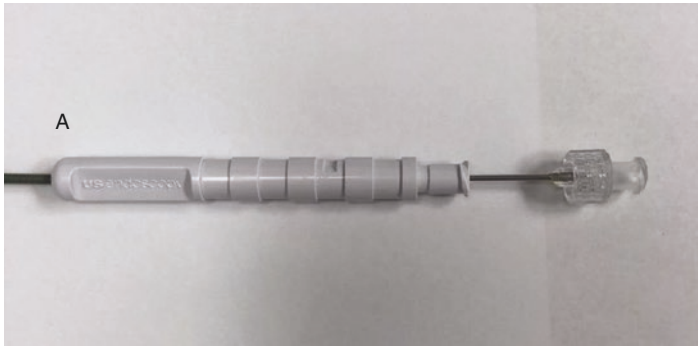

FIGURE 2.7 The handle of an endoscopic injection catheter. A indicates the attachment site for a syringe for injection

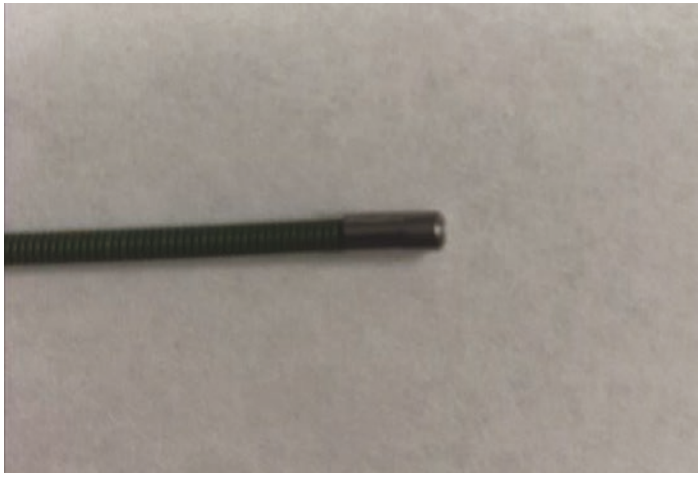

FIG. 2.8 The distal end of an endoscopic injection catheter with the needle sheathed

FIGURE 2.9 The distal end of the endoscopic injection catheter with the needle advanced

Endoscopic Cutting Tools

The endoscopic cutting tools are similarly designed as the injection catheters with a protective plastic outer sheath encasing the inner tool. The difference is that instead of an injection catheter inside the protective sheath there is a cutting instrument. These tools have become vital to perform more advanced therapeutic endoscopic procedures, such as the submucosal dissection in per oral endoscopic myotomies, endoscopic mucosal resection, and per oral pyloromyotomy. The cutting tools vary in tip design like a sharpened needle or a sharpened triangular device. The handle for these devices will have an attachment site for electrosurgical application in order to aid in both the dissection and hemostasis.

Retrieval Devices

Retrieval devices are typically designed with a protective plastic sheath that contains the specific retrieval device such as a net. The device is passed through the endoscope channel within the sheath and then deployed at the area of interest by

depressing the handle aspect of the device. The nets come in various sizes that will allow the endoscopist to retrieve different sized objects.

Nets can be used to retrieve previously resected lesions. They are often also used to remove ingested or inserted foreign bodies. Due to the net containing a large specimen or foreign body, one will have to remove the endoscope from the patient in order to retrieve the object of interest (Figs. 2.10, 2.11 and 2.12).

FIGURE 2.10 Handle end of an endoscopic net

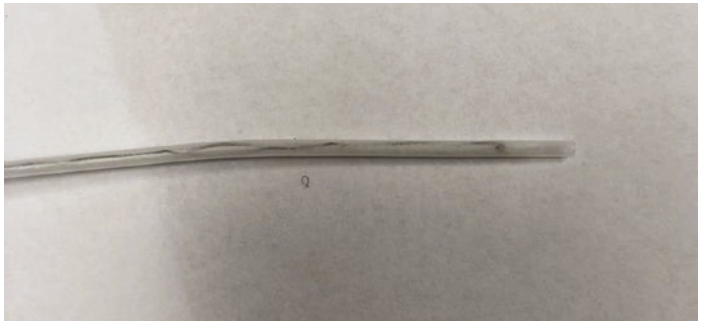

FIGURE 2.11 Distal end of a sheathed endoscopic net

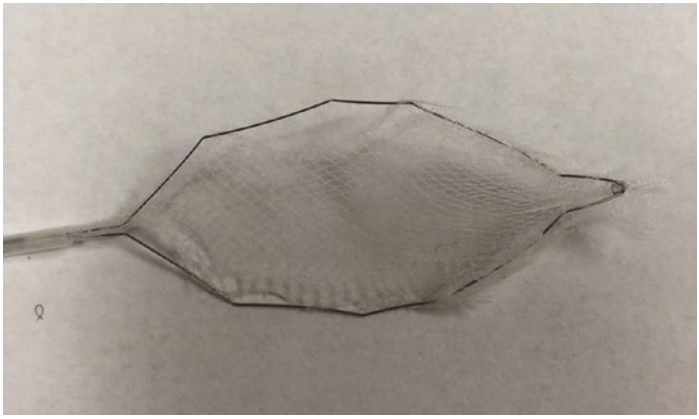

FIGURE 2.12 Distal end of an endoscopic net deployed

Endoscopic Wires

Wires produced with various material and designed with monofilaments, braided options, and varying stiffness. Wires primarily are used to serve a guide for other devices such as dilators. The ends of the wires can be either straight or angled. Some wires allow for spinning to make traversing a narrowed area easier (Figs. 2.13 and 2.14).

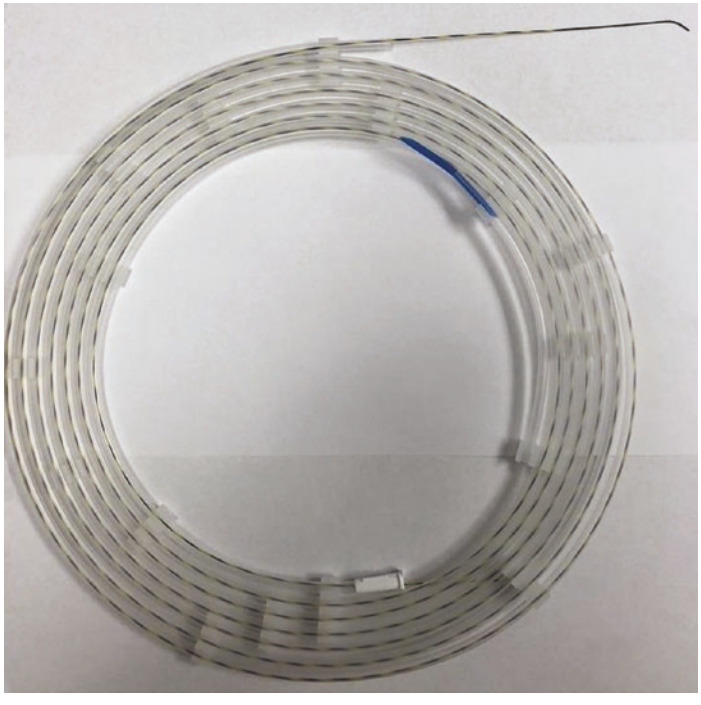

FIGURE 2.13 Endoscopic wire within its housing

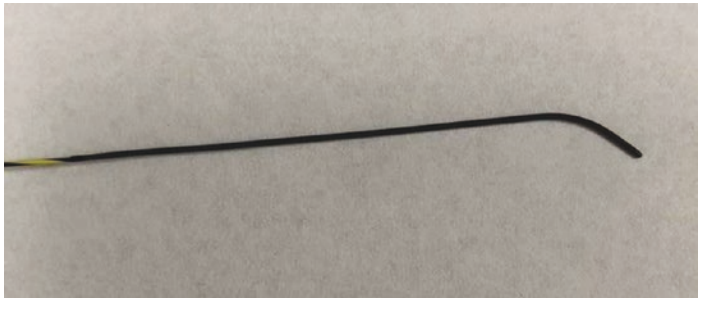

FIGURE 2.14 Distal tip of an endoscopic wire

Balloon Catheters

Balloons are used primarily for dilation. However, they can be used for temporary hemostasis as well. The size of the balloon will vary in both length and diameter. Balloons can be compliant and will adapt to luminal channel of what it is being dilated. Non-compliant balloons will maintain a predetermined shape no matter the contour of the stricture being dilated. The balloon is attached to a catheter that one passes through the endoscope's working channel or over a previously placed endoscopic wire. The balloon is then inflated under direction vision if using a through-the-scope (TTS) balloon or under fluoroscopic guidance if over a wire. The external handle portion of the balloon catheter will have two ports. One port is used for passage of a wire or injection of contrast. The other port is used to inflate the balloon.

TTS balloons are passed through the working channel of the endoscope and then under direct endoscopic vision placed across the stricture. The balloon is then inflated under direct visualization to allow for mucosal observation in order to limit the chance of perforation. A balloon can also be passed over a wire using fluoroscopy. No matter which technique is used the endoscopist must be vigilant to keep the balloon in the correct position during the dilation. Also, it is important to endoscopically view the area after the dilation to assess for resolution of the stricture as well as assess for perforation (Figs. 2.15, 2.16 and 2.17).

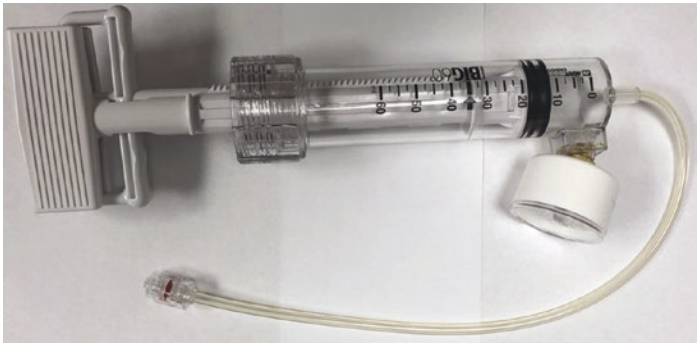

FIGURE 2.15 Pump handle of an endoscopic balloon

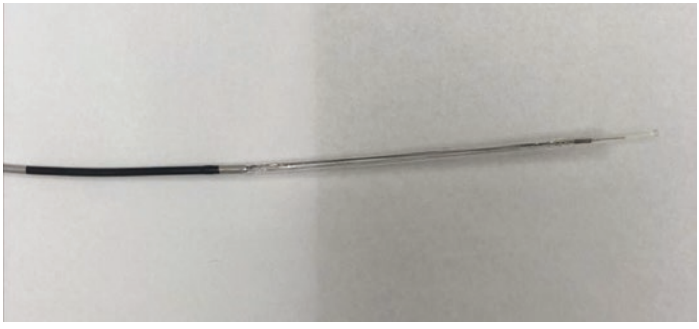

FIGURE 2.16 Distal end of an endoscopic balloon deflated

FIGURE 2.17 Distal end of an endoscopic balloon inflated

Clips

Endoscopic clips come in various sizes. Through-the-scope clips (TTSC) typically have a long sheath with a head piece on one end and a handle on the other. This type of endoscopic clips is passed through the working channel of the endoscope to get to the tissue. On the head piece, the jaws can be opened and then shut together on the tissue. Once in place, the head and clip are released from the rest of the device with the clip being deployed onto the tissue. Some of the clips are designed to be able to be opened and closed multiple times before being released while others are only able to be closed once. Also, some clips are able to rotate or spin along the axis that allows for a more precise placement.

These clips are often used to control bleeding by applying pressure and tissue apposition. This is useful for bleeding ulcers in addition to other hemostatic interventions such as epinephrine injection or cautery [3]. If a vessel is visible within the ulcer, the clip is placed on the vessel to occlude the vessel. After a polypectomy that has mucosal bleeding, clips can be applied to provide hemostasis instead of an energy device. This lowers the risk of a thermal injury to thin-walled areas of the gastrointestinal tract such as the cecum. As the clips are radiopaque they can serve as a marker for subsequent endovascular attempts at hemostasis if there is rebleeding (Fig. 2.18).

Figure 2.18 Distal end of a clip device in the open position

A second type of clip is the over-the-scope option. These clips serve a similar function but are much larger. Due to this size, they are deployed differently as they do not fit through the endoscope channel. Instead, the clip is placed on the tip of the endoscope and attached to a deployment device with a wire and crank mechanism. To deploy an over-the-scope clip, the endoscope tip is placed up against the tissue of interest and suction is applied to oppose that tissue to the tip of the endoscope. Then the clip is deployed by turning the handle similar to how one deploys endoscopic bands for ligation. Over-the-scope clips are capable of closing full-thickness defects in some instances [4].

Band Ligation

Similar to the over-the-scope clips the band ligation device is deployed from a cap that fits on the distal end of the scope. The technique is also similar to the over-the-scope clips whereby the endoscope tip is placed against the tissue of interest and suction is applied. This brings that tissue up to the endoscope's tip within the band ligation cap. Then using a crank mechanism at the control aspect of the endoscope one deploys a band. Multiple bands are preplaced over a cap that is positioned at the end of the endoscope. The deployment crank allows multiple bands prior to having to remove the endoscope to reload. These bands are useful for control of bleeding and specifically for esophageal varices. This is similar to hemorrhoid band ligation devices and will apply compression to the varix to achieve hemostasis and eventually the thrombosed varix will slough off. Also, they can be used during endoscopic mucosal resection procedures to facilitate lift prior to snare removal of mucosa (Figs. 2.19 and 2.20).

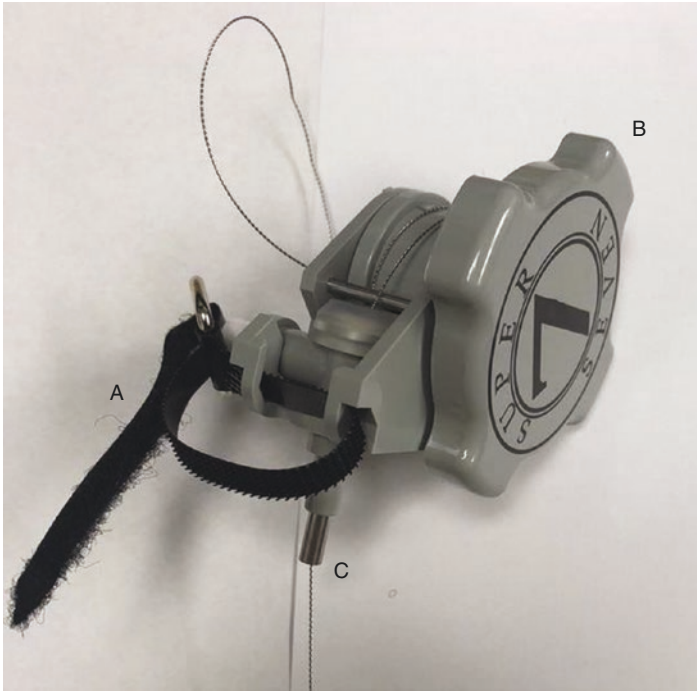

FIGURE 2.19 Hand with Velcro strap that secures the device to the endoscope (A) and crank mechanism (B). The metal adapter (C) is placed into the opening to the working channel of the endoscope

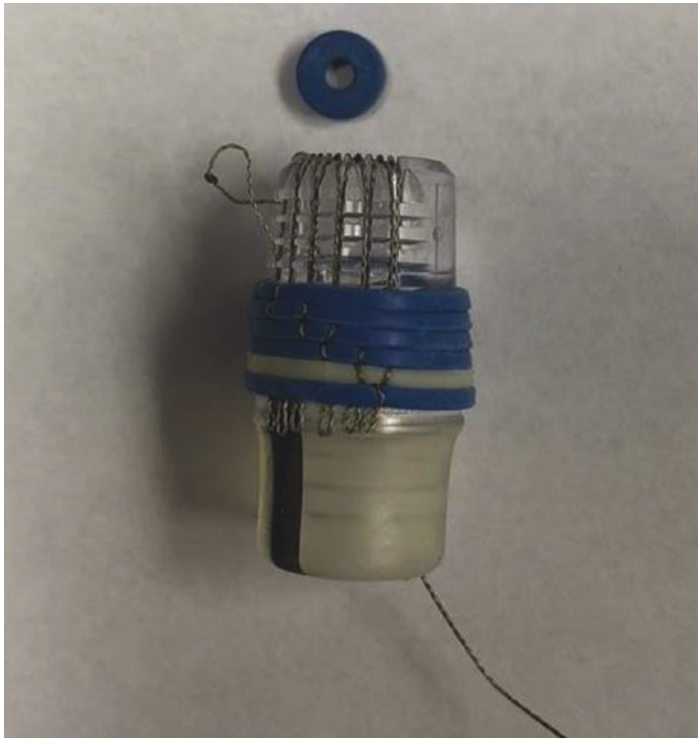

FIGURE 2.20 The cap end of a banding device with one band deployed

Energy Devices

Electrocautery and Thermocoagulation Probes

Electrocautery is the application of a hot device to achieve hemostasis. There are very few medical devices that qualify as true cautery. The hemostasis probes (gold probes) are such an example. The gold probe is used to achieve hemostasis by applying pressure and heat to the area of interest. Some newer probes instead use bipolar electrosurgery to achieve the same effect such as the gold probe (Fig. 2.21). These

FIGURE 2.21 The distal end of a gold probe

instruments are advanced through the working channel of the endoscope, placed onto the tissue of interest with slight pressure, and then the energy is applied [3, 5].

Radiofrequency Ablation Catheters

Radiofrequency ablation catheters have various uses depending on the effect that is desired. One such device, the Barrx™ catheter, is used most frequently for ablation of Barrett's tissue in the esophagus [6].

Argon Plasma Coagulation Catheters

Argon plasma coagulation works best for areas of diffuse yet superficial bleeding. This is due the fact it has very low penetration of tissue. The catheter has a hollow channel through which argon gas passes. The catheter advanced through the endoscopic working channel and placed next to but not

directly contacting the tissue of interest. The tip of the catheter has a monopolar aspect that will cause an electric spark when energy is applied, thus causing the argon gas stream to ignite to a plasma ring that achieves hemostasis. As this has a low tissue penetration it can be used in thin tissue. Also, it works well in instances such as radiation proctitis or gastric antral vascular ectasia which have a large area of superficial bleeding [3, 5].

ERCP Instruments

Sphincterotome

A sphincterotome is a catheter designed to be used in a duodenoscope specifically for endoscopic retrograde cholangiopancreaticography procedures. These scopes are side viewing to help with location and access of the biliary tree through the ampulla of Vater. There are multiple types of different sphincterotomes with their own pluses and minuses. The basic design is similar among them. The catheter is passed through the endoscopes working channel. The catheter can also be passed over a wire to aid in its placement at the level of the biliary tree. The distal tip of the catheter is able to be deflected or bent by use of the external handle. This will expose a wire to perform the sphincterotomy using electrosurgical energy applied to the exposed wire (Figs. 2.22 and 2.23) [7].

The external handle of a sphincterotome has a similar design as many snares for control of the amount of tip deflection being dictated by an assistant opening the handle. There is then a location for the attachment of a syringe to flush contrast through as well as a spot to attach the energy cord in order to be able to apply electrosurgical energy to the wire within the sphincterotome. Finally, at the junction of the handle and the catheter this is the area where a wire is passed through the catheter (Fig. 2.24).

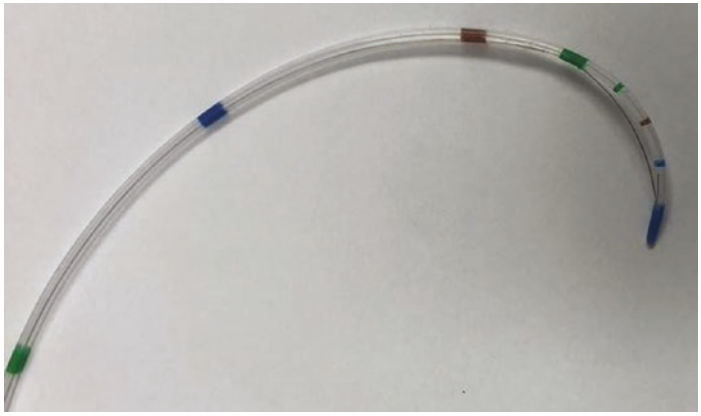

FIGURE 2.22 The distal end of a sphincterotomy with no bowing

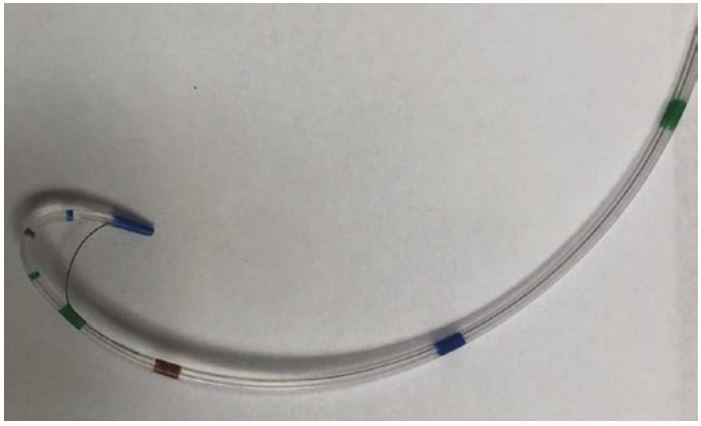

FIGURE 2.23 The distal end of a sphincterotomy with a full bow applied

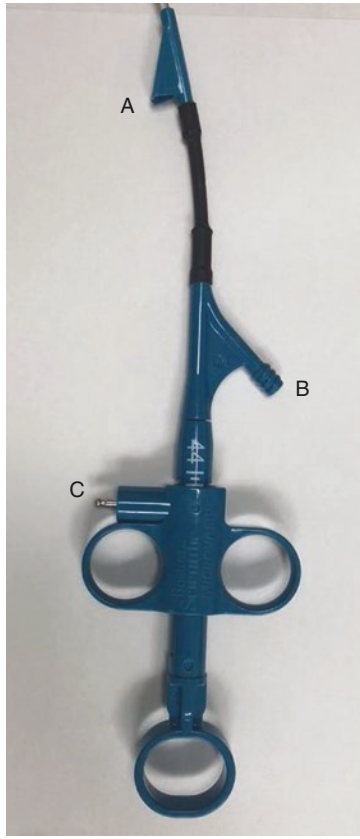

FIGURE 2.24 The handle end of a sphincterotome. A is labeling the area that a wire will pass through. B is labeling the connection site for a syringe to inject contrast through if performing a cholangiogram or pancreaticogram. C is labeling the attachment site for the electrosurgical unit

Endoscopic Balloons

An endoscopic balloon is a catheter that has a balloon on the distal tip that can be inflated to various sizes. Also depending on the type, one can inject contrast through the catheter with it exiting either above/distal or below/proximal to the balloon. A balloon will commonly be positioned within the biliary tree by passing the catheter over a previously placed wire. The balloons are often used during an ERCP to help clear the biliary tree. Using fluoroscopic guidance, the deflated balloon

is positioned upstream of any stone or sludge within the biliary tree. It is then inflated, and pulled back toward the endoscope until the balloon is withdrawn through the ampulla. One must be careful during this maneuver to not dislodge the wire within the biliary tree. The external handle of the balloon catheter will have a port for injecting contrast, a port for inflating the balloon, and a port or location where the wire will come through (Figs. 2.25, 2.26 and 2.27).

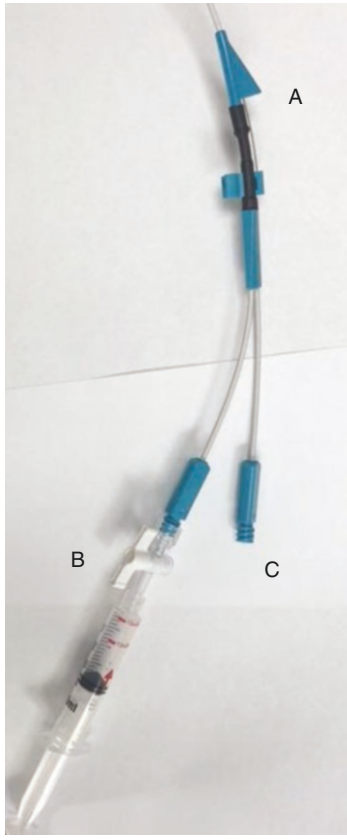

FIGURE 2.25 The external handle portion of a balloon catheter. A is the site where the wire will pass through. B is the site for the inflation port for the balloon. C is the port for instillation of contrast that exits at the distal end of the catheter

FIGURE 2.26 A balloon inflated

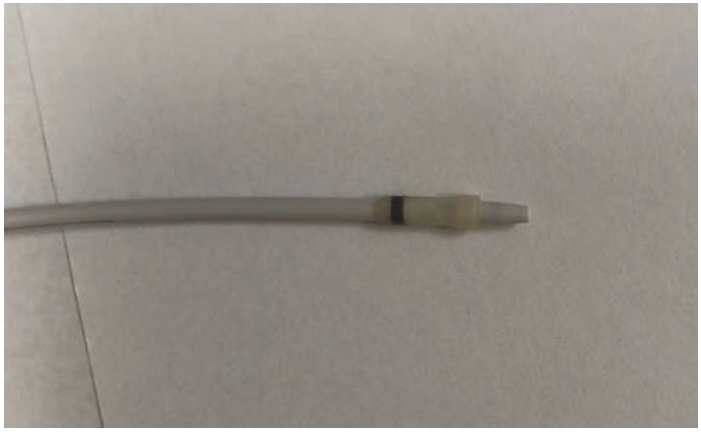

FIGURE 2.27 A balloon deflated

Endoscopic Baskets

Endoscopic baskets are similar in design to the Roth nets mentioned earlier. The difference is that the baskets are much smaller in order to be used within the biliary tree. Most do not

come with a netting material but instead are made out of metal wire. The catheter has a protective plastic sleeve around the basket. The catheter is passed through the channel of the endoscope. By depressing the handle, the basket is deployed out of the protective sheath. Under fluoroscopy the basket is placed around a stone or other lesion one is wanting to retrieve. Then, by closing the handle the basket will close around the lesion or stone. The catheter is withdrawn to the tip of the endoscope and out of the ampulla (Figs. 2.28 and 2.29) [2].

FIGURE 2.28 The distal end of an endoscopic balloon in the closed position

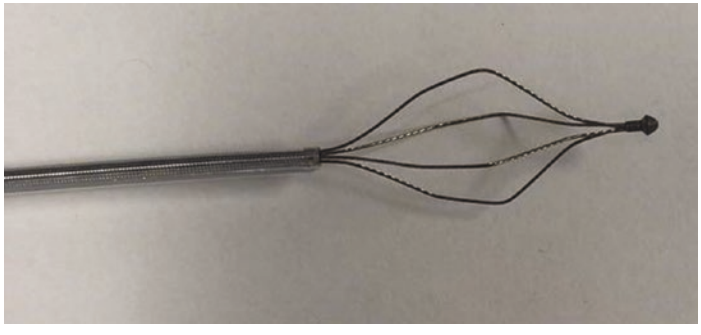

FIGURE 2.29 The distal end of the endoscopic balloon in the open position

Biliary Stents

Biliary stents come in two basic types: metal and plastic. The plastic stents can have flaps on one of both ends that help keep stent migration from happening. The plastic stents are deployed through the channel of the endoscope over a wire. Fluoroscopy is used to guide the placement and there are radiopaque markers on the deployment system to guide the endoscopist during the deployment. The handle end of the deployment system will have a locked and unlocked position [7]. Different stent brands have slightly different deployment steps so it is important for the endoscopist to be familiar with the types used in his/her endoscopy center. The plastic stents will come in various sizes based on the diameter (which is listed in French sizes) and the length of the stent (listed in centimeters) (Figs. 2.30 and 2.31).

The self-expanding metal stents have a similar design with a catheter placed over a wire and positioned in the biliary tree under fluoroscopic guidance. There are radiopaque markers designed in the deployment system to guide this positioning. Unlike plastic stents which are pushed into position, self-expanding metal stents are deployed at the handle end by pulling back on a wire (Figs. 2.32 and 2.33) [7].

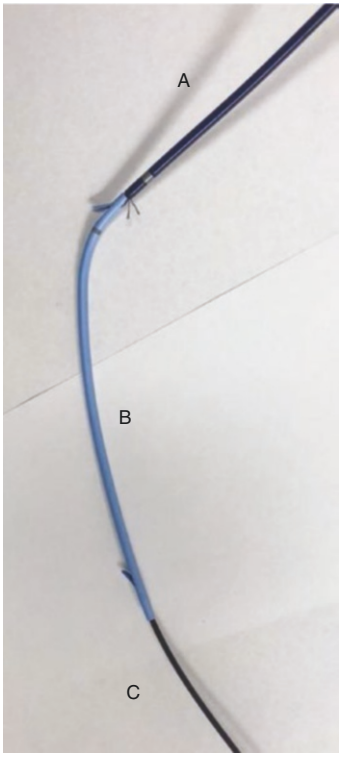

FIGURE 2.30 The proximal end is near A which is the pusher that once in position the endoscopist uses to advance the plastic stent, B, over the inner cannula, C

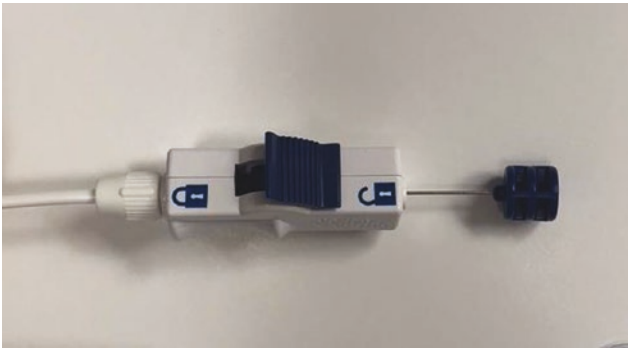

FIGURE 2.31 The external part of the stent with the locking mechanism shown

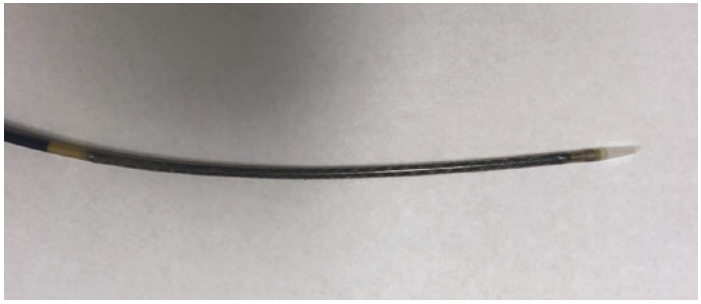

FIGURE 2.32 Metal stent in the closed position

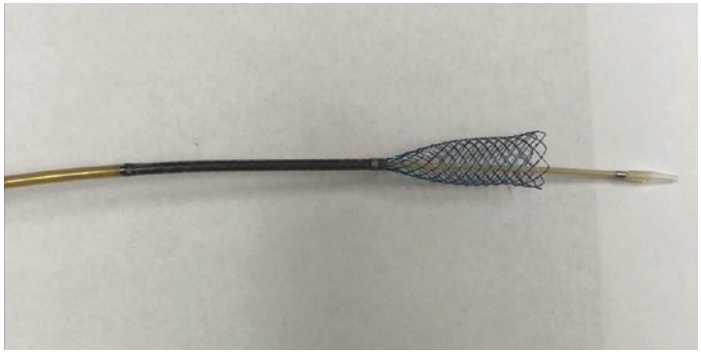

FIGURE 2.33 Metal stent in the partially open position

Cholangioscopy

One of the newer instruments to add to the armament of the advanced endoscopist is the single-use cholangioscope that is passed down through the working channel of a duodenoscope. This allows for direct visualization of the bile and pancreatic ducts. It has various uses and has its own working channel as well. Further details of this device are discussed in later chapters (Fig. 2.34).

Figure 2.34 The external portion of the Spyglass cholangioscope. The distal end is seen in the superior aspect of the image

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Chapter 3
Operating Platforms for Surgical Endoscopy

Thomas R. McCarty and Christopher C. Thompson

Introduction

The field of surgical endoscopy has experienced a sharp rise and adoption of technology, and evolved significantly over the last four decades. From the introduction of the first digital endoscope to the implementation and utilization of operating platforms for surgical endoscopy, the field as a whole has seen an influx of ground-breaking technology and innovative solutions to provide minimally invasive treatments for a variety of gastrointestinal pathologies. While traditional endoscopes provide access to the gastrointestinal tract, more novel task-specific operating platforms have been developed out of necessity to assist the surgeon or endoscopist in the treatment of multiple conditions. These platforms may include fully integrated optics and visualization platforms or rely upon visualization from traditional endoscopes (Table 3.1).

T. R. McCarty · C. C. Thompson (✉)
Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, MA, USA
e-mail: trmccarty@bwh.harvard.edu; cthompson@hms.harvard.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_3

Table 3.1 Summary of operating platforms

Available Surgical Endoscopy Platforms	Company	Pre-Clinical Data	Clinical Studies	FDA Approval	Commercially Available in US	Number of Instrument Channels	Platform Length (cm)	Outer Diameter (mm)
Endoscopic-Assisted Platforms								
Direct Drive Endoscopic System (DDES)	Boston Scientific (Marlborough, MA, US)	Yes	No	No	No	3	55	22
Incisionless Operating Platform (IOP)	USGI (San Clemente, CA, US)	Yes	Yes	Yes	Yes	4	110	18
Endomina System	Endo Tools Therapeutics (Gosselies, Belgium)	Yes	Yes	No	No	1	–	20
DiLumen C2	Lumendi (Westport, CT, US)	Yes	Yes	Yes	Yes	–	125	11.8

LumenR	Boston Scientific (Marlborough, MA, US)	Yes	Yes	No	No			
Integrated Visual Platforms								
EndoSamurai	Olympus (Tokyo, Japan)	Yes	No	No	No	3	103	18
ANUBIScope	IRCAD and Karl Storz (Strasbourg, France and Tuttlingen, Germany)	Yes	Yes	No	No	3	103	16
Flex Robotic System	Medrobotics (Raynham, MA, US)	Yes	Yes	Yes	No	2	28	18
Robotic Platforms								
ViaCath System	Auris Health (Redwood City, CA, US)	Yes	No	No	No	–	90	16

(continued)

Table 3.1 (continued)

Available Surgical Endoscopy Platforms	Company	Pre-Clinical Data	Clinical Studies	FDA Approval	Commercially Available in US	Number of Instrument Channels	Platform Length (cm)	Outer Diameter (mm)
Master and Slave Endoscopic Robot (MASTER)	Nanyang University (Singapore)	Yes	Yes	No	No	2	154	22
Endoluminal Surgical (ESL)	ColubrisMX (Houston, TX, US)	Yes	Yes	No	No	–	–	–
Other Gastrointestinal Platforms								
Invendoscopy E200 System	Invendo Medical (Kissing, Germany)	Yes	Yes	Yes	No	1	200	
NeoGuide Endoscopy System	Intuitive Surgical (Sunnyvale, CA, US)	Yes	Yes	Yes	No	1	161	20

Aer-O-Scope System	GI View (Ramat Gan, Israel)	Yes	Yes	Yes	No	2	230	13
Sightline ColonoSight	Stryker GI (Haifa, Israel),	Yes	Yes	Yes	No	3	–	–
Endotics System	ERA Endoscopy Srl (Pisa, Italy)	Yes	Yes	Yes	No	–	180	17
Bronchoscopy Platforms								
Monarch	Auris Health (Redwood City, CA, US)	Yes	Yes	Yes	Yes	1	–	6
Ion Endoluminal Platform (IEP)	Intuitive Surgical (Sunnyvale, CA, US)	Yes	Yes	Yes	Yes	1	–	3.5

Despite multiple platforms having been designed for surgical endoscopy, few of these systems have successfully navigated the regulatory process and become commercially available in the United States (US). Mechanistically, perhaps the most important aspect in surgical endoscopy includes the issue of hysteresis—the phenomenon of a degradation in task performance due to tendon-sheath mechanisms (i.e., decreased responsiveness or control with increasing flexibility) [1]. Ensuring ideal responsiveness within the angulated gastrointestinal tract is critical. Furthermore, distal tip stability and the ability to deliver adequate and precise force in tortuous configurations continues to be challenging within the gastrointestinal tract. Other key technical aspects to platform design include the ability to create an effective space to perform the procedure (i.e., therapeutic zone), as well as ensuring visibility of end effector instruments. Each platform has attempted to address these barriers and improve upon perceived shortcomings in design. In this review, we will highlight the history of operating platforms within the field, describe current approaches and systems in practice currently, as well as preview the future of surgical endoscopy via robotic platforms.

History of Surgical Endoscopy

One of the most influential aspects of surgical endoscopy that led to the development of multiple operating platforms was the introduction of natural orifice trans-luminal endoscopic surgery (NOTES). NOTES was a technique that allowed access to the intra-abdominal cavity via the trans-oral, trans-vesicular, trans-colonic, or trans-vaginal route. This technique provided the realization that apposition of tissues, closure of transmural defects, and multiple other procedures could be successfully achieved in a minimally invasive fashion through natural orifices and thus avoid the associated morbidity of

surgery [2–4]. This NOTES concept of flexible trans-luminal endoscopy was initially conceived in the early 2000s and grew to become a revolution in endoscopy—blurring the boundaries of endoscopy and surgery and igniting a paradigm shift in what was possible within the realm of gastroenterology [4, 5].

While these results were promising and ushered in a generation of forward thinking proceduralists and modernization, the NOTES technique was limited by the reproducibility of results and a lack of available endoscopic tools and platforms. In fact, in 2005, the American Society for Gastrointestinal Endoscopy (ASGE) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) created a working group called the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) to discuss the state of NOTES and review several challenges of the technique [6, 7]. One of the fundamental barriers and critical areas of need to the expansion of NOTES was the development of multi-tasking operating platforms and need for instrumentation to help perform these minimally invasive procedures and manage potential complications.

These limitations, as well the lack of consistent reimbursement, rapidly decreased the use of NOTES and stifled its early popularity, with many surgeons opting instead for minimally invasive laparoscopic techniques [8]. Within the field of laparoscopy, robotic platforms, perhaps the most commonly utilized da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, US), have seen a tremendous adoption. However, endoscopic platforms have not yet experienced this same success in translation to the patient and widespread adoption. Yet, despite this limitation in adoption and non-sustained momentum, the principles and concepts of surgical endoscopy sparked a revolution of innovation and development to produce future operating platforms within surgical endoscopy.

Traditional Endoscope-Assisted Visualization Platforms

Direct Drive Endoscopic System (DDES)

In effort to expand upon the concepts of NOTES and improve associated outcomes, a novel operating platform called the Direct Drive Endoscopic System (DDES, Boston Scientific, Marlborough, MA, US) was created. This DDES was a flexible multi-tasking laparoscopic platform that consisted of an overtube-like sheath which housed three channels [1, 3, 9]. These channels allowed for the interchange of multiple, separately-controlled articulating instruments through a single, flexible, access system [10]. This access system was composed of a 16 mm diameter sheath [9]. The platform was comprised of two articulating arms fitted to the tip of an overtube. An ultra-slim upper endoscope was then inserted through this overtube to provide visualization for the procedure, possessing the advantage of articulating instruments that were not synchronized with that of the endoscope [11]. A rail-based system was used to stabilize the platform and guide manipulation of the end effectors along with two drive handles, which allowed for seven degrees of freedom: surge, pitch, yaw, roll, tool action, heave, and sway (Fig. 3.1) [3].

Importantly, the instruments attached to the overtube could be grasping or scissor forceps—optimized to complement the specific procedure/task [12]. Furthermore, given the novel design, the platform did allow for suturing and knot tying. However, while these instruments varied to ensure the ideal endoscopic tool, the flexible instruments were traction cable-controlled, and therefore possessed the problem of hysteresis. Additionally, with a working length of 55 cm, the platform was unable to access pathology or perform procedures in the distal stomach or small bowel as well as the proximal colon. Another potential disadvantage of this system was the occasional need for two independent operators: one manipulating the two instruments while another

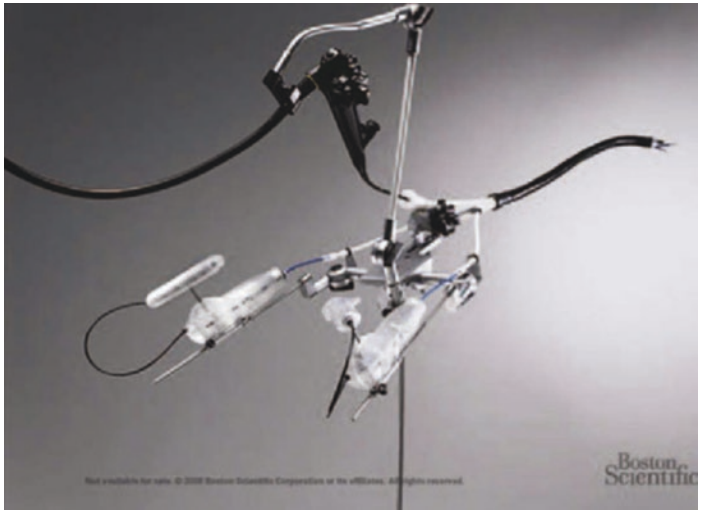

Figure 3.1 Direct Drive Endoscopic System (DDES, Boston Scientific, Marlborough, MA, US)

endoscopist performs conventional endoscopy using a standard endoscope through the overtube [10]. However, the endoscope could be parked in a stable position which could allow for a single operator to perform the procedure. Furthermore, given the angle of view and visual limitations, learning curves and challenges existed for surgeons and endoscopists. Perhaps, most importantly, the system did not allow for a channel dedicated to suction or irrigation—further limiting the visibility during complex procedures. At this time, the DDES is not commercially available and its use has been discontinued.

Incisionless Operating Platform (IOP)

Another multi-tasking surgical platform is the Incisionless Operating Platform (IOP, USGI Medical, San Clemente, CA, US). The platform is able to accomplish tissue apposition and possesses a unique market within the field of bariatric

endoscopy. This USGI platform has received US Food and Drug Administration (FDA) 510(k) approval for general tissue apposition; however, the IOP itself does not have a specific indication for weight loss [13, 14]. Unlike the Apollo Overstitch device (Apollo Endosurgery, Austin, TX, US) which is an attachment to a traditional single channel, or more commonly double channel upper endoscope, the USGI system is a plication platform. The IOP can be used to perform primary endoscopic weight loss procedures, as well as endoscopic revisional procedures for patients with adverse events or complications from bariatric surgery (i.e., weight regain after sleeve gastrectomy or Roux-en-Y gastric bypass as well as management of gastrogastric fistula formation). There is robust clinical data to support its use for bariatric endoscopy [15–17]. Prior to its adoption within the field of bariatric endoscopy, this multi-functional, flexible surgery platform successfully performed NOTES—including cholecystectomy and appendectomy via trans-vaginal, trans-gastric, and trans-umbilical access [18]. The platform has also been utilized to perform anti-reflux procedures as well given its ease of use in the retroflexed position [19].

The IOP, specifically the TransPort system, is similar in appearance to a traditional endoscope; however, the system is larger with multiple ports and directional wheels at the user interface (Fig. 3.2) [3]. The TransPort device consists of a

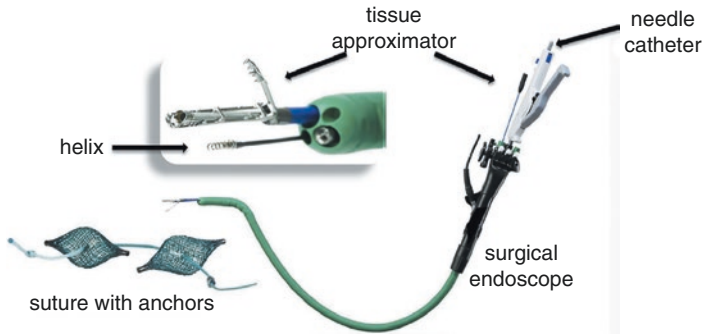

Figure 3.2 Incisionless Operating Platform (IOP, USGI Medical, San Clemente, CA, US)

110 cm by 18 mm overtube-like design with a steerable shaft and four channels (one 7 mm, one 6 mm, and two 4 mm). The 7 mm channel allows for the passage of an ultra-slim upper endoscope down the channel to provide visualization during the procedure. Outside of the TransPort system, the platform is composed of 3 specialized instruments: (1) g-Prox EZ Endoscopic Grasper, (2) g-Lix Tissue Grasper, and (3) g-Cath EZ Suture Anchor Delivery Catheter [15, 16]. The g-Prox is a flexible shaft with a grasper which closes at a 45 degree angle to the axis of the device shaft and allows for approximating full-thickness tissue folds. The g-Lix is a distal helical catheter designed to assist the g-Prox in capturing target tissue while the g-Cath is a catheter system with a hollow needle at its distal tip that, after advancement through the lumen of the gProx, penetrates the gastric wall and creates a plication using polyester mesh snowshoe tissue anchors to create durable serosal fusion [13, 20–22]. At present, the IOP is commercially available in both in the US and worldwide for the treatment of a variety of conditions.

Endomina System

Another bariatric plication platform within the field of surgical endoscopy, the Endomina system (Endo Tools Therapeutics, Gosselies, Belgium), performs tissue apposition and has received a CE mark in Europe. Despite approval in Europe, the device is not commercially available in the US. The Endomina system utilizes an over-the-scope triangulation platform to create transoral anterior-to-posterior greater curvature plications, thereby reducing gastric volume [22]. The platform has two instrument channels with a preloaded needle (TAPES, Endo Tools Therapeutics, Gosselies, Belgium) with suture that is introduced into the platform with a single interrupted suture secured by two T-tags anchors (Fig. 3.3) [23]. The platform is inserted over guidewires into the stomach and can then be opened and tightened around the endoscope which allows the proceduralist to assemble/detach the system when needed without the need for an over-

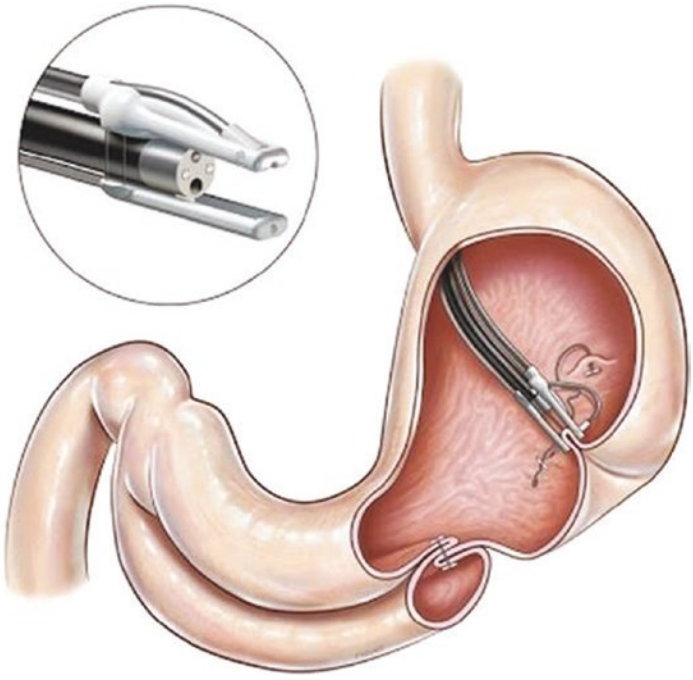

FIGURE 3.3 Endomina system (Endo Tools Therapeutics, Gosselies, Belgium)

tube nor need to remove the device [24]. Endoscopic forceps utilized through the working channel of the endoscope acquire gastric tissue inside the Endomina platform, and the needle for tissue piercing. Each TAPES needle is pre-loaded with two T-tag anchors which are connected by suture material. The anchors are then tightened using a snare until the formation of a tight serosa-to-serosa apposition [24]. In addition to bariatric endoscopy, the platform has also been studied in proof-of-concept cases performing endoscopic submucosal dissection (ESD) as well as endoscopic full-thickness resection (EFTR) [24, 25].

DiLumen C² and the Endolumenal Interventional Platform (EIP)

The DiLumen C² system (Lumendi, Westport, CT, US), including the Endolumenal Interventional Platform (EIP) is a multi-tasking non-robotic ESD platform specifically designed for endoluminal therapy. The platform was designed to improve stability and manipulation of tissue throughout the colon to overcome the complexity and technical issues with conventional ESD and to decrease the steep learning curve associated with training. Similar to the IOP, DiLumen C² is a single-use, disposable system that has received 510(k) approval by the US FDA. Currently, the DiLumen and DiLumenC² platform is commercially available and utilized worldwide. The device has been shown to be safe and effective as well as reduce the substantial learning curve when compared to conventional ESD [26–28]. The first incisionless appendectomy using the DiLumen interventional platform has also been described.

The dual balloon platform can be utilized with endoscope possessing an outer diameter of 8.9 to 11.8 mm and consists of a flexible sheath attached over a standard endoscope. The dual balloon system, one fore (distal) and one aft (proximal) balloon, aims to create a stable, therapeutic zone for endoluminal interventions [29]. The platform also includes two 6-mm working channels at the 3 o'clock and 9 o'clock positions of the hydrophilic sheath which allows for insertion of articulating endoluminal instruments, including interventional graspers, to assist with tissue dissection (Fig. 3.4). Each endoluminal device possesses a wheel and trigger mechanism to allow for rotation, opening, and closing of the device, while the joystick allows providers to control the articulation of the device. The endoluminal DeBakey jaws at the end of the device can be repositioned and can be locked into position at a specific orientation to facilitate visualization and tension on the tissue for dissection. The shaft of the device is 125 cm in length, with a 5 mm outer diameter for use in the 6 mm channel.

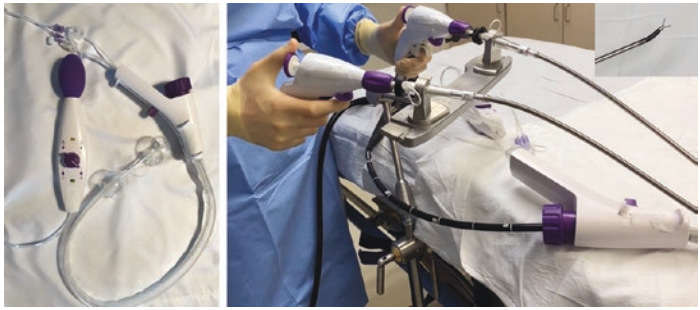

FIGURE 3.4 DiLumen C^2 system and Endolumenal Interventional Platform (EIP) [Lumendi, Westport, CT, US]

LumenR Tissue Retractor System

Initially designed by Sergey Kantsevoy and LumenR LLC (Oxford, Connecticut, US) and later acquired by Boston Scientific, the LumenR Tissue Retractor System (Boston Scientific, Marlborough, MA, US) was designed to improve endoscopic intraluminal removal of colorectal lesions and provide an alternative to invasive surgical resection [25]. This innovative platform aimed to improve ESD and endoscopic mucosal resection (EMR) for the removal of superficial neoplasms within the gastrointestinal tract. The system enabled enhanced visualization of lesions and created a stable working environment to perform dissection. The LumenR platform consisted of a flexible, multi-channel tube with an expandable operating chamber on its distal end, and two associated, specially designed, instrument guides [25]. These articulating guides allowed for four degrees of freedom and insertion of flexible endoscopic instruments (both traditional endoscopic tools and more novel instruments) to perform resection (Fig. 3.5).

The device, though associated with limited data in human cases, was designed to be fit over a pediatric colonoscope to perform endoscopic resection. The guides/arms were able to function to provide traction and ESD knives to facilitate easier dissection. While the device theoretically could be used

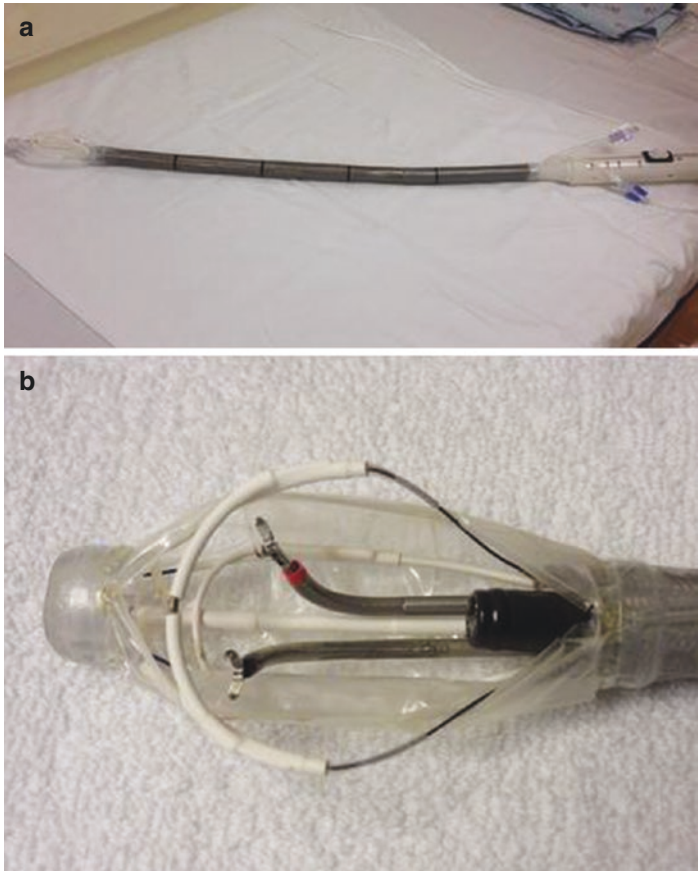

FIGURE 3.5 LumenR Tissue Retractor System. (**a**) Entire device. (**b**) Ebd effector close-up (Boston Scientific, Marlborough, MA, US)

to perform ESD in the upper GI tract as well, it was mostly studied in animal colon models which showed a significant decrease in learning curve and complete, *en-bloc* resection of lesions [30]. One published abstract detailed ESD in human cases [31]. At present, the device is no longer commercially available.

Integrated Visual Function Platforms

EndoSamurai

While we have discussed operating platforms that rely upon conventional endoscopic optics for visualization, the EndoSamurai (Olympus, Tokyo, Japan) is a multi-tasking platform with integrated visual function. The EndoSamurai is comprised of a 15 mm flexible endoscope integrated with lens irrigation function, insufflation/irrigation, two articulating arms, and one conventional operating channel [1]. The overtube-like sheath is similar to that of the DDES system as discussed above though is slightly largely in diameter at 18 mm. This system was designed to operate as a flexible laparoscopic hybrid platform with remote working station to mechanically control the articulating arms (Fig. 3.6) [9]. The working station is similar to robotic or laparoscopic instruments which likely translates to a reduced learning curve for surgeons with this expertise.

One of the main advantages of the EndoSamurai system is the customizability of the platform, allowing for multiple instrument types to assist the proceduralist; including use of standard endoscopic electrosurgical knives, grasper, and forceps—all without the need to remove the endoscope [1]. Again, similar to the DDES system, EndoSamurai requires two individual operators: one for guiding the overtube sheath

Fig. 3.6 EndoSamurai (Olympus, Tokyo, Japan)

and irrigation/suction channel and another to manipulate the articulating instruments [32]. With regard to the articulating arms, the instruments are very long and difficult to maneuver in the retroflexed position, thereby making it perhaps a more ideal platform for intraperitoneal procedures and less intuitive/useful for endoluminal therapies [1, 32]. Overall, data is confined mostly to ex vivo models at this time with limited data translating to human studies [33].

ANUBIScope

Beginning in 2005, the Institut de Recherche contre les Cancers de l'Appareil Digestif (IRCAD) and Karl Storz collaborated on the development of an endoscopic platform to address the need to treat complex endoluminal and transluminal conditions [34]. This collaboration eventually lead to an integrated visual platform called the ANUBIScope (IRCAD, Strasbourg, France, and Karl Storz, Tuttlingen, Germany). This prototype platform consists of a flexible, 110 cm long, four-way articulating endoscope with a 16 mm articulating vertebrae section and an 18 mm tulip-shaped distal tip [34]. The distal tip incorporates two opposing, articulating instruments that contain 4.2 mm working channels and a central 3.4 mm channel which allow for four degrees of freedom to perform dissection or suturing (Fig. 3.7). Unlike the EndoSamurai, an overtube is required for instrument exchange. However, the specialized instrument flaps limited platform maneuverability in narrow spaces with difficulty translating success in ex vivo models to human cases [1]. Similar to DDES and EndoSamurai platforms, the ANUBIScope suffers from difficulty with tip stabilization and articulation making the working arms more difficult to manipulate. Despite these limitations, the ANUBIScope platform received a CE mark. Subsequently a modified robotic system was created using a shortened version of the manual ANUBIScope platform [34, 35]. This newer generation platform has been studied to help providers perform ESD.

Figure 3.7 EndoANUBIScope (IRCAD, Strasbourg, France, and Karl Storz, Tuttlingen, Germany)

Flex Robotic System

The original Flex Robotic System (Medrobotics, Raynham, MA, US) was developed for minimally invasive transoral surgery of the oropharynx, hypopharynx, and larynx; however, its use was later expanded to endoluminal interventions and FDA cleared in 2007. This platform possesses the potential to reduce the steep learning curve associated with ESD and broaden the adoption of complex endoscopic procedures [36]. The Flex Robotic System is comprised of four main components: (1) a stable platform, (2) a console with a user interface to control movement of the robot, (3) a drive to execute robotic positioning, and (4) an instrument support assembly. The platform has a flexible and steerable distal end, providing access to lesions up to 25 cm from the anal verge. The dimensions of the flexible robotic scope are 18 mm by 28 mm, including two 4-mm working channels. The system allows for

the simultaneous use of two manually controlled flexible instruments, including a complete set of 2.0–4.0 mm articulating instruments for grasping, cutting, and suturing under high-definition visualization. The flexible robotic scope is operated via a joystick which the articulating arms are manually manipulated, similar to flexible laparoscopic instruments (Fig. 3.8) [37, 38]. Despite not being entirely robotic, the platform was shown to improve *en bloc* resection and decrease length of procedures among novice ESD providers in ex vivo animal models [36, 39]. The articulating instruments are analogous to transanal endoscopic microsurgery (TEM) or

FIGURE 3.8 Flex Robotic System (Medrobotics, Raynham, MA, US)

transanal minimally invasive surgery (TEMIS). However, due to design and length of the device, the Flex Robotic System only allows for access to distal colorectal lesions up to 25 cm from the anal verge [36].

Robotic Platforms

ViaCath System

Initially developed by EndoVia (Norwood, MA, US), the ViaCath System was a first-generation teleoperated robotic platform for endoluminal surgery which utilized a working endoscope for visualization [40]. The system was comprised of a master console and a slave drive system with an instrument channel fixed alongside the endoscope via an overtube [41, 42]. The master console and the slave manipulators have a haptic interface, with seven degrees of freedom (Fig. 3.9) [43]. The system was developed based upon a previously designed laparoscopic surgical platform developed by EndoVia (i.e., Laprotek System) [44]. ViaCath has been shown to be effective in pre-clinical and in vivo animal testing [45]. However, there is limited data in human cases, as the manipulation forces are likely insufficient to navigate luminal folds and successfully perform endoscopic surgery [40]. In 2005, Hansen Medical (Mountain View, CA, US) acquired EndoVia. That same year, Hansen Medical and Intuitive

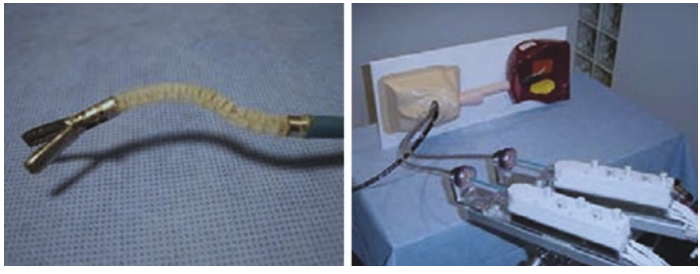

FIGURE 3.9 ViaCath System (Auris Health, Redwood City, CA, US)

Surgical entered into a cross-licensing agreement; however, Hansen was later acquired by Auris Health (Redwood City, CA, US). The ViaCath platform is no longer commercially available at this time.

Master and Slave Translumenal Endoscopic Robot (MASTER) System

The Master and Slave Translumenal Endoscopic Robot (MASTER, Nanyang University, Singapore) is a cable-driven flexible robotic platform that allows bimanual steering of two articulating instruments (Fig. 3.10). The MASTER platform also provides dexterity, triangulation, haptic feedback to maintain spatial orientation, and a navigation system that allows a three-dimensional reconstruction that can be utilized to maneuver in real time [46]. Similar to other platforms, MASTER requires two independent operators: the first operator controlling the master interface slave manipulator and the second directing the endoscope to the desired location and controlling suction/insufflation [38]. Despite demonstrating early improvement in training for ESD for treatment of gastric neoplasms, issues with hysteresis and haptic feedback have been noted to occur [47]. Pre-clinical and limited human studies have demonstrated the effectiveness of the MASTER platform when performing ESD for upper gastrointestinal tract lesions [48–51].

Figure 3.10 Master and Slave Translumenal Endoscopic Robot (MASTER, Nanyang University, Singapore)

Endoluminal Surgical (ELS) System

The Endoluminal Surgical (ELS) System (ColubrisMX, Houston, TX, US) is a next-generation, advanced flexible robotic system that has the benefit of being the first fully robotic endoscopic platform to be evaluated in US clinical trials (Fig. 3.11). The system is designed for upper and lower endoscopy and consists of a patient cart [including instrument controller, conventional flexible endoscope, flexible overtube (colubriscope), and mobile base cart as well as a surgeon console (including high-definition display, master controller, arm rest, and foot pedals). This innovative platform utilizes a flexible shaft with articulating wrist and elbow joints that have 7 degrees of freedom. There are a variety of instruments, including needle driver, pinching forceps, Cadière forceps, monopolar cautery knife, monopolar curved scissors, and rat tooth forceps. The additional working channel of the endoscope also allows for use of conventional endoscopic instruments. At present, the company is undergoing an investigational device exemption (IDE) clinical study to support FDA clearance.

Figure 3.11 Endoluminal Surgical (ELS) System [ColubrisMX, Houston, TX, US]

Additional Gastrointestinal Platforms

Robotic operating platforms have also extended to traditional endoscopy as well. The Invendoscopy E200 system (Invendo Medical, Kissing, Germany) is a robotically assisted colonoscopy system that uses the single-use Invendoscope SC200 as the colonoscope. The handheld controller (ScopeController) is a joystick, which is detachable from the colonoscope (Invendo SC200) and allows for tip deflection, insufflation, suction, and image capture to be completed using only one hand [44, 52]. Similarly designed for diagnostic colonoscopy, the NeoGuide Endoscopy System (NeoGuide Endoscopy System, Los Gatos, CA, US) is a computer-aided colonoscope that utilizes computerized mapping to travel along the natural curves of the colon, resulting in less force applied to the walls of the organ [38, 52]. The scope is comprised of 16 electromechanically controlled segments which allows it to traverse the colonoscope in a snake-like pathway and reduce pressure and force applied to the colonic wall [52]. Perhaps most importantly, NeoGuide which was acquired by Intuitive Surgical (Sunnyvale, CA) in 2009, reduces the formation of colonic loops which may occur during colonoscopy—thereby potentially enabling the procedure to occur with little to no sedation. Multiple other self-advancing colonoscope systems are also underway including the Aer-O-Scope System (GI View, Ramat Gan, Israel), the Sightline ColonoSight (Stryker GI, Haifa, Israel), and the Endotics System (ERA Endoscopy Srl, Pisa, Italy) [53].

Bronchoscopy Platforms

Two additional platforms that are both FDA approved include the Monarch Platform (Auris Health, Redwood City, CA, US) and the Ion Endoluminal Platform (IEP; Intuitive Surgical, Sunnyvale, CA, US). Similar to the platforms designed for the gastrointestinal tract, the Monarch system and bronchoscope consists of an 130° articulating sheath and

an inner bronchoscope that telescopes out of the sheath and can flex 180 degrees in any direction [54]. However, unlike current endoscopic models which are largely analogous to laparoscopic or endoscopic training or equipment, the teleoperated endoluminal bronchoscope model is similar to game controllers with two joysticks and minimal buttons [54, 55]. On the other hand, IEP is comprised of a single bronchoscope, catheter system, and robotic arm. Both platforms have shown promising results and are commercially available [56–61].

Conclusion

There are a variety of potential tools available to the surgeon and endoscopist. These operating platforms have attempted to address the need to provide minimally invasive treatment options for a variety of endoluminal interventions. As such, the field of surgical endoscopy has seen a dramatic shift toward innovation, pushing the boundaries of what is considered possible. In this review, we have discussed the history of the field, early platform designs, and innovative approaches, as well as highlighted new and future robotic options. While many of the operating platforms require more study, future design and innovation are likely to continue to blur the lines between surgery and endoscopy and radically change the future of operating through the endoscope [9].

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Chapter 4
Endolumenal Electrosurgical Energy

J. Christian Brown and Ricard Corcelles

Overview of Endolumenal Electrosurgery

Radiofrequency electrosurgical energy (RFE) has become a critical tool in the armamentarium of the surgeon necessary for the safe and proficient use during endolumenal surgery [1–3]. Although cautery is often used interchangeably with radiofrequency electrosurgical energy, the term is imprecise and implies the denaturation of protein molecules via passive transfer of heat to achieve tissue effects [4]. The capabilities of RFE are multiple, including coagulation and coaptation, desiccation, fulguration, and vaporization. In order to achieve these effects, energy conversion is required; specifically, applied electromagnetic energy is converted to kinetic and converted again to thermal energy. The resultant effect is determined by the properties of the tissue, the length of time which RFE is applied, and the shape of RFE electrode.

Common physical definitions belying RFE are listed in Table 4.1. The most important concept to understand prior to utilizing RFE in surgical and endoscopic procedures is that of

J. C. Brown · R. Corcelles (✉)
Bariatric and Metabolic Institute, Department of General Surgery, Cleveland Clinic, Cleveland, OH, USA
e-mail: BROWNJ59@ccf.org; CORCELR@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_4

Table 4.1 Common electrosurgical definitions

	Symbol	Units	Definition
Voltage	V	Volts	The difference in electrical potential between two circuit points
Current	I	Amperes	Flux of electrons past a circuit point per unit time
Impedance	R	Ohms	Degree to which the circuit components impede the current
Power	P	Watts	Amount of energy delivered per unit time

current density [5]. Current density is electrical current per cross-sectional area and is measured in amperes per square meter (Am^2). As related to RFE, directed and controlled current density can lead to the desired tissue effects [6]. The excessive application of high current densities may have unintended consequences including the indiscriminate dissipation of energy in the form of heat to tissue outside the intended surgical target either by adjacent heat transfer or coupling. The resultant damage can increase the morbidity associated with RFE, including burns, hemorrhage, enteric perforation, and post-polypectomy syndrome. Therefore, it is a common practice to use the lowest power output possible to achieve the desired tissue effect.

Endosurgical Units and Common Endolumenal Devices

The electrosurgical unit (ESU) is a generator that transforms alternating current (AC) electrical energy from low frequency, low voltage (60 Hz, 120 V) to high frequency, high voltage radiofrequency energy (300–500 kHz, 1400–9000 V). Additionally, it controls the power output which can be modified to achieve varying tissue effects; the ESU modifies these effects solely by increasing the voltage through the circuit.

The current is inversely proportional to the impedance of the tissue conducting the current. This tissue characteristic cannot be modified by the ESU. Lastly, the ESU controls the duty cycle, or the frequency (cycles per second) which describes the percentage of time which the unit is delivering energy. By modifying the duty cycle, the tissue effects can also be changed. Of note, the "cut mode" of electrocautery delivers a continuous, low voltage electrical energy to the electrode. The "coag mode," short for coagulation, intermittently delivers high voltage electrical energy.

Electrosurgical devices used in endoscopy can be categorized as unipolar or bipolar categories based upon the circuit design of the instrument. Monopolar, although used interchangeably with the term unipolar, is imprecise. All RFE is bipolar, and therefore, requires two electrodes. Unipolar devices have a singular surgeon-wielded electrode and a dispersive second electrode allowing current passage with interposition of and through the patient [7]. The dispersive electrode distributes the current density over a large skin surface area, thereby reducing tissue effects and preventing tissue injury. Bipolar devices are composed of two mounted electrodes with the passage of current only through the target tissue between the two electrodes.

Endoscopic Unipolar Devices:

- *Snares* (Fig. 4.1a) are designed as a metal loop that can be used to lift and resect tissue, most commonly pedunculated polyps. They can be monofilament or braided and come in a variety of sizes and loop shapes. The target polyp is encircled and tightened, shearing the tissue with or without the application of RFE. If energy is applied, the process is referred to as a "hot snare," allowing tissue biopsy and hemostasis simultaneously. When used in combination with endoscopic mucosal resection (EMR) techniques, snares allow the capture of sessile pathology.
- *Forceps* (Fig. 4.1b) are designed as a metal pair of pincers that can be used to grab and bite to obtain a tissue sample. Like snares, it can be used with or without RFE, and if energy is applied, is known as a "hot forceps." Forceps

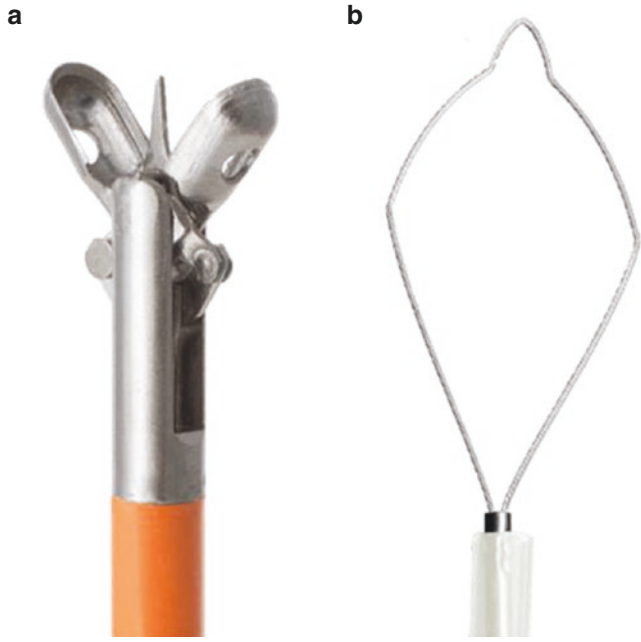

FIGURE 4.1 (**a**) Micro-Tech biopsy forceps and (**b**) snare [26]

come in a variety of sizes, jaw shapes, and textures. A central spike allows collection of multiple tissue samples without removing the forceps, facilitating retained view of tissue targets and reduced tissue sample variation.

- *Endoscopic submucosal dissection (ESD) knives* (Fig. 4.2) come in a variety of tip shapes and sizes, offering a tailored knife tip for varying procedures and surgeon preferences. ESD is most commonly used for larger lesions, typically greater than 2 cm in diameter. The procedure involves submucosal lift, mucosotomy, and submucosal tunneling with creation of a mucosal flap specimen.
- *Sphincterotomes* (Fig. 4.3) employed in endoscopic retrograde cholangiopancreatography (ERCP) are available in two shapes: needle knife and pull sphincterotomes. Pull sphincterotomies are most commonly utilized by endolu-

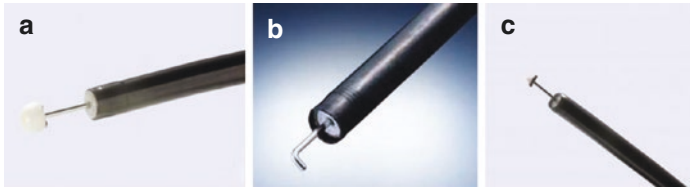

FIGURE 4.2 A variety of electrosurgical knives. (**a**) ceramic-tipped Olympus IT (**b**) hook, and (**c**) triangle tip knife [27]

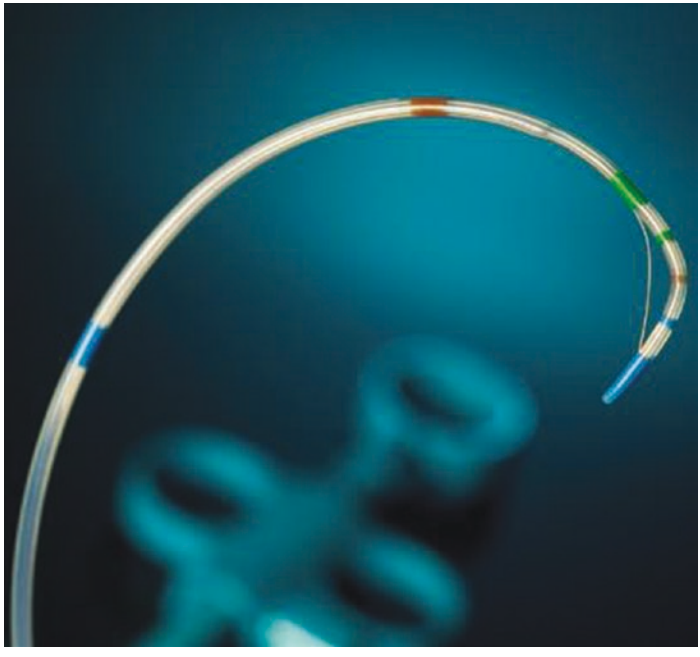

FIGURE 4.3 A duct-cannulating, pull-type sphincterotome [28]

menal surgeons, because needle knife techniques require the placement of a pancreatic duct stent prior to incision of the sphincter [8]. The pull sphincterotome is bow shaped, with a tense, bowing wire, and flexible plastic catheter.

- *Balloon-based thermocoupled electrode arrays (Stretta® catheters)* are designed to allow the radial application of RFE to the muscularis propria of the lower esophageal sphincter (LES). Application of this low power, low intensity radiofrequency energy leads to augmentation of LES function. Stretta's mechanism of action is incompletely understood, though it is thought secondary to both interruption of LES-relaxing neural pathways and increased thickness of the LES muscle complex [9].

Endoscopic Bipolar Devices:

- *Multipolar electrocoagulation probes (MPEC, "Gold" probes)* (Fig. 4.4) are designed with a gold electrode mounted upon a flexible plastic tip useful for hemorrhage

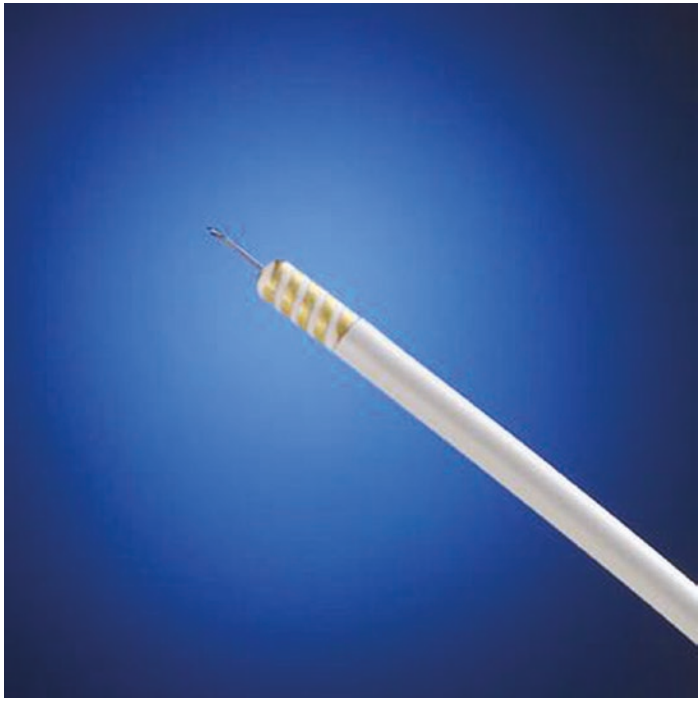

FIGURE 4.4 Bipolar hemostasis catheter known as an "MPEC" or "Gold probe" catheter [29]

control and mucosal desiccation. It is available in two sizes, and with supplemental features such as an irrigation channel and injection needle. The most important technique used with this technology is the direct compression of the bleeding vessel prior to activation in order to achieve complete coaptation of the vessel walls.

- *Radiofrequency array (RFA) catheters* (Fig. 4.5) exist as two distinctly shaped electrode endings: a paddle shape and a balloon-based circumferential array. These catheters are designed to ablate large areas of mucosa. RFA catheters are commonly used within the enteric lumen for obliteration of esophageal mucosal metaplasia, arteriovenous malformations, and radiation proctitis.

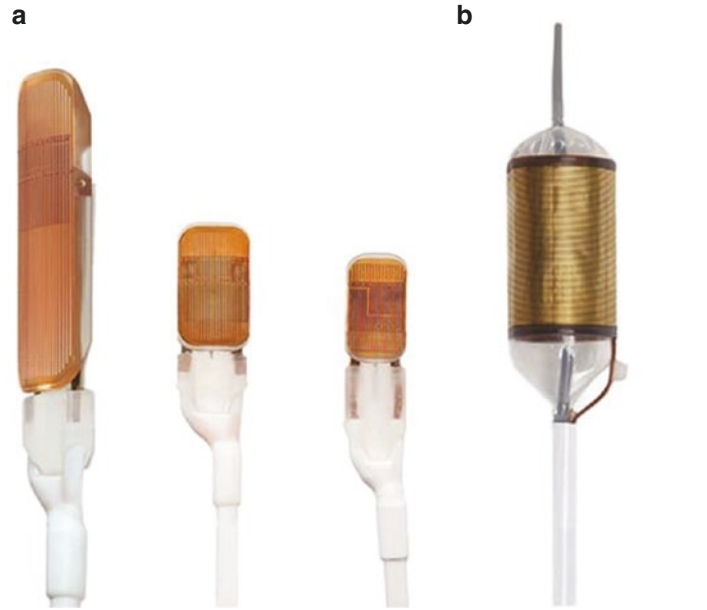

FIGURE 4.5 A variety of radiofrequency ablation catheters. (**a**) Barrx™Focal paddle catheter and (**b**) Barrx™360 balloon catheters [30]

Risk Associated with Endolumenal Electrosurgical Devices

Surgeons utilizing radiofrequency energy should be facile with its use and understand the hazards unique to specific electrodes and endolumenal environment in order to minimize risk. In general, it is advised to use the lowest energy setting on the ESU to achieve the desired tissue effect.

- *Hemorrhage*: If attempting to control hemorrhage endolumenally, the use of two modalities (e.g., application of RFE, clipping, or injection) significantly reduces the risk of recurrent hemorrhage [10, 11]. Hemorrhage is the most common complication of a polypectomy procedure. In the acute phase, a risk of immediate bleeding decreases with the use of high voltage power setting, but cut and coagulation mode bleeding rates are equivalent, estimated at 2–4% [12]. However, coagulation mode is also associated with an increased rate of delayed bleed (3–5 days) [13]. Additionally, the use of coagulation mode may lead to decreased histological quality of pathological specimens and increased depths of mucosal injury [14, 15].
- *Perforation*: There is no difference in perforation rates when using cut or coagulation modes, when the site of cautery is controlled as a study variable [16]. The largest determinate of perforation rate is the thickness of the tissue being subjected to RFE; thin-walled structures such as the duodenum and cecum are more likely to perforate than thicker structures such as the stomach and rectum [17]. The use of a saline lift at the target tissue base may reduce the risk of perforation by increasing the distance of the highest current density and heat generation from the enteric serosa [18, 19]. Tenting the mucosa away from the adjacent muscularis propria prior to application of electrosurgical energy may also reduce perforation risk [20].
- *Coupling*: Couple can be categorized as direct, capacitive, or antenna coupling. Direct coupling involves direct contact between the endoscope and electrode or the polyp and the mucosa in contact opposite the target tissue.

Direct coupling of the opposite wall may be reduced by actively recognizing the electrode tip position and enteric lumen diameter, as well as taking care to minimize overtenting of target tissue. Electrothermal injury may also be the result of capacitive coupling defined as electrical current in metal instruments running in parallel but not directly contacting the active electrode, despite intact insulation [21]. A variation of this is called "antenna coupling," requiring only the close, parallel alignment of the device cords as opposed to the electrodes. Tissues in closest proximity to the camera port of the endoscope are at highest risk of injury, as this port experiences the greatest change in temperature. The device yielding the highest risk is the biopsy forceps, generating the greatest temperature change of 31° C at 60W ESU output.

Future Directions

A fundamental understanding of electrosurgery and its uses permits surgical safety and active research. From October 2017 to 2021, there are more than 597 unique publications evaluating some aspect of electrosurgery available on the PubMed search engine [22]. Additionally, more than 270 trials evaluating the effects of RFE are registered with clinicaltrials.gov [23]. Independent consulting firms have estimated a year-over-year electrosurgical device market compound growth rate of approximately 4% in the five-year period between 2019 and 2024, with a total global market valuation of $6.64 billion [24]. Outlooks are more impressive when the global electrosurgical device market is combined with the endoscopy device market on which it is dependent, with the total value in 2027 estimated at $43.8 billion [25].

Given the scientific, clinical, and market activity surrounding RFE, it is no surprise that future directions of RFE research include improving the safety profile of devices used in radiofrequency electrosurgery, but also the development of novel devices, techniques, and procedures for advancement of endolumenal surgery.

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Chapter 5
Endoscopic Training—Surgeon and GI Paradigms

Matthew D. Burstein and Eleanor C. Fung

Abbreviations

ABS	American Board of Surgery
ACE	Assessment of Competency in Endoscopy
ACGME	Accreditation Council for Graduate Medical Education
ASGE	American Society for Gastrointestinal Endoscopy
EGD	Esophagogastroduodenoscopy
EMR	Endoscopic Mucosal Resection
ERCP	Endoscopic Retrograde Cholangiopancreatography
ESD	Endoscopic Submucosal Dissection
EUS	Endoscopic Ultrasonography
FEC	Flexible Endoscopy Curriculum

M. D. Burstein (✉)
Department of Surgery, University Hospitals, Cleveland, OH, USA
e-mail: Matthew.Burstein@uhhospitals.org

E. C. Fung
Department of Surgery, University at Buffalo, Buffalo, NY, USA
e-mail: ecfung@buffalo.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_5

FES	Fundamentals of Endoscopic Surgery
FNA	Fine-Needle Aspiration
GAGES-C	Global Assessment of Gastrointestinal Endoscopic Skills - Colonoscopy
GAGES-UE	Global Assessment of Gastrointestinal Endoscopic Skills - Upper Endoscopy
GCC	Gastroenterology Core Curriculum
GLC	Gastroenterology Leadership Council
GIS	Gastrointestinal surgery
MIS	Minimally Invasive Surgery
MCSAT	Mayo Colonoscopy Skills Assessment Tool
MRCP	Magnetic Resonance Cholangiopancreatography
PEG	Percutaneous Endoscopic Gastrostomy
POEM	Per-Oral Endoscopic Myotomy
POP	Per-Oral Pyloromyotomy
RRC-S	Residency Review Committee for Surgery
SAGES	Society of American Gastrointestinal and Endoscopic Surgeons

Scope of Practice for GI Endoscopists vs General Surgeons

Endoscopy as a concentration developed much later than gastroenterology as a subspecialty, with the adoption of short, large diameter fiber optic scopes in the late 1950s. These tools were solely diagnostic in nature. An exhaustive history of endoscopy is reserved for other mediums, but suffice to say the existence of this book is testament to the explosive growth of endoscopy as a tool with little present limitations in the diagnosis, and now treatment of a wide spectrum of gastrointestinal diseases. The practice of such a varied and complex set of procedures is justifiably heterogeneous, not just between dedicated GI endoscopists and their surgical colleagues, but even within endoscopic practitioners.

There is no need for endoscopists to perform every available procedure. Nontherapeutic gastroenterologists perform a myriad of diagnostic procedures including routine upper and lower endoscopy, and some interventional proce-

dures including tattooing of lesions, small polypectomy, limited hemostatic procedures, and even percutaneous gastrostomy tube placement [1]. General surgeons train during modern residency within the subset of these basic procedures. Therapeutic gastroenterologists may go a step further, pursuing advanced training and practice certifications in endoscopic submucosal dissection (ESD), endoscopic retrograde cholangiopancreatography (ERCP), advanced stenting and dilations, endoscopic ultrasound including cholecystostomies and gastroenterostomies, and procedures that augment or replace classical surgical approaches such as POP (Per-Oral Pyloromyotomy) and POEM (Per-Oral Endoscopic Myotomy). Flexible endoscopy fellowship for general surgeons may expand surgical training into many of these minimally invasive techniques as well. This chapter seeks to summarize the unique pathways and accreditations required for both groups as they gain increasing endoscopic competencies.

ACGME/ABS Requirements for Surgical Trainees

While endoscopy has historically not been the primary focus of general surgery training across the country, the adoption of more minimally invasive approaches in recent decades has folded endoscopy training into the resident core curriculum. For many procedures once commonplace in general surgery training, minimally invasive techniques have nearly eclipsed open more invasive approaches [2]. There is evidence that trainees graduating in 2011 have conducted nearly double the endoscopies of their 2005 peers, and that colonoscopy is the second most common procedure performed by a resident now [3]. This is of course both the result of the increasing necessity of endoscopy and also investments the American Board of Surgery (ABS) made in endoscopic training beginning in 1980.

As the major US accreditation body for general and subspecialty general surgery, the ABS mandated that all graduating surgeons perform a variety of endoscopic interventions

such as bronchoscopy, esophagoscopy, gastroscopy, colonoscopy, and choledochoscopy. The ABS then began formalizing the endoscopy curriculum of surgical residents. For surgical residents graduating in 2009, the Residency Review Committee for Surgery (RRC-S) changed endoscopy requirements from 29 endoscopies to 50 colonoscopies and 35 upper endoscopies [4]. By most accounts, these thresholds have been met without heavy reliance on cases from outside general surgery departments. However, in 2011, the American Society for Gastrointestinal Endoscopy, the American Association for the Study of Liver Diseases, the American College of Gastroenterology, and the American Gastroenterological Association released a joint position paper stating that these requirements are not sufficient to achieve competency. The groups expressed concern "that this brief exposure to endoscopy during surgical endoscopy training is then being used to obtain privileges in endoscopy once a surgical resident completes training." The joint society position paper cited two studies providing evidence that 200 to 500 lower endoscopies are necessary to reach competency based solely on gastroenterology fellows [5, 6]. In response, the ABS cited a prospective study that examined outcomes of 13,580 lower endoscopies performed by surgeons, surgical fellows, and surgical residents which revealed markers of competency achieved after 50 procedures, with only modest improvement thereafter [7]. A similar study for upper endoscopy recommended against minimum thresholds, as completion rates were not influenced by experience, only procedure time [8]. Finally, lesion detection and lower endoscopy performance metrics between gastroenterologists and their surgical colleagues were equivocal [9, 10]. It is unlikely an exact threshold of cases dictates safety and competency for every individual trainee, but all societies should agree that more comprehensive assessments were appropriate.

The main surgical body concerned with flexible endoscopy, the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), developed the Fundamentals of Endoscopic Surgery (FES) as one part of the proposed ABS

flexible endoscopy curriculum to better assess surgical trainees. The FES includes a comprehensive web-based didactic component of flexible endoscopy with 12 modules, a high-stakes written multiple-choice test, and a five-module virtual reality skills exam - all designed to teach and validate basic endoscopic knowledge and skills [11]. The written exam is highly correlated with resident training level [12]. The skills simulation has a high test–retest reliability, correlates with participant endoscopic experience [13], and mirrors other established measures of clinical colonoscopy performance [14]. The successful passing of FES has been mandated by the ABS for all surgical residents completing residency in 2018. Early comparisons of general surgery residents to 1st year GI fellows using these tests demonstrate that there is a spectrum of technical competency across institutions and trainees, with endoscopic loop reduction as an especially challenging hurdle to overcome [15]. Gastroenterology fellows do more consistently pass the cognitive portion of the exam, perhaps owing to their immersion in the subject. As regimented curriculum in endoscopy is more widely adopted in surgery programs, this gap should close.

Complementary to the FES simulation skills assessment are the clinical assessment tools known as GAGES-UE (Global Assessment of Gastrointestinal Endoscopic Skills—Upper Endoscopy; Fig. 5.1) and GAGES-C (colonoscopy; Fig. 5.2) which monitor skills acquisition over the years of training [16]. Developed by expert upper and lower endoscopists, GAGES was developed as a method of objectively scoring clinical performance more accurately over the course of training, starting in their post-graduate year (PGY) 2 or 3 (Table 5.1). The expectation is that by the PGY 4 year residents should achieve GAGES scores that are on par with "experienced" endoscopists. It is interesting to note that when applied to residents as they performed more cases, there was no significant increase in score between the 35 to 130 cases and those who had performed more than 130 upper endoscopies. The curve of procedures versus GAGES plateaued at 50 cases. A similar phenomenon was present with

GAGES - UPPER GI ENDOSCOPY SCORESHEET

GLOBAL ASSESSMENT OF GASTROINTESTINAL ENDOSCOPIC SKILLS

INTUBATION OF THE ESOPHAGUS — SCORE ☐

Reflects patient management, understanding of anatomy and sedation

5 Able to independently (successfully) intubate esophagus without patient discomfort
4
3 Requires detailed prompting and cues
2
1 Unable to properly intubate requiring take over

SCOPE NAVIGATION — SCORE ☐

Reflects navigation of the GI tract using tip deflection, advancement/withdrawal and torque

5 Expertly able to manipulate the scope in the upper GI tract autonomously.
4
3 Requires verbal guidance to completely navigate the upper GI tract
2
1 Not able to achieve goals despite detailed verbal cues, requiring take over

ABILITY TO KEEP A CLEAR ENDOSCOPIC FIELD — SCORE ☐

Utilization of insufflation, suction and/or irrigation to maximize mucosal evaluation

5 Uses insufflation, suction, and irrigation optimally to maintain clear view of endoscopic field
4
3 Requires moderate prompting to maintain clear view
2
1 Inability to maintain view despite extensive verbal cues

INSTRUMENTATION (if applicable; leave blank if not applicable) — SCORE ☐

Random biopsy: targeting is assessed by asking the endoscopist to take another biopsy from the identical site. Targeted instrumentation: evaluation is based on ability to direct the instrument to the target.

5 Expertly directs instrument to desired target
4
3 Requires some guidance and/or multiple attempts to direct instrument to target
2
1 Unable to direct instrument to target despite coaching

QUALITY OF EXAMINATION — SCORE ☐

Reflects attention to patient comfort, efficiency, and completeness of mucosal evaluation

5 Expertly completes the exam efficiently and comfortably
4
3 Requires moderate assistance to accomplish a complete and comfortable exam
2
1 Could not perform a satisfactory exam despite verbal and manual assistance requiring takeover of the procedure

OVERALL SCORE: ☐

FIGURE 5.1 Global Assessment of Gastrointestinal Endoscopic Skills - Upper Endoscopy

75 colonoscopies, though there was a significant increase in score between residents at a 50 case cutoff and also at the 140 case proficiency cutoffs [17]. The overall expectations for residents in US surgical programs are summarized from the

GAGES - COLONOSCOPY SCORESHEET

GLOBAL ASSESSMENT OF GASTROINTESTINAL ENDOSCOPIC SKILLS

SCOPE NAVIGATION — SCORE ☐

Reflects navigation of the GI tract using tip deflection, advancement/withdrawal and torque

5 Expertly able to manipulate the scope in the GI tract autonomously
4
3 Requires verbal guidance to completely navigate the lower GI tract
2
1 Not able to achieve goals despite detailed verbal guidance requiring takeover

USE OF STRATEGIES — SCORE ☐

Examines use of patient positions, abdominal pressure, insufflation, suction and loop reduction to comfortably complete the procedure

5 Expert use of appropriate strategies for advancement of the scope while optimizing patient comfort
4
3 Use of some strategies appropriately, but requires moderate verbal guidance
2
1 Unable to utilize appropriate strategies for scope advancement despite verbal assistance

ABILITY TO KEEP A CLEAR ENDOSCOPIC FIELD — SCORE ☐

Utilization of insufflation, suction and/or irrigation to maximize mucosal evaluation

5 Uses insufflation, suction, and irrigation optimally to maintain clear view of endoscopic field
4
3 Requires moderate prompting to maintain clear view
2
1 Inability to maintain view despite extensive verbal cues

INSTRUMENTATION (if applicable; leave blank if not applicable) — SCORE ☐

Random biopsy: targeting is assessed by asking the endoscopist to take another biopsy from the identical site. Targeted instrumentation: evaluation is based on ability to direct the instrument to the target.

5 Expertly directs instrument to desired target
4
3 Requires some guidance and/or multiple attempts to direct instrument to target
2
1 Unable to direct instrument to target despite coaching

QUALITY OF EXAMINATION — SCORE ☐

Reflects attention to patient comfort, efficiency, and completeness of mucosal evaluation

5 Expertly completes the exam efficiently and comfortably
4
3 Requires moderate assistance to accomplish a complete and comfortable exam
2
1 Could not perform a satisfactory exam despite verbal and manual assistance requiring takeover of the procedure

OVERALL SCORE: ☐

FIGURE 5.2 Global Assessment of Gastrointestinal Endoscopic Skills - Colonoscopy

Flexible Endoscopy Curriculum for General Surgery Residents [18]. It is anticipated that by the fourth year of surgical training residents consistently achieve a minimum GAGES score of 18.

Table 5.1 Flexible endoscopy curriculum for general surgery residents [18]

Level	Cognitive milestones	Technical milestones
I (PGY 1-2)	Basic understanding of GI diseases and endoscopic GI anatomy.	Simulation or clinical tutorial exposure with an emphasis on basic scope manipulation including one-handed wheel deflection, control of suction, irrigation, and insufflation, and passage of instruments through the working channel.
II (PGY 1-2)	Basic understanding of flexible endoscope function.	Simulation or clinical exposure with demonstration of proper endoscope setup and function, troubleshooting of common problems, and a continued emphasis on basic scope manipulation.
III (PGY 2-3)	Indications and contraindications of upper and lower flexible endoscopy, periprocedural patient management.	Simulation exposure or clinical tutorial, dedicated endoscopy experience, intraoperative endoscopy, ICU endoscopy.
IV (PGY 3-4)	Image differentiation of normal/abnormal pathology, understanding intraoperative and postoperative GI anatomy, appropriate use of endoscopy.	Intraoperative endoscopy, ICU endoscopy, continued endoscopic experience.
V (PGY 4-5)	Tools/adjuncts for therapeutic endoscopy.	Intraoperative endoscopy, ICU endoscopy, continued endoscopic experience. In this module any skills listed under the description of a surgical endoscopist that have not been mastered should be performed until a GAGES score of 18 or greater is achieved.

Advanced Surgical Endoscopy Training

As procedures are progressively augmented or replaced by their endoscopic equivalents, the development of advanced training for general surgery residents was inevitable. In contrast to the now regimented training recommendations for general surgery residents seeking basic endoscopy skills and knowledge, advanced training beyond diagnostic and limited therapeutic endoscopy has not been historically well-structured. The American Surgical Association Blue Ribbon Committee issued a report in 2004, stating these programs were "unregulated, unsupervised, nonuniform, and uncertified" [19]. Three main GI surgical societies (The Society of American Gastrointestinal and Endoscopic Surgeons, the American Hepato-Pancreato-Biliary Association, and the Society for Surgery of the Alimentary Tract) formed the Fellowship Council, a joint institution representing the MIS/GIS programs throughout North America, and developed a formalized match process with published fellowship guidelines. A joint agreement was approved by the Accreditation Council for Graduate Medical Education (ACGME) to allow for review and accreditation for institutions interested in providing such fellowships. Those processes continue today, with published guidelines for variants in GI and thoracic surgery sub-specialization which regulate almost 150 programs.

Presently Advanced GI MIS fellows are required to conduct 50 endoscopies, without set thresholds on specific procedures. Dedicated Flexible Endoscopy fellowships exist that require at least 100 procedures. There were four listed by the Fellowship Council in 2020, but it is worth noting that many programs incorporate aspects of these programs into minimally invasive surgery fellowships. The associated curriculum for Flexible Endoscopy consists of 6 major units, some with subunits:

Unit 1—Acid-peptic disease
Unit 2—Biliary tract diseases and pancreatic disorders
Unit 3—Gastrointestinal malignancy

Unit 4—Motility
Unit 5—GI Pathology
Unit 6—Endoscopy

While the Fellowship Council guidelines reference the recommended numbers from the ASGE (discussed later) to achieve privileges, there are no hard thresholds for the fellowship beyond 100 procedures. Upper endoscopy, including pH probes and manometry, is considered required skills. For endoscopic retrograde cholangiopancreatography, if the fellow intends to practice the expectation is a minimum 80% cannulation success rate, with at least 60% of cases therapeutic. The fellow should have exposure to sphincterotomy, stone extraction, and stenting [20]. The variation in practice patterns and the relatively new adoption of many of these techniques hinder a regimented approach proscribed to the more common Advanced GI/MIS, Bariatric, and Foregut fellowships where cases are more predictable.

ASGE Requirements for Gastroenterology Fellows

Specialization in gastroenterology, a three-year fellowship at the conclusion of internal medicine training, is a focused process that involves both cognitive and technical elements. Fellows are required to maintain a broad range of knowledge related to endoscopy including indications, contraindications, and complications of an expanding panel of possible procedures. Successful practice requires the ability to perform, interpret, and integrate findings into the management of patients. Skills are acquired in a stepwise approach beginning with maneuvers (such as loop reduction, retroflexion, torque, etc.) toward the mastery of standard and occasionally advanced procedures, depending on the fellowship.

The Gastroenterology Core Curriculum (GCC) was first developed in 1996, when training expanded from 2 to 3 years, and revised in 2007 by the Gastroenterology Leadership Council (GLC). The gastroenterology fellowship now includes

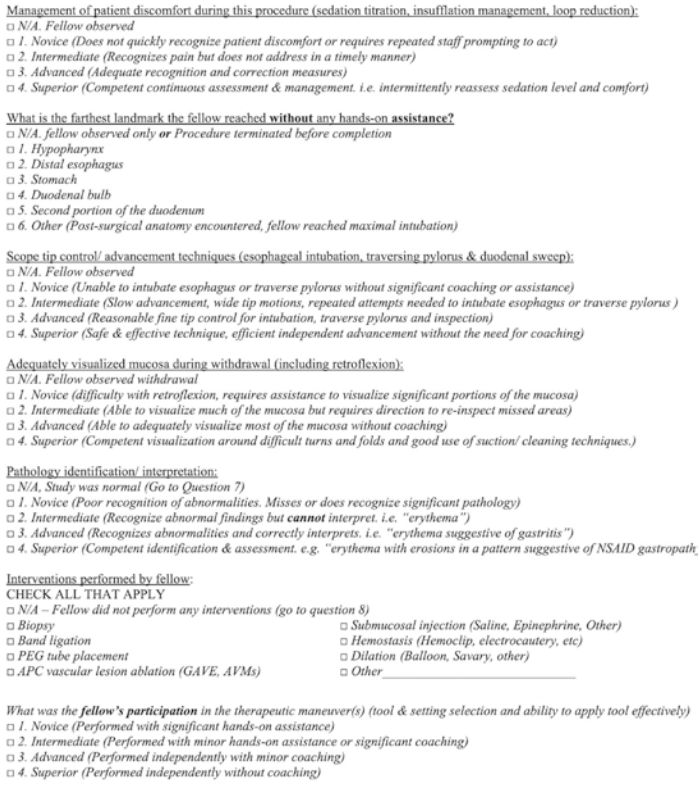
18 months of core curriculum clinical experience, with 3–6 months of research and an additional 12 months of specialty training. The GCC represents best practices in training consensus by four gastroenterology societies (The American Gastroenterological Association, the American Association for the Study of Liver Disease, the American Society for Gastrointestinal Endoscopy, and the American College of Gastroenterology). The recommendations outline training processes in 17 different topics of gastroenterology and list skills and knowledge desired at the time of fellowship completion. The endoscopy section of the GCC describes goals of training, processes of endoscopic training including facility and faculty, competence evaluation, and threshold numbers of standard endoscopic procedures fellows are to complete prior to graduation. The ASGE website makes these requirements available as "Principles of Training in Gastrointestinal Endoscopy" [21], "Esophagogastroduodenoscopy (EGD) Core Curriculum" [22], and "Colonoscopy Core Curriculum" [23].

Specific requirements for technical training have evolved since inception since the American College of Physicians had initially proposed a minimum of 50 colonoscopies with 15 polypectomies, and 50 upper endoscopies to achieve competency for hospital privileges back in 1987 [24]. The ASGE proposed a basic minimum in 1991 of 100 supervised colonoscopies with a mandatory 20 polypectomies, and 100 upper endoscopies based on the endoscopic experiences of only seven gastroenterology fellows and five surgical residents. The study observed that cecal intubation was successful in 84% of patients after 100 endoscopies, and esophageal intubation was successful in 90% after 100 procedures [25]. In 2002, the minimum procedure counts reached their present incarnation, with the ASGE requiring 140 colonoscopies and 130 upper endoscopies [26, 27]. These ASGE recommendations are somewhat modest compared to other international organizations [28] listed in Table 5.2. Especially with regard to independent cecal intubation rate, the required minimums do not seem to yield reliable competencies when studied broadly [29].

Table 5.2 International recommendations for minimum number of procedures to ensure competency [28]

Organization	Minimum colonoscopy	Minimum EGD
Joint Advisory Group on Gastrointestinal Endoscopy (JAG)—United Kingdom	100 (*200 for ileal intubation*)	200
American Society for Gastrointestinal Endoscopy (ASGE)	140	130
Canadian Association of Gastroenterology (CAG)	100	125
European Board of Gastroenterology (EBG)	100	300
Conjoint Committee for Recognition of Training in Gastrointestinal Endoscopy of Australia	100	200

In addition to simple case counts, the ASGE has also sought to validate indexes of technical performance in the practice of colonoscopy. Standardization of assessment is favored over the subjective assessments of supervising staff. The Mayo Colonoscopy Skills Assessment Tool (MCSAT) was developed as a method of ongoing, formalized assessment that spans a broad range of both motor and cognitive skills in a standardized and measurable way. Fellow progress can be tracked and objectively compared to mean anticipated performance at levels of training and number of procedures performed [30]. Competency marks using the MCSAT were achieved by 275 procedures on average while studying 41 GI fellows at a single institution. Independent cecal intubation rates of 85% and cecal intubation times of 16 min or less were also achieved at 275 procedures on average [31], much higher than the minimum case counts internationally. Building on the validations of the MCSAT, the ASGE developed the Assessment of Competency in Endoscopy (ACE) skills



Management of patient discomfort during this procedure (sedation titration, insufflation management, loop reduction):
□ *N/A. Fellow observed*
□ *1. Novice (Does not quickly recognize patient discomfort or requires repeated staff prompting to act)*
□ *2. Intermediate (Recognizes pain but does not address in a timely manner)*
□ *3. Advanced (Adequate recognition and correction measures)*
□ *4. Superior (Competent continuous assessment & management. i.e. intermittently reassess sedation level and comfort)*

What is the farthest landmark the fellow reached **without** any hands-on **assistance?**
□ *N/A. fellow observed only* ***or*** *Procedure terminated before completion*
□ *1. Hypopharynx*
□ *2. Distal esophagus*
□ *3. Stomach*
□ *4. Duodenal bulb*
□ *5. Second portion of the duodenum*
□ *6. Other (Post-surgical anatomy encountered, fellow reached maximal intubation)*

Scope tip control/ advancement techniques (esophageal intubation, traversing pylorus & duodenal sweep):
□ *N/A. Fellow observed*
□ *1. Novice (Unable to intubate esophagus or traverse pylorus without significant coaching or assistance)*
□ *2. Intermediate (Slow advancement, wide tip motions, repeated attempts needed to intubate esophagus or traverse pylorus)*
□ *3. Advanced (Reasonable fine tip control for intubation, traverse pylorus and inspection)*
□ *4. Superior (Safe & effective technique, efficient independent advancement without the need for coaching)*

Adequately visualized mucosa during withdrawal (including retroflexion):
□ *N/A. Fellow observed withdrawal*
□ *1. Novice (difficulty with retroflexion, requires assistance to visualize significant portions of the mucosa)*
□ *2. Intermediate (Able to visualize much of the mucosa but requires direction to re-inspect missed areas)*
□ *3. Advanced (Able to adequately visualize most of the mucosa without coaching)*
□ *4. Superior (Competent visualization around difficult turns and folds and good use of suction/ cleaning techniques.)*

Pathology identification/ interpretation:
□ *N/A, Study was normal (Go to Question 7)*
□ *1. Novice (Poor recognition of abnormalities. Misses or does recognize significant pathology)*
□ *2. Intermediate (Recognize abnormal findings but* ***cannot*** *interpret. i.e. "erythema")*
□ *3. Advanced (Recognizes abnormalities and correctly interprets. i.e. "erythema suggestive of gastritis")*
□ *4. Superior (Competent identification & assessment. e.g. "erythema with erosions in a pattern suggestive of NSAID gastropath*

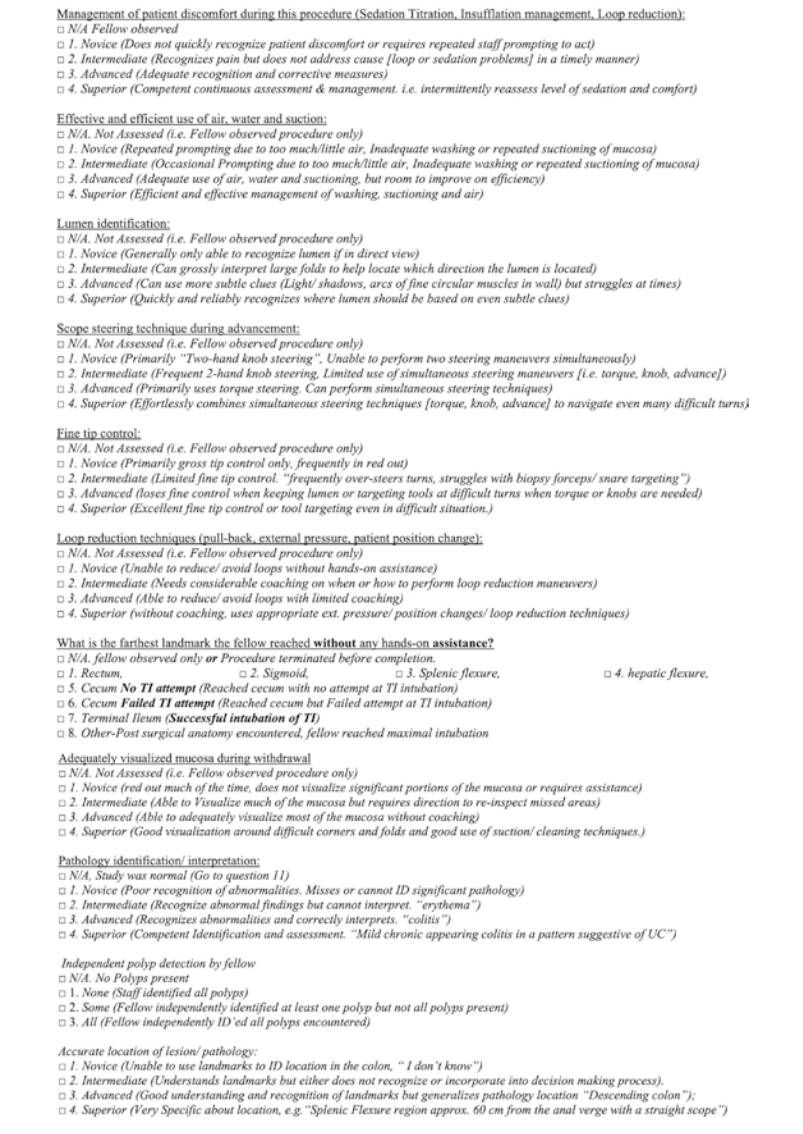
Interventions performed by fellow:
CHECK ALL THAT APPLY
□ *N/A – Fellow did not perform any interventions (go to question 8)*
□ *Biopsy*
□ *Band ligation*
□ *PEG tube placement*
□ *APC vascular lesion ablation (GAVE, AVMs)*
□ *Submucosal injection (Saline, Epinephrine, Other)*
□ *Hemostasis (Hemoclip, electrocautery, etc)*
□ *Dilation (Balloon, Savary, other)*
□ *Other*_____

What was the ***fellow's participation*** *in the therapeutic maneuver(s) (tool & setting selection and ability to apply tool effectively)*
□ *1. Novice (Performed with significant hands-on assistance)*
□ *2. Intermediate (Performed with minor hands-on assistance or significant coaching)*
□ *3. Advanced (Performed independently with minor coaching)*
□ *4. Superior (Performed independently without coaching)*

FIGURE 5.3 Technical components only, ASGE ACE in Endoscopy—EGD

assessment tools for upper and lower endoscopy [32]. Validation of the ACE for colonoscopy approximates the MCSAT [33]. The technical components of the ACE tools are reproduced in Fig. 5.3 (EGD) and Fig. 5.4 (colonoscopy) for comparison against the GAGES used in General Surgery training.

At this time, all US GI fellows are required to complete the ASGE requirements set above, and must be able to provide routine screening endoscopy and common therapeutic procedures such as polypectomies and hemostasis techniques



Management of patient discomfort during this procedure (Sedation Titration, Insufflation management, Loop reduction):
□ *N/A Fellow observed*
□ *1. Novice (Does not quickly recognize patient discomfort or requires repeated staff prompting to act)*
□ *2. Intermediate (Recognizes pain but does not address cause [loop or sedation problems] in a timely manner)*
□ *3. Advanced (Adequate recognition and corrective measures)*
□ *4. Superior (Competent continuous assessment & management. i.e. intermittently reassess level of sedation and comfort)*

Effective and efficient use of air, water and suction:
□ *N/A. Not Assessed (i.e. Fellow observed procedure only)*
□ *1. Novice (Repeated prompting due to too much/little air, Inadequate washing or repeated suctioning of mucosa)*
□ *2. Intermediate (Occasional Prompting due to too much/little air, Inadequate washing or repeated suctioning of mucosa)*
□ *3. Advanced (Adequate use of air, water and suctioning, but room to improve on efficiency)*
□ *4. Superior (Efficient and effective management of washing, suctioning and air)*

Lumen identification:
□ *N/A. Not Assessed (i.e. Fellow observed procedure only)*
□ *1. Novice (Generally only able to recognize lumen if in direct view)*
□ *2. Intermediate (Can grossly interpret large folds to help locate which direction the lumen is located)*
□ *3. Advanced (Can use more subtle clues (Light/ shadows, arcs of fine circular muscles in wall) but struggles at times)*
□ *4. Superior (Quickly and reliably recognizes where lumen should be based on even subtle clues)*

Scope steering technique during advancement:
□ *N/A. Not Assessed (i.e. Fellow observed procedure only)*
□ *1. Novice (Primarily "Two-hand knob steering", Unable to perform two steering maneuvers simultaneously)*
□ *2. Intermediate (Frequent 2-hand knob steering, Limited use of simultaneous steering maneuvers [i.e. torque, knob, advance])*
□ *3. Advanced (Primarily uses torque steering. Can perform simultaneous steering techniques)*
□ *4. Superior (Effortlessly combines simultaneous steering techniques [torque, knob, advance] to navigate even many difficult turns)*

Fine tip control:
□ *N/A. Not Assessed (i.e. Fellow observed procedure only)*
□ *1. Novice (Primarily gross tip control only, frequently in red out)*
□ *2. Intermediate (Limited fine tip control. "frequently over-steers turns, struggles with biopsy forceps/ snare targeting")*
□ *3. Advanced (loses fine control when keeping lumen or targeting tools at difficult turns when torque or knobs are needed)*
□ *4. Superior (Excellent fine tip control or tool targeting even in difficult situation.)*

Loop reduction techniques (pull-back, external pressure, patient position change):
□ *N/A. Not Assessed (i.e. Fellow observed procedure only)*
□ *1. Novice (Unable to reduce/ avoid loops without hands-on assistance)*
□ *2. Intermediate (Needs considerable coaching on when or how to perform loop reduction maneuvers)*
□ *3. Advanced (Able to reduce/ avoid loops with limited coaching)*
□ *4. Superior (without coaching, uses appropriate ext. pressure/ position changes/ loop reduction techniques)*

What is the farthest landmark the fellow reached **without** any hands-on **assistance?**
□ *N/A. fellow observed only* ***or*** *Procedure terminated before completion.*
□ *1. Rectum,* □ *2. Sigmoid,* □ *3. Splenic flexure,* □ *4. hepatic flexure,*
□ *5. Cecum* ***No TI attempt*** *(Reached cecum with no attempt at TI intubation)*
□ *6. Cecum* ***Failed TI attempt*** *(Reached cecum but Failed attempt at TI intubation)*
□ *7. Terminal Ileum* ***(Successful intubation of TI)***
□ *8. Other-Post surgical anatomy encountered, fellow reached maximal intubation*

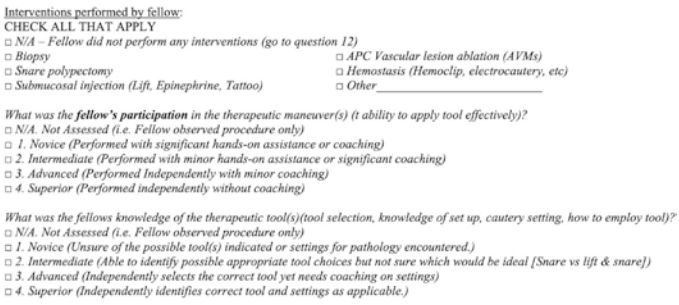
Adequately visualized mucosa during withdrawal
□ *N/A. Not Assessed (i.e. Fellow observed procedure only)*
□ *1. Novice (red out much of the time, does not visualize significant portions of the mucosa or requires assistance)*
□ *2. Intermediate (Able to Visualize much of the mucosa but requires direction to re-inspect missed areas)*
□ *3. Advanced (Able to adequately visualize most of the mucosa without coaching)*
□ *4. Superior (Good visualization around difficult corners and folds and good use of suction/ cleaning techniques.)*

Pathology identification/ interpretation:
□ *N/A, Study was normal (Go to question 11)*
□ *1. Novice (Poor recognition of abnormalities. Misses or cannot ID significant pathology)*
□ *2. Intermediate (Recognize abnormal findings but cannot interpret. "erythema")*
□ *3. Advanced (Recognizes abnormalities and correctly interprets. "colitis")*
□ *4. Superior (Competent Identification and assessment. "Mild chronic appearing colitis in a pattern suggestive of UC")*

Independent polyp detection by fellow
□ *N/A. No Polyps present*
□ 1. *None (Staff identified all polyps)*
□ 2. *Some (Fellow independently identified at least one polyp but not all polyps present)*
□ 3. *All (Fellow independently ID'ed all polyps encountered)*

Accurate location of lesion/ pathology:
□ *1. Novice (Unable to use landmarks to ID location in the colon, " I don't know")*
□ *2. Intermediate (Understands landmarks but either does not recognize or incorporate into decision making process).*
□ *3. Advanced (Good understanding and recognition of landmarks but generalizes pathology location "Descending colon");*
□ *4. Superior (Very Specific about location, e.g."Splenic Flexure region approx. 60 cm from the anal verge with a straight scope")*

FIGURE 5.4 Technical components only, ASGE ACE in Endoscopy—Colonoscopy


Interventions performed by fellow:
CHECK ALL THAT APPLY
□ N/A – Fellow did not perform any interventions (go to question 12)
□ Biopsy
□ Snare polypectomy
□ Submucosal injection (Lift, Epinephrine, Tattoo)
□ APC Vascular lesion ablation (AVMs)
□ Hemostasis (Hemoclip, electrocautery, etc)
□ Other_____

What was the **fellow's participation** in the therapeutic maneuver(s) (t ability to apply tool effectively)?
□ N/A. Not Assessed (i.e. Fellow observed procedure only)
□ 1. Novice (Performed with significant hands-on assistance or coaching)
□ 2. Intermediate (Performed with minor hands-on assistance or significant coaching)
□ 3. Advanced (Performed Independently with minor coaching)
□ 4. Superior (Performed independently without coaching)

What was the fellows knowledge of the therapeutic tool(s)(tool selection, knowledge of set up, cautery setting, how to employ tool)?
□ N/A. Not Assessed (i.e. Fellow observed procedure only)
□ 1. Novice (Unsure of the possible tool(s) indicated or settings for pathology encountered.)
□ 2. Intermediate (Able to identify possible appropriate tool choices but not sure which would be ideal [Snare vs lift & snare])
□ 3. Advanced (Independently selects the correct tool yet needs coaching on settings)
□ 4. Superior (Independently identifies correct tool and settings as applicable.)

FIGURE 5.4 (continued)

as part of "Level 1" training. A Level 1 gastroenterologist is trained in "performing routine gastrointestinal endoscopic and non-endoscopic procedures as part of the practice of gastroenterology and gastroenterologists specializing in non-endoscopic aspects of gastroenterology, including but not limited to, the study of liver diseases, motility, nutrition, and basic science research." Level 2 trained gastroenterologists focus on advanced endoscopic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), endoscopic GERD therapy, and may require an additional fourth year of training depending on volumes achieved during the first 3 years.

The need for Level 2 gastroenterologists is the result of incredible pace of innovation within endoscopy. ERCP, a pillar of Level 2 training, has been widely adopted since the first biliary cannulation in 1968, biliary sphincterotomy in 1974, and utilization of video endoscopy in the 1980s. By the 1980s, endoscopic ultrasound (EUS) was available, which was later enhanced by fine-needle aspiration in the 1990s. With the combined availability of MRCP and EUS, ERCPs are now primarily therapeutic. While many advanced endoscopy training programs focus on ERCP and EUS, trainees are also gaining exposure to a number of other techniques. EMR was

developed in Japan in the 1990s as a means to treat early gastric cancers without surgical intervention. Dissection was limited to piecemeal removal of lesions for larger tumors, which was circumvented with ESD dissections using submucosal fluid injection, mucosal incisions surrounding the lesion, followed by submucosal dissection beneath the lesion. The increased complexity of these advanced Level 2 procedures requires a dedicated year of training following the 18-month core competencies in both upper endoscopy and colonoscopy, polypectomy, injection, and hemostasis. There are just over 60 programs available in the USA at the time of this publication for such additional dedicated training [34].

Proficiency in ERCP is a subject of considerable debate. The initial number required for credentialing in the Gastroenterology Core Curriculum of 1996 was 100 ERCPs, including 25 therapeutic cases consisting of 20 sphincterotomies and five stent placements. Available literature suggested that was inadequate, with a minimum number of 180 diagnostic ERCPs shown as minimum to achieve proficiency in cannulating the desired duct with a success rate of at least 80% [35]. As a result, the GI Core Curriculum increased its minimum threshold for assessing competence in ERCP to 200 cases involving normal anatomy. In a single-operator learning curve longitudinal study, the required number of cases was even more, and approached 400 [36], but somewhere closer to 200 while in training is likely to yield a canulation rate approaching 90% in active practice [37].

Modern standards of training require minimum thresholds and also objective grading of progress, given that ERCP is a therapeutic procedure now. A grading system was devised which uses benchmarks to gauge competency [38], which was adopted by the ASGE, and validated in 1057 ERCP procedures. The study concluded that success rates declined while complication rates of ERCP such as pancreatitis, cholangitis, and perforation, increased in concordance with a higher degree of procedural difficulty [39]. The grading scale for case difficulty is summarized in Table 5.3.

Table 5.3 Grading scale for ERCP based on difficulty

Grade	Biliary procedures	Pancreatic procedures
I	Diagnostic cholangiogram Biliary brush cytology Standard sphincterotomy ± stone removal <10 mm Stricture dilation/stent/NBD for extrahepatic stricture or bile leak	Diagnostic pancreatogram Pancreatic cytology
II	Diagnostic cholangiogram with BII anatomy Removal of CBD stones >10 mm Stricture dilation/stent/NBD for hilar tumors or benign intrahepatic strictures	Diagnostic pancreatogram with BII anatomy minor papilla cannulation
III	Cholangioscopy Any therapy with BII anatomy Removal of intrahepatic stones or any stones with lithotripsy	All pancreatic therapy, including pseudocyst drainage

EUS is now a vital diagnostic test in the standard of care and staging of several GI malignancies, including gastric, pancreatic, esophageal, and rectal lesions. Interventional EUS practices are vast and very difficult to formulate consensus on training recommendations. They include celiac plexus blockade and neurolysis, pancreatic pseudocyst drainage and debridement, abscess and gallbladder drainage, ablation of solid and cystic neoplasms, and even gastro-enteric anastomoses. An ASGE guideline for credentialing and granting privileges for diagnostic EUS published in 2001 suggested that a minimum of 125 supervised procedures be performed prior to assessing for competency in the evaluation of imaging [40]. Individual procedure thresholds are reproduced in Table 5.4.

Table 5.4 Minimum number of EUS procedures before competency should be assessed

Site/lesion	Cases required
Mucosal tumors (cancers of esophagus, stomach, rectum)	75
Submucosal abnormalities	40
Pancreaticobiliary	75
EUS-guided FNA	
Nonpancreatic	25
Pancreatic	25

Unlike ERCP and EUS, specific criteria regarding obtaining competency or proficiency in EMR or ESD has not been well studied. Nor has POEM or POP, which share some of the same technical hurdles as ESD. The practice of these interventional procedures in the USA is growing and is on the horizon for more standardized assessments of competency and credentialing.

Training Adjuncts for Fellows and Residents

Mechanical, animal, and more recently computer endoscopy simulators allow the practice of invasive procedures without risk to patients. Mechanical simulators are the least expensive, but in many ways also represent the least similarity to live procedures. Animal models, specifically pigs which have been historically utilized for ERCP training, are the most realistic but come with a high cost, ethical concerns, and need for comprehensive animal facilities with veterinarians. Computer-aided simulations have advanced greatly in the last few decades, with most basic laparoscopic and endoscopic procedures having technical step accurate equivalents in the virtual space. Some of these simulations were previously discussed and are actively utilized for endoscopic com-

petency evaluations of general surgery residents. Many of these systems have begun validation with expert endoscopists [41]. Performance on virtual and physical models of endoscopy is highly correlated with experience, as could be expected [42].

In an attempt to elucidate the benefits of computer-based virtual reality colonoscopy simulations on patient-based colonoscopy performance, a prospective trial was performed on colonoscopy naïve residents. The residents were randomized to receive 16 h of virtual reality simulator training or no training. The primary outcome was the number of proctor assists required per colonoscopy. Secondary outcomes included insertion time, depth of insertion, cecal intubation rate, proctor and nurse assigned competence, and patient-rated pain. The simulator group required 43% fewer proctor assists than the control group, inserted the colonoscope 79% further unassisted, and intubated the cecum 2.6-fold more often. The simulator group received higher ratings of competence from both the proctors and the endoscopy nurses. In total, this suggests that simulation has a role for jump starting the learning curve and certainly is in the interest of patient safety [43]. To that end, a Cochrane review from 2012 found that virtual reality endoscopy training is useful as an effective supplement to early conventional endoscopy training [44]. These conclusions should come as no surprise to the general surgery community, which actively employs laparoscopic training simulation in most programs to ready residents for live tissue handling.

The Effect of COVID-19 on Endoscopy Training

COVID 19 has disrupted the training of two academic calendar years in the USA to date (March–May 2020, and December 2020–January 2021 in most populated states). To protect personnel and preserve PPE, many institutions have

limited the hands-on time of trainees in the endoscopy suite and OR. While the long-term effects of these clinical gaps on practice patterns are yet to be known, it is safe to assume that PGY 2/3 surgical residents and PGY 1 GI fellows during these pauses in the 2020 and 2021 academic years likely received reduced procedural exposure compared to their supervising staff and more senior trainees.

One such study has begun the process of counting these differences during the first wave in 2020. By following the eleven fellows at a single institution, a 25% reduction in procedures performed during 2020 was observed [45]. In an international survey completed by 770 trainees from 63 countries, endoscopic procedures declined 85%–100% during shutdowns, with the median being 99%. Not surprisingly, urgent procedures like ERCP and UGI for bleeding persisted with reductions closer to 60%–75%. This implies a larger training gap at Level 1 endoscopy for both surgical and gastroenterology trainees, though the effect was less extreme in the USA during the first wave compared to Europe. Sixty percent of trainees surveyed worried that these global events would prolong training [46].

Thankfully, there is evidence that small breaks in training averaging 8 weeks or less have minimum impact on skills decay. In a study which analyzed 6485 colonoscopies performed by 24 fellows with 87 breaks in training, breaks exceeding 8 weeks had worsening cecal intubation rates. These deviations from the anticipated performance curves normalized by the end of the next rotation [47]. This seems to imply that most trainees can resume their learning curve, within reason, during the COVID-19 interruptions in training. While arguments have been made against minimum procedure counts as a surrogate for competency, the current pandemic crisis, with no certain end in sight, reinforces the need for more robust forms of trainee evaluation beyond case counts.

Community Practice Patterns and the Need for General Surgeon Endoscopists

Endoscopy procedure completion rates, complication rates, and other quality metrics are comparable among different specialties performing endoscopy (general surgery, gastroenterology, colorectal surgery). Minimal shared quality metrics for colonoscopy should include cecal intubation rate greater than 90%, screening colonoscopy adenoma detection rate greater than 25%, perforation rate less than 0.2%, and appropriate colonoscopy surveillance recommended in greater than 95% of patients. A recent study of almost 60,000 colonoscopies showed no difference in quality outcomes according to specialty (gastroenterologist, surgery, other) or setting (hospital or office) [48]. Another recent study of over 10,000 colonoscopies done by surgeons and gastroenterologists showed equivalent adenoma detection rate, completion rates, and complications [49]. As discussed previously, the completion rate of EGDs was very high with only time to completion being associated with experience. For these basic procedures, it appears there is a safety equivalency for patients between the different training paradigms. Looking past the need for surgeons to better define anatomy and pathology prior to the OR, is there a profound need for surgeons to perform endoscopy?

At the time of the 2010 Decennial Census, almost 60 million people, or about 19 percent of the population, lived in rural areas of the USA. A significant gap exists between the rural and urban surgical force, finding a ratio of 4.48 rural surgeons to 100,000 patients compared to 6.36 surgeons per 100,000 people in the urban setting. In some of these environments, surgeons are the only clinical resource local to the patient capable of providing screening or preoperative evaluations. In a telephone interview study, 1700 rural surgeons versus 154 urban surgeons were administered the same ques-

tionnaire. Seventy-four percent of rural surgeons performed more than 50 flexible endoscopies a year in contrast to 33% of nonrural surgeons. Approximately 42% of rural surgeons reported doing more than 200 procedures annually, whereas only 12% of the nonrural surgeons did so [50]. A review of the recertification case logs for the ABS revealed that endoscopy among general surgeons nearly doubled in the studied decade, and in large rural, small rural, and isolated communities surgeons performed 5 to 8 fold more endoscopies than their urban counterparts [51]. The study also revealed a rural physician density of gastroenterologists of 0.39 per 100,000 patients, compared to 4.8 per 100,000 patients of general surgeons.

While there can be discord between specialties, especially with the divergent training and accreditation processes, there can be no denying general surgeons will continue to seek endoscopic training and privileges. From the early history of these procedures, which were rooted deeply with the surgical community, to the present expansion of endoscopic replacements for even operations where laparoscopic approaches exist, surgeons have consistently pushed endoscopy forward. As part of this shared history of endoscopy and as active endoscopists in rural centers of this country, surgeons will continue to lead and practice medicine with an endoscope. The only true question is how education will evolve as we apply new methods to train and assess the true competency of residents, as they learn to safely conduct these vital skill sets to the betterment of their patients.

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Chapter 6
Advanced Training and Certifications in Endoscopy

Allison R. Schulman and Dana Telem

Introduction

The landscape of endoscopy is rapidly evolving with the development of new devices, technologies, and techniques as the endoscopic treatment of any disease requires technical skill, in addition to a thorough understanding of pathophysiology. Appropriate gastrointestinal (GI) endoscopy training through either GI or surgical fellowship is critical. The skillset and degree of training required for these advanced endoscopic procedures will vary based on multiple factors, including but not limited to the complexity of the technique and the trainee's skill. This chapter will review the expansive array of

A. R. Schulman (✉)
Division of Gastroenterology and Hepatology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA

Department of Surgery, University of Michigan, Ann Arbor, MI, USA
e-mail: arschulm@med.umich.edu

D. Telem
Department of Surgery, University of Michigan, Ann Arbor, MI, USA
e-mail: dtelem@med.umich.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_6

endoscopic interventions and the existing frameworks for defining and measuring competence during training to ultimately attain certification for performing these procedures.

Training in Endoscopy

The Society of American Gastrointestinal Endoscopic Surgeons (SAGES) and the American Society of Colon and Rectal Surgeons (ASCRS) partnered with the American Society for Gastrointestinal Endoscopy (ASGE) to establish training guidelines for endoscopy in 2002 [1, 2]. The joint statement reflected that acquisition of endoscopic skills should be in the context of training programs in either GI or surgery.

The ASGE later updated these guidelines in 2017 and, along with other medical and surgical digestive disease organizations, have led to the development of Standards of Practice of Gastrointestinal Endoscopy and a statement of Principles of Endoscopic Training [2]. These recommendations state that formal structured residency or fellowship training in endoscopy is necessary, with documentation of skills and competence.

While traditional postgraduate training in advanced endoscopic techniques has focused on endoscopic retrograde cholangiopancreatography (ERCP) and diagnostic endoscopic ultrasound (EUS), the increasing demand for therapeutic endoscopy has led to a considerable expansion in the breadth of training. More GI and surgical trainees are attaining exposure to numerous other procedures, including but not limited to luminal stenting, ablative therapies, endoscopic bariatric and metabolic therapies (EBMT), therapeutic EUS, and advanced tissue resection, and "third space" endoscopy. While the primary mission of all GI and surgical societies is to promote high-quality patient care by ensuring competence in endoscopy, training and skills assessment remain variable across the country [2–6].

Defining Competence

Several quality indicators have been selected to establish competence in performing more basic endoscopic procedures. For example, in colonoscopy, intubation of the cecum and a detailed mucosal inspection contribute to the definition of competence in terms of technical success. The ASGE suggests that effective practicing colonoscopists should be able to intubate the cecum in >90% of all cases and>95% of cases when the indication is screening a healthy adult. Furthermore, careful mucosal inspection is essential to effective colorectal cancer prevention and reduction of cancer mortality. The rate of detection of neoplastic and pre-neoplastic lesions, i.e., adenoma detection rate (ADR), is the primary goal of most colonoscopic examinations [7].

Training and competency assessment in advanced endoscopic procedures, on the other hand, have traditionally been based on an apprenticeship model. As such, the volume of cases through both observation and performance of procedures under supervision has commonly been used as a surrogate for assessing competence. Despite extensive attempts to identify and validate minimal procedural numbers necessary for defining competence, thresholds between publications have varied tremendously. This variability is highlighted in the ERCP literature, which contains many flaws in using volume as a marker of procedural competence, including defining performance of only a single intervention (such as biliary cannulation) and the lack of recognition that trainees learn skills at variable rates and have different educational backgrounds [2, 8–14]. For example, proceduralists with an extensive surgical or advanced endoscopy background may not require the same volume of cases in learning a new technique as a provider who only focuses on general endoscopy. There is also variability in the teaching trainees receive from faculty, which invariably plays a role.

Thus, the previously adopted dictum of “see one, do one, teach one” is now considered obsolete and replaced by a shift

toward competency-based medical education [15]. While minimal threshold numbers are integral to training, they do not guarantee competence.

Many of the principles for introducing new technology and techniques in the surgical literature may apply to endoscopic interventions. Guidelines published in 2014 by SAGES based on a systematic review of published literature and expert opinion reported a majority agreement that familiarization, cognitive training, hands-on practice, performance assessment, patient disclosure, and outcome monitoring were necessary steps to ensure competence during the introduction of a new device or surgical technique [16]. A strong recommendation was made for the device- or procedure-specific training to decrease the learning curve-related complications and thus improve safety. Furthermore, the necessary training steps were dependent on the degree of novelty/change and could include a variety of different components, including but not limited to video review, cadaveric training models, course participation at society meetings, and proctoring [16].

The ASGE has defined competence as the "minimum level of skill, knowledge, and/or expertise, derived through training and experience, required to safely and proficiently perform a task or procedure" [2]. A given individual's level of exposure and engagement during or after training to a specific procedure or skillset should help dictate whether that provider is competent to perform procedures independently. Defining competence in endoscopy must be procedure-specific, starting with the identification of core skills and establishing quality metrics and benchmarks for a given technique. Commonly performed advanced endoscopic procedures and standardization measurement tools that aim at providing quantitative and qualitative assessment in endoscopic training will be reviewed below. It is important to recognize that some of the presented suggestions are based on expert opinion, and robust data to substantiate many of the training recommendations are lacking.

Ablative Therapies

Commonly used ablative techniques include radiofrequency ablation (RFA), argon plasma coagulation (APC), and cryotherapy. These are primarily used for esophageal dysplastic lesions and early-stage malignancy, gastric antral vascular ectasia (GAVE), and for treatment of radiation proctitis.

In order to safely and effectively perform these procedures, trainees must first seek to master the cognitive component of these interventions [3]. For example, it is essential to understand the role of RFA after EMR of superficial cancers with remnant dysplastic mucosa. The technical component includes learning and understanding the technical equipment (devices and accessories) used in each of these ablative techniques. For example, it is critical to characterize columnar lined esophagus (Barrett's esophagus) prior to intervention, use a mucolytic agent if necessary, and understand whether to remove eschar in between treatments depending on the procedure being performed. Cognitive and technical competency is particularly important with these types of advanced endoscopic procedures.

Endoscopic Bariatric and Metabolic Therapies (EBMTs)

EBMTs encompass a broad array of procedures, including primary weight-loss interventions and treatment of adverse events after bariatric surgery. Endoscopic devices and techniques are rapidly evolving in this space, several of which have demonstrated safety and efficacy in prospective randomized controlled trials. These interventions have markedly increased in popularity over the last several years, leading to a growing number of endoscopists seeking training in these procedures.

A position statement authored by the Association of Bariatric Endoscopy (ABE)/ASGE on training and privileges in EBMT described three essential principles for the provision of quality therapies [6]. These principles include a broad and in-depth understanding of the management of patients with obesity, mastery of GI endoscopic skills, and procedure- and device-specific knowledge necessary to provide specific EBMTs and manage potential associated adverse events. Endoscopists interested in learning EBMT must have a comprehensive knowledge of the indications, contraindications, risks, benefits, and outcomes. Both the ASGE and the American Society for Metabolic and Bariatric Surgery (ASMBS) emphasize that EBT should not be carried out in isolation and that endoscopists performing EBMT should be part of a multidisciplinary comprehensive obesity program.

Similar to other emerging technologies, there is a paucity of data regarding training requirements in EBMT. The ASGE suggests that focused training via dedicated courses are potential settings to gain further expertise in certain aspects of EBMT. Many of these courses are sponsored and organized by industry, which plays a vital role in the training and education of these new devices. Moreover, EBMTs of greater complexity may require proctoring and a structured training program [17, 18]. Furthermore, due to the spectrum of requisite technical skill and procedural risk, privileges may be granted on a procedure-specific basis with the demonstration of competency.

"Third space" Endoscopy

Third-space endoscopy is also known as intramural or submucosal endoscopy. This field is based on the concept that the deeper layers of the GI tract can be approached via the submucosal space and has led to widespread dissemination of procedures such as endoscopic submucosal dissection (ESD) and per-oral endoscopic myotomy (POEM).

ESD

ESD was first described in Japan as a minimally invasive strategy for the management of early gastric cancer. Over time, this technique has evolved to include resection of lesions in other parts of the GI tract, including the esophagus, small bowel, and colon.

There is a steep learning curve to training in ESD. In Japan, trainees traditionally followed a master–apprentice model, but this approach is not easily translatable in Western countries [2, 5]. Trainees should be supervised by experts and should have focused fellowships dedicated to this technique before performing complex endoscopic procedures in humans independently. Furthermore, EMR skills should be a prerequisite to training in ESD, in addition to proficiency in advanced diagnostic techniques and endoscopic classification systems [4]. Hands-on training, even on animal models, is invaluable, with some guidelines proposing at least 20 procedures prior to performing ESD on humans [19].

The European Society of Gastrointestinal Endoscopy (ESGE) recently issued a position statement on training in ESD [19]. These guidelines contain a core curriculum that defines the skills and competence needed before ESD training, establishes minimum standards in order to perform ESD, and defines the necessary training program for proceduralists who want to include ESD in their practice. This model may be difficult to adopt in the USA, where cases are sporadic, even in specialized centers. Furthermore, endoscopists interested in ESD are often full-time interventional endoscopists at their own institutions, and travel arrangements for either the trainee or the proctor can be limited.

POEM

POEM is used to treat achalasia and other motility disorders of the esophagus and has quickly gained excitement throughout the advanced endoscopy community. Training in this pro-

cedure is complicated, given both the technical complexity and the knowledge to be able to manage significant adverse events.

The Japan Gastroenterological Endoscopy Society released clinical guidelines on training in POEM in 2017 [20]. This position statement recommends that initial skill acquisition be met through training on animal models, including organ and live models, and then ultimately progressing to observation followed by direct supervision and proctoring of live human cases by an experienced endoscopist. The number of procedures required to be competent in POEM is disputed in the literature, with a wide discrepancy on the learning curve ranging from 7 to 100 cases. This discrepancy again supports that emphasis should be shifted away from the number of procedures performed and toward well-defined and validated competency thresholds.

Future Directions

As the field of endoscopy evolves, the generation of robust data to substantiate many of the aforementioned training recommendations and standardization measurement tools for advanced endoscopic procedures will be important. Furthermore, the increasing complexity of emerging endoscopic interventions, in combination with an emphasis on competency-based medical education, will require a transformation of the curriculum to ensure adequate training without compromising best patient practices. Perhaps national consensus standards for endoscopic privileging of many of these advanced techniques should be required to standardize endoscopy practice and ensure that all patients are managed optimally.

Conclusion

The primary mission of all endoscopists is to promote high-quality patient care and safety in the field of GI and surgical endoscopy. With the increasing diversity and complexity of

emerging endoscopic interventions, there has been a shift from time or number-based training toward competency-based education. Learning curves vary among trainees of all stages, and a specific case volume does not ensure competence in performing these procedures. Furthermore, defining competence in endoscopy must be procedure-specific, starting with identifying core skills and establishing quality metrics and benchmarks for a given technique, as evidenced by the discussion of select interventions throughout this chapter. Surgical and GI endoscopists who desire to perform existing or new procedures should ensure adequate dedication of time to acquire technical and cognitive endoscopic skills, knowledge of endoscopic anatomy, comprehension of the pathophysiology of digestive diseases, and competency and proficiency of performance.

Financial Support/Potential Competing Interests A.R. Schulman—Apollo Endosurgery (consultant); Boston Scientific (consultant); Olympus (consultant); MicroTech (consultant); GI Dynamics (research, grant support), Fractyl (research, grant support). D. Telem has no disclosures.

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Chapter 7
Upper Gastrointestinal Tract Bleeding

Voranaddha Vacharathit and Kevin El-Hayek

Introduction

Upper gastrointestinal bleeding (UGIB) is defined as bleeding proximal to the ligament of Treitz and can present as massive bleeding or as a slower chronic ooze. A 1991 study reported that 59% of acute upper G.I. bleeding in the USA is caused by peptic ulcer disease, with a range of 28–59% when examining other Western countries such as the United Kingdom, Scotland, France, and Greece [1]. Though patient outcomes from UGIB have improved over the past decade

V. Vacharathit
Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

King Chulalongkorn Memorial Hospital, Thai Red Cross Society, Bangkok, Thailand

K. El-Hayek (✉)
Division of General Surgery and Division of Surgical Oncology, MetroHealth System, Cleveland, OH, USA

Case Western Reserve University School of Medicine, Cleveland, OH, USA

Northeast Ohio Medical University, Rootstown, OH, USA
e-mail: kelhayek@metrohealth.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_7

due to advancements in medical and interventional therapies, mortality from UGIB remains between 10 and 14% [2, 3]. This chapter will review the presentation, assessment, and endoscopic management strategies for UGIB, focusing on differences in device management and considerations based on bleed etiology.

Clinical Presentation

Depending on the location and volume of blood loss, UGIB can manifest quite variably. The appearance of hematemesis—bright red blood or the oft soft-described "coffee ground emesis" suggests a location proximal to the ligament of Treitz. Brighter blood can suggest a more rapid or more recent bleed, while darker "coffee ground" characteristic symbolizes blood that has been partially digested by gastric acid. Melena refers to dark, tarry stools that result from heme degradation as it travels through the gastrointestinal tract and often signals an upper gastrointestinal source. However, a rapid or massive upper gastrointestinal hemorrhage can also manifest itself as hematochezia—the appearance of bright blood from the rectum. Failure to recognize the upper gastrointestinal tract as a potential source of the bleeding needs to be avoided, as it can have fatal results.

The patient may have a completely benign abdominal exam seen in slow upper or obscure G.I. bleeding. Conversely, colicky abdominal pain and loose stools may be elicited due to the cathartic effect of blood in the lower gastrointestinal tract. A rectal exam should always be performed in suspected gastrointestinal bleeding; hemoccult blood testing should accompany exams without gross evidence of bleeding. Furthermore, attention must be paid to signs of liver disease, including ascites, jaundice, spider angiomas, and gynecomastia. In a patient with gastrointestinal hemorrhage, these should raise the suspicion for variceal bleeding.

Initial Assessment

Proper evaluation and assessment are critical in patients with UGIB (Fig. 7.1). Patients presenting with hematemesis should be evaluated for airway compromise, and if present, a secure airway should be promptly established. A complete set of vital signs should be obtained, including orthostatic vital signs, as aberrations such as tachycardia or postural hypotension can be the first signs of impending hypovolemic shock (Table 7.1).

A focused history and review of systems should be performed to elicit important comorbid or concomitant conditions that may affect medical or endoscopic management. Queries regarding weight loss, change in bowel habits, medications (including anticoagulation use), alcohol use, and prior endoscopies can often provide insight into the bleed location and etiology. Complete blood count, comprehensive metabolic panel with liver function tests, assessment of coagulation with prothrombin time and partial thromboplastin time, and blood type and crossmatch should be obtained with blood work.

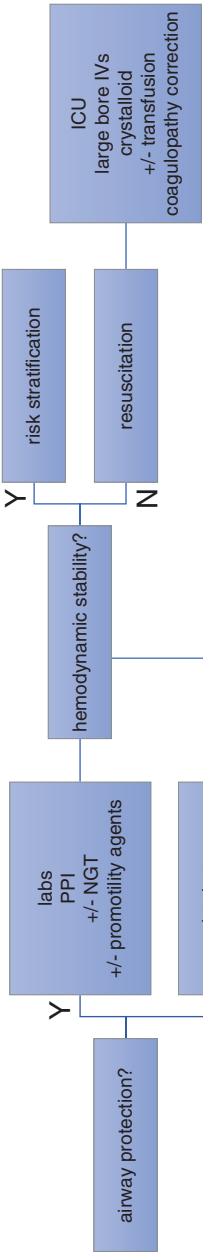


FIGURE 7.1 Initial Assessment Decision Tree for Patients Presenting with Acute UGIB

Table 7.1 Classification of hypovolemic shock

	Class I	Class II	Class III	Class IV
Blood loss (mL)	≤750	750–1000	1500–2000	
Blood loss (%)	≤15	15–30	30–40	
Heart rate (beats/min)	<100	≥100	>120	
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure	Normal or increased	Decreased	Decreased	Decreased
Mental status	Slightly anxious	Mildly anxious	Anxious/ confused	Confused/ lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid, blood	Crystalloid, blood

Nasogastric Tubes

Nasogastric (N.G.) tube use in the assessment and management of UGIB is controversial. As alluded to earlier, placement of an N.G. tube can facilitate localization of bleeding with the presence of "coffee grounds" or fresh blood in the N.G. aspirate. However, it should not be used in lieu of a careful history and physical. Up to 15% of actual upper gastrointestinal sources of bleeding may be missed if the N.G. aspirate is falsely clear, and bilious aspirate suggests the pylorus is patent [4, 5]. An N.G. tube may also be used to lavage the stomach in preparation for endoscopic intervention. Care must also be taken in the insertion of N.G. tubes, especially if the etiology of the gastrointestinal bleeding is unknown. Bleeding from esophageal varices or Mallory–Weiss tears may be exacerbated by a traumatic insertion.

Resuscitation and Transfusion

Patients with acute UGIB should have two large-bore peripheral intravenous lines placed and resuscitation undertaken. Classical teaching supports early resuscitation with crystalloid fluid infusion, such as 0.9% normal saline or lactated Ringers, to restore intravascular circulating volume from ongoing losses and prevent inadequate tissue perfusion [6]. Recent years have seen controversy over the type of fluid—colloid versus crystalloid, used for resuscitation in shock. A 2012 Cochrane Database Review of randomized controlled trials examining resuscitation with crystalloid versus colloid solutions demonstrated no survival benefit to colloids. Given the increased cost of colloid solutions–coupled with its failure to provide a survival benefit and increased mortality associated with hydroxyethyl starch—the authors recommend using the crystalloid solution in resuscitation during UGIB [7].

A restrictive transfusion strategy targeting hemoglobin of 7 mg/dL for patients without significant cardiovascular disease and 9 mg/dL for those with significant cardiovascular disease is recommended, as such a strategy carries a lower risk of all-cause mortality and rebleeding [8–10]. A recent international consensus guideline recommends transfusion for hemoglobin levels <8 mg/dL, although the threshold is higher in patients with significant cardiovascular comorbidities [11].

Any clinical or laboratory evidence of coagulopathy should be quickly corrected to assist in controlling the hemorrhage. However, reversal of anticoagulant drugs should be carefully considered on a case-by-case basis per patient clinical status and risk–benefit analysis [12–14]. Care should be taken in those patients with blood loss requiring massive transfusion of red blood cells (greater than ten units), as these patients are at risk of developing a concomitant dilutional coagulopathy. The massive transfusion of red blood cells

results in a relative deficit in platelets and clotting factors. Unless corrected with transfusions of platelets and plasma, it will further exacerbate any existing coagulopathies [15].

Risk Stratification

Most gastrointestinal hemorrhages resolve spontaneously or with medical management and do not require endoscopic or surgical intervention. In contrast, patients with massive gastrointestinal hemorrhage may require admission to an intensive care unit for close monitoring and aggressive resuscitation with multiple transfusions and interventions. Thus, a way to stratify these patients into low-risk and high-risk groups is useful for developing management strategies, allocating resources, and predicting prognosis and outcomes. One of the most common ways to classify UGIB into low- and high-risk patient populations is by using endoscopy to assess for stigmata of active or recent bleeding. In 1974, Forrest et al. developed a classification system for these characteristics (Table 7.2).

The most extensively validated scoring models are the Blatchford and Rockall scores. The Rockall scoring system uses age, presence and severity of hemodynamic compromise, diagnosis, and stigmata of recent hemorrhage to calculate a risk score. While the score is easy to calculate, it requires endoscopy to diagnose and assess stigmata of bleeding [16] (Table 7.3).

Table 7.2 Forrest classification

Forrest class	Lesion
1A	Arterial spurting
1B	Active oozing
2A	Ulcer with nonbleeding visible vessel
2B	Ulcer with adherent clot on surface
2C	Ulcer with red or dark blue flat spot
3	Ulcer with clean base

Table 7.3 Rockall Score

	Score			
Variable	**0**	**1**	**2**	**3**
Age (years)	<60	60–79	≥80	
Shock	None Systolic blood pressure ≥ 100	Tachycardia SBP ≥ 100	Hypotension SBP < 100	
	Pulse < 100	Pulse ≥ 100		
Comorbidity	None		Cardiac failure Ischemic heart disease Any major comorbidity	Renal failure Liver failure Disseminated malignancy
Diagnosis	Mallory–Weiss No lesion No SRH	All other diagnoses	Malignancy of upper GI tract	
Major stigmata of recent hemorrhage (SRH)	None Dark spot		Blood visible in upper Gl tract Adherent clot Visible or spurting vessel	

The Blatchford score was developed out of the desire to predict and identify which patients need treatment. Using variables such as hemoglobin, blood urea levels, pulse, and systolic blood pressure, combined with presenting features of syncope or melena and medical history including liver disease or cardiac failure, the authors created a screening score that can be used at initial presentation (Table 7.4). Patients who were identified as low-risk of needing clinical intervention for upper G.I. hemorrhage had a blood urea level less than 6.5 mmol/L, hemoglobin greater than 13 g/dL and

Table 7.4 Blatchford score

Admission Risk Marker			**Score component value**	
BUN (mmol/L)	6.5–8		2	
	8–10		3	
	10–25		4	
	>25		6	
Hemoglobin (g/dL)	*Men*	*Women*	*Men*	*Women*
	12–13	10–12	1	1
	10–12	<10	3	6
	<10		6	
Systolic blood pressure	100–109		1	
	90–99		2	
	<90		3	
Other markers	Pulse > 100 beats/min		1	
	Melena		1	
	Syncope		2	
	Hepatic disease		2	
	Cardiac failure		2	

12 g/dL for men and women, respectively, systolic blood pressure greater than 110 mmHg, and heart rate less than 100 bpm [17]. A score of ≤1 predicts successful outpatient management, whereas a threshold score of 7 or higher has been shown to predict the need for endoscopic treatment and a higher risk of death [18, 19].

Timing of Endoscopic Intervention

A 2019 International Consensus Group guideline recommends endoscopy within 24 h of presentation for acute non-variceal upper gastrointestinal bleeds (NVUGIB) [11]. A recent 2020 randomized controlled trial by Lau et al. further clarifies that there is no difference in 30-day mortality among patients in stable condition hospitalized with acute UGIB in whom endoscopy performed at a mean of 9.9 h as compared with 24.7 h after initial presentation [20]. Although most practice guidelines similarly advocate for early endoscopy within 12 h of presentation in patients with variceal upper gastrointestinal bleeds (VUGIB) [21], the effect of endoscopy timing on outcomes in this subset of patients is controversial. A 2020 meta-analysis by Jung et al., which included five retrospective studies with a corresponding 1307 patients, demonstrated no significant difference in overall mortality, rebleeding rate, need for salvage therapy, length of hospital stay, and a number of blood transfusions in patients with VUGIB who had an endoscopic intervention less than or equal to 12 h after presentation compared to more than 12 h after presentation [22].

The ultimate timing of endoscopic intervention should be guided by best practices and should not be delayed. However, clinicians should consider the patient's hemodynamic status, the feasibility of the endoscopic intervention, progress in resuscitation efforts, and adequate preparation to optimize chances of endoscopic success.

Endoscopic Management of UGIB

UGIB can be categorized as either NVUGIB or VUGIB. The most common causes of acute NVUGIB are peptic ulcers (Fig. 7.2). Consideration of the specific modality to be employed should take into consideration the cause of bleeding.

A multi-channel endoscope is preferred if available as it allows for simultaneous irrigation and deployment of devices such as needles, clips, and other instruments. Endoscopic

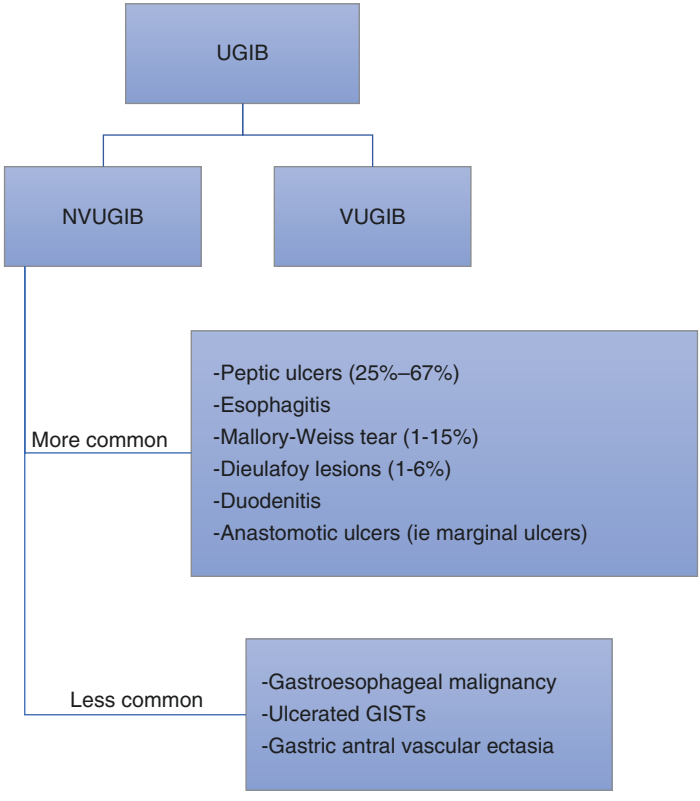


Figure 7.2 Common causes of UGIB

therapy should only be delivered to actively bleeding lesions, as well as those with an increased risk of rebleeding, such as lesions with non-bleeding visible vessels (50% risk of rebleed) and ulcers with an adherent blood clot (30% risk of rebleed), otherwise stated: Forrest class 1A–2B lesions [23, 24]. Time permitting, a single dose of intravenous erythromycin or metoclopramide may be given pre-endoscopy to promote gastric emptying of the clot to improve visualization. These medications must be used with caution in patients with prolonged Q.T. intervals.

Management of Nonvariceal UGIB (NVUGIB): The Arsenal

The therapy of nonvariceal bleeding—which is most commonly what surgical endoscopists would treat—can be classified into the following broad categories: injection therapy, thermal therapy, mechanical therapy, topical therapy, or a combination of each.

Injection Therapy

A vasoconstricting solution, such as epinephrine, is most commonly used and injected via a needle comprised of an outer sheath with an inner retractable 19-25-gauge hollow needle. The epinephrine is diluted at 1:10,000 (100 mcg/mL) in normal saline and injected circumferentially around the lesion, with a recommended total volume of 13–30 ml, as this lowers rebleeding risk compared to injection of a lesser total volume [25, 26]. Using more than 30 ml of diluted epinephrine may increase the risk of perforation [27]. The injection sites selected should be no closer than 2–3 mm from the bleeding source to reduce the risk of iatrogenic bleeding [28].

Lo and colleagues [29] demonstrated that combination therapy using injection and clips was superior to injection of epinephrine alone in reducing rebleeding (3.8% vs. 21%, $P = 0.008$) and the need for urgent surgery (0% vs. 9%, $P = 0.023$). Furthermore, among patients who had recurrent bleeding, repeat combination therapy was more effective in achieving hemostasis than repeat injection therapy alone (100% vs. 33%, $P = 0.02$). A meta-analysis of 16 studies including 1673 patients by Calvet et al. compared epinephrine injection versus epinephrine injection in combination with a second method. Combination therapy had lower rebleeding rates by approximately 8%, decreased the need for surgical intervention by about 4%, and decreased mortality by around 3%. Furthermore, the risk of rebleeding decreased as long as a second modality was used, regardless of type [30].

Other than epinephrine, sclerosants can also be injected into the tissue to induce thrombosis and necrosis for hemostasis—the most common ones include ethanol, polidocanol, ethanolamine, sodium morrhuate, and sodium tetradecyl sulfate. See Fig. 7.3: Endoscopic Injector Needle.

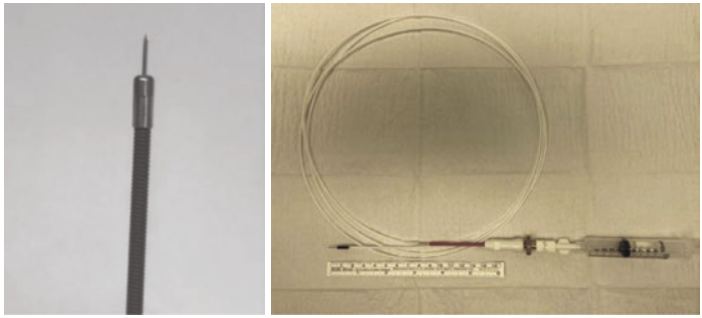


FIGURE 7.3 Endoscopic injector needle and handle. The inner retractable hollow needle is available as 19–25 gauge. Images used with permission, Kevin El-Hayek, M.D

Mechanical Therapy

Mechanical reapproximation of tissue allows for tamponade of bleeding and can be achieved by various devices, broadly categorized as through-the-scope (TTS) clips, cap-mounted clips (CMCs), endoscopic banding devices, stents, and endoscopic suturing devices.

Various devices are available with different features such as jaw opening width, rotational capability, and the ability to be re-opened and re-closed before final deployment. An example of those available in the USA is listed in Table 7.5. Several techniques in clip deployment need to be adhered to for optimal results (Fig. 7.4). These include holding the clip close to the opening of the endoscope to allow for maximal

Table 7.5 Examples of through-the-scope (TTS) hemostatic clips

Clip name	*Manufacturer*	*Jaw Opening Width (mm)*	*Rotation*	*Re-opening/ closing*	*MRI conditional (to 3 Tesla)*
Resolution™	Boston Scientific	11			
Resolution 360 ®	Boston Scientific	11			
QuickClip2/long™	Olympus America	9/11			
QuickClip Pro™	Olympus America	11			
Instinct ®	Cook Medical	16			
DuraClip™	ConMed	11/16			
SureClip/Plus ®	Micro-Tech Endoscopy USA	11/16			

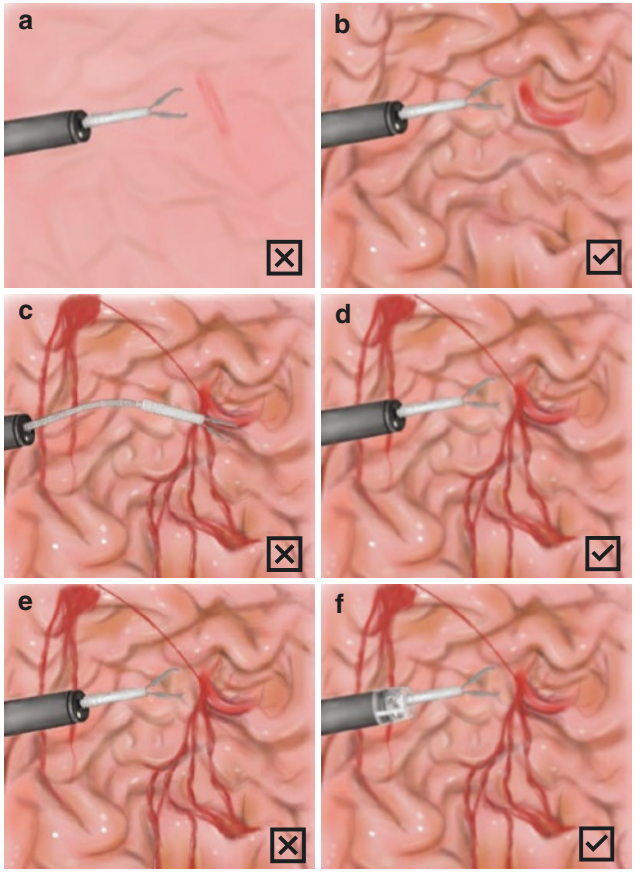


FIGURE 7.4 Recommended tips and techniques in endoscopic hemostasis (**a**) Difficulty in the precise deployment of TTS clips or adequate tissue capture in a fully distended stomach can be reduced by (**b**) slight desufflation and suctioning during the clip placement, which may allow for improved tissue capture. (**c**) Non-precise clip positioning and deployment (**e**) can be improved by holding the clip close to the opening of the endoscope (**d**) to allow for maximal precision and adequate tactile pressure in clip application. (**e**) To access in difficult upper gastrointestinal bleeding (UGIB) endoscopic hemostasis anatomical locations and stabilize the scope for proper target orientation and capture, (**f**) a transparent cap can be used. Images used with permission, Vimvara Vacharathit, Ph.D.

precision in clip deployment. An initial tangential approach with the first clip usually allows for improved tissue capture; however, should this prove unfeasible, an en face approach with tenting the tissue with the first clip can facilitate subsequent clip placement. Non-optimal placement of the first clip can often impede the correct placement of subsequent clips. Slight deflation and suctioning during clip placement may allow for improved tissue capture. Another technique to improve precise clip deployment and access in difficult anatomical locations involves using a transparent cap (i.e., band ligator or endoscopic mucosal resection cap—see Fig. 7.5) to stabilize the scope for proper target orientation and capture [31].

Other than TTS clips, cap-mounted clips are gaining popularity and are recommended for use as rescue therapy when TTS clips fail or are projected to fail [14] as they allow for a greater volume of tissue capture [33]. Commercially available options are the over-the-scope clip system (OTSC®, Ovesco Endoscopy AG, Tübingen, Germany) and the Padlock® sys-

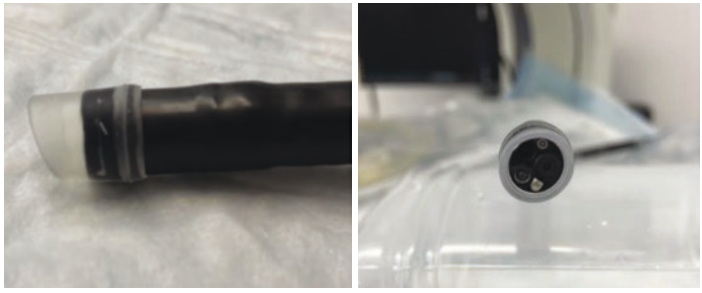


FIGURE 7.5 Clear tapered cap fitted to endoscope tip (views from side and head-on). Images courtesy of Kevin El-Hayek

tem (U.S. Endoscopy), both of which are FDA-approved for use in hemostasis. Both are available with a variety of application cap sizes corresponding to different endoscope outer diameters (Padlock®: endoscope outer diameter between 9.5–11 mm; Padlock Pro-Select® outer diameter between 11.5 mm and 14 mm; OTSC® outer diameter between 8.5 mm and 14.5 mm divided between 3 sizes) [32]. For the OTSC® clip, generally, the a-type (atraumatic) is used for hemostasis purposes.

Thermal Therapy

Thermal devices in the endoscopic control of hemorrhage can be categorized as either contact or non-contact. Current contact devices include heater, multipolar electrocautery, monopolar, and coagulation forceps (Coagrasper™; Olympus Corp., Tokyo, Japan).

Thermal coagulation with contact probes achieves acute hemostasis and prevents recurrent bleeding by applying pressure to the vessel to compress it while coagulation is performed (coaptive coagulation). This results in sealing (coaptation) of the vessel. Many devices are currently on the market with slight differences in their mechanism of action that affect their clinical use. For a summary, refer to Table 7.6.

On the other hand, non-contact thermal techniques include APC, which employs ionized argon gas to deliver thermal energy. Another example is Nd:YAG laser coagulation, which is effective for hemostasis; however, technical considerations such as the large size of the laser delivery unit, need for unique electrical and water supplies, and costliness prevent its widespread use.

Table 7.6 Summary of endoscopic arsenal for UGIB

Modality	Mechanism of Action	Benefits	Considerations
Injection Therapy			
Injection therapy (ie: epinephrine)	- Local vasoconstriction and tamponade from volume of injection - diluted epinephrine 1:10,000 (100 mcg/mL) in normal saline injected circumferentially with recommended 13-30mL total volume [25,26,27]	May allow for temporary cessation of bleeding for deployment of second intervention with improved visualization	- Not sufficient as monotherapy due to high rebleeding risk - Pretreatment with epinephrine prior to clip placement may mislead the endoscopist as to the actual effectiveness of clip positioning
Mechanical Therapy			
Through the scope clips	Tissue reapproximation and tamponade	Wide range of options allows for different kinds of grasps, rotational mechanisms	- May be difficult to place in specific anatomic locations (iecardia, lesser curvature, posterior duodenum) - Not as effective in large ulcers with fibrous base or in areas with non-yielding scar tissue
Cap mounted clips	Tissue reapproximation and tamponade	Increased tissue volume hold	- More time consuming to mount and deploy than TTS, requires learning curve - Difficult to reapproximate hard chronically fibrotic tissue
Thermal Therapy			
Heater probe (contact)	- Heat generated by both passage of electrical current through tissue and high voltage (can be as high as 1000V) - Requires firm tamponade on tissue during application for coaptive coagulation -25-30J per pulse for 4-5 pulses recommended [14]	- Allows for deep penetration of tissue irrespective of tissue resistance or desiccation	- Carbonized eschar due to tissue incineration at high voltage which can rebleed with eschar detachment - May be challenging to achieve close and perpendicular contact in active bleeding and in some anatomic peristalsing locations - Deep tissue injury can occur
Monopolar hemostatic forceps (contact) I.e.: Coagrasper™	- Heat generated by passage of electric current through tissue causing coagulation - Using Soft Coagulation (80W, Effect 4, 1-2 seconds on ERBE VIO®generators limits peak voltage and tissue damage[14]	- Allows for tissue coagulation without carbonation - Works at a lower voltage than other thermal treatments limiting risk of perforation	- May not sufficiently provide coagulation in a pool of blood or fluid - Requires tissue contact either by grasping or tangentially touching bleeding source - Requires patient grounding pad
Multipolar probes (contact) Ie: Gold Probe™, Quicksilver® Bipolar Probe, BICAP® Superconductor™	- Electricity passes through tissue between positive and negative electrodes at the tip of the device - 15-20W settings recommended [14]	- Simultaneous water irrigation at the tip of the probe allows for unsticking to treated tissue and for better visualization - Injection-Gold probe allows for combination of injection and thermal therapy without need to exchange catheters	- Coagulation depth is increased with increasing French size, using lower energy over a longer period of time, and increased tamponade over the desired area - Does not require patient grounding pad
Argon plasma coagulation (APC) (non-contact)	- Ionized argon gas delivers thermal energy to tissue - Local coagulation and tissue necrosis to depth of 2-3mm	- Ease of application without need for direct tissue contact - Allows for wide area of application rapidly, with small depth of penetration	- Good for superficial, not deeper lesions - Requires an operative distance from the probe tip to the tissue ranging from 2 to 8 mm, where tissue contact may result in pneumatosis and extraintestinal gas
Radiofrequency ablation (RFA)	Electricity (450 to 500 kHz) travels through contacted tissue between electrode arrays of the device, generating thermal energy which results in coagulation of the targeted tissue	- compatible with all modern electrosurgical generators - can treat a wide surface area at once	Limited studies on usage for UGIB etiologies other than GAVE
Topical Therapy			
Hemostatic powders I.e.: Hemospray®, EndoClot®	Different powders which promote hemostasis by forming a mechanical, tamponading barrier	- Touch-free application - Allows for coverage of large surface area - relatively easy to use	- If used as primary therapy and fails, the resulting powder layer may impede visualization and subsequent usage of other modalities - Theoretic side effects: embolization, bowel obstruction, allergic reaction - Care must be taken to prevent premature activation of powder in delivery catheter by limiting moisture in endoscope accessory channel

Topical Therapy

Examples of topical therapies utilizing hemostatic powders include Hemostatic Spray® (Cook Medical, Winston-Salem, NC, United States), also known as H.S. or TC-325, and EndoClot® (EC, Micro-Tech Europe, Düsseldorf, Germany). H.S. is delivered as a powder that then absorbs water and adheres to the bleeding site forming a tamponading mechanical barrier. Endoclot® similarly forms a mechanical barrier over the bleeding area. In a 2019 meta-analysis evaluating hemostatic powders in UGIB comprised of 24 studies, three of which were randomized controlled trials for a total of 1063 patients, hemostatic powders showed similar efficacy compared to conventional endoscopic therapy [34]. In the latest 2020 American Gastroenterological Association guidelines, the use of hemostatic powders was recommended as an option in cases of massive bleeding with poor visualization, as salvage therapy, or in diffuse bleeding secondary to malignancy; however, its routine use preferentially for primary hemostasis in cases other than the aforementioned was not recommended [14].

The Right Intervention for the Right Pathology

Peptic Ulcer Disease (PUD)

PUD is typically classified into five categories based on location and causative factors. Type I ulcers, the most common, make up approximately 60% of gastric ulcers and are located on the lesser curvature, often near the incisura angularis. They are associated with normal gastric acid secretion. On the other hand, type II ulcers are usually located in the body of the stomach and are commonly seen in conjunction with duodenal ulcers. They comprise approximately 15% of gastric ulcers and are associated with excess acid secretion. Type III ulcers are typically found in the pre-pyloric region of the stomach. They account for approximately 20% of ulcers. Like type II ulcers, these are also often seen in states with elevated

acid levels. Type IV ulcers occur near the gastroesophageal junction, high along the lesser curvature. They account for less than 10% of ulcers and tend not to have an association with excess acid secretion. Type V ulcers are variable in location and are associated with chronic nonsteroidal anti-inflammatory drug use rather than elevated acid levels.

In terms of endoscopic intervention, as previously mentioned, epinephrine injection used as monotherapy should be avoided, as combination therapy results in lower rates of rebleeding, decreased need for surgical intervention, and decreased mortality. However, epinephrine with another endoscopic intervention combination therapy has no demonstrated advantage over properly applied thermal or mechanical monotherapy [35]. Conversely, prior meta-analyses and randomized controlled trials suggest that clips are also not superior to other endoscopic modalities in terms of initial hemostasis, rebleeding rate, emergency surgery, and the mortality rate for treatment of PUD [36].

A recent 2019 randomized controlled trial of 112 patients comparing monopolar hemostatic forceps with soft coagulation (MPSC) versus TTS clip placement for peptic ulcer bleeding demonstrated improved initial hemostasis success rate with MPSC (98.2%) as compared to clips (80.4%, $P = 0.004$). Vessels that were greater than 2 mm in diameter were not grasped initially by the monopolar forceps but were coagulated at four sites around the vessel with closed forceps then on the vessel itself (4 + 1 contact method). There was a lower recurrent bleeding rate (3.6%) in the MPSC group compared to the TTS group (17.7%, $P = 0.04$), as well as a significantly shorter length of procedure and length of stay [37]. A 2020 meta-analysis that included six studies (of which 5 were randomized controlled trials) with 693 patients looked at a pooled sample of 320 patients treated with MPSC, 98 patients treated with heater probe, 200 patients with TTS clips, and 75 patients with APC. This analysis suggests that usage of MPSC is superior to both clips and heater probes in the prevention of rebleeding. It was also superior to the heater probe in achieving initial hemostasis with no difference in this regard when compared to clips [38].

The most current 2020 guidelines from the American Gastroenterological Association and from several international societies are summarized below in Table 7.7. Ultimately,

Table 7.7 Summary of most current guidelines and evidence in the endoscopic management of NVUGIB

Bleeding Etiology	Epi Inj (cRx)	Heat probe	MPSC	Multi-polar	APC	RFA	TTS clips	CMCs	HP/HS	EBL
PUD	abc	abc	abc	abc			abc	(a)(c)	(a)(b)(c)	
MWT							b			
DL	c	c	c	c			c			c
PSAB	d	d								
Tumor							d		(a)	
GAVE					d				c	d

Epi Inj epinephrine injection, *cRx* combination therapy, not for usage as monotherapy, *MPSC* monopolar hemostatic forceps with soft coagulation, *APC* Argon plasma coagulation, *RFA* radiofrequency ablation, *TTS* through the scope, *CMCs* cap-mounted clips, *HS/HP* Hemostatic sprays/hemostatic powders, *EBL* endoscopic band ligation, *PUD* peptic ulcer disease, *MWT* Mallory–Weiss tear, *DL* Dieulafoy's lesion, *PSAB* post-surgical acute bleeding, *GAVE* Gastric antral vascular ectasia

Green box: moderate quality evidence; Yellow box: low-quality evidence. **Note: there is no high-quality evidence available regarding the effectiveness of each of these modalities vis a vis each other**

[a] American Gastroenterological Association guidelines (2020)

[b] International Consensus Group guidelines (2019): recommends the use of thermocoagulation, TTS, sclerosant injection in bleeding ulcers with epinephrine injection NOT recommended as monotherapy

[c] 2015 European Society of Gastrointestinal Endoscopy (ESGE) Guidelines recommend the use of thermocoagulation, TTS, sclerosant injection in bleeding ulcers with epinephrine injection NOT recommended as monotherapy

[d] 2020 American Gastroenterological Association guidelines as salvage/rescue therapy. Hemostatic powders not recommended as monotherapy for PUD with high-risk stigmata of bleeding

[e] International Consensus Group guidelines as salvage/rescue therapy

[f] 2016 Japan Gastroenterological Endoscopy Society Guidelines recommend the use of thermocoagulation, TTS, sclerosant injection in bleeding ulcers with epinephrine injection NOT recommended as monotherapy

the choice of modality to be used in specific patient PUD scenarios must take into account not only the mechanism of action and limitations of each of the modalities available but also the experience of the endoscopist, the location of the ulcer, and the quality of the tissue to be intervened on.

Mallory–Weiss Tears (MWT)

MWTs are responsible for 1–15% of upper G.I. hemorrhages. These tears are caused most often by forceful retching or vomiting, which propels the gastric cardia into the thorax, resulting in longitudinal mucosal tears at the gastroesophageal junction and lesser curvature. Hiatal hernia and alcohol ingestion commonly accompany MWTs [39]. However, there are also several reported cases of iatrogenic MWT, as a rare complication of endoscopic submucosal dissection [40]. Management of such a tear depends on the presence of active bleeding. Non-bleeding lesions can be treated with a high-dose proton pump inhibitor alone [41]. Laine et al. demonstrated the superiority of multipolar thermal therapy to medical treatment in achieving hemostasis in Mallory–Weiss bleeding [42]. Cho and colleagues examined EBL and clip placement for patients with actively bleeding Mallory–Weiss lesions in a prospective randomized study. Primary hemostasis was obtained for all 41 patients who underwent endoscopic therapy. No differences were noted in rates of primary hemostasis, recurrent bleeding, or permanent hemostasis. The authors concluded that EBL and clip placement were equally safe and effective in the management of bleeding secondary to Mallory–Weiss lesions [43].

In general, thermal and mechanical therapy or a combination of these with epinephrine injection appear efficacious in obtaining hemostasis in MWTs, with no high-level evidence demonstrating the superiority of one modality over another. For this reason, few guidelines recommend a specific modality in the approach to bleeding MWTs. However, the 2016 Japan Gastroenterological Endoscopy Society Guidelines

recommend the use of TTS clips as the primary modality of treatment of MWT (Table 7.7). This is due to concerns that epinephrine injection may result in harmful effects in patients with preexisting cardiovascular disease and that bipolar coagulation may cause a penetrating injury, especially in mucosal injuries [44].

Dieulafoy's Lesion (DL)

Also known as a caliber persistent artery, DL is an uncommon, though the potentially devastating and morbid cause of upper G.I. hemorrhage. It is believed to account for approximately 1–2% of acute G.I. bleeding, although an incidence as high as 5.8% has been reported [45]. First described by Gallard in 1884 as "miliary aneurysms of the stomach," its description was later amended by Georges Dieulafoy in 1898 to "exulceratio simplex," which reflected the belief that the lesion represented a precursor to peptic ulcers. Today, the term DL describes a large caliber arteriole within the gastric submucosa that protrudes into the gastric lumen via a mucosal defect, with fibrinoid necrosis. The suspected pathogenesis of bleeding is erosion of the mucosa due to compression from the larger than normal vessel, which then bleeds into the gastrointestinal tract lumen [46]. A 1993 study demonstrated approximately 60% of lesions occur at the gastroesophageal junction as classically described, but also noted 14% of lesions occurring in the duodenum [45]. Similar to endoscopic therapies of peptic ulcer disease, combination therapy involving injection of epinephrine or sclerosing agents with one other modality appears to be more effective than monotherapy at providing hemostasis. In a Mayo Clinic series, 19 of 1124 consecutive patients with UGIB were found to have DL and underwent combination therapy with epinephrine injection and thermal therapy. They demonstrated a 100% rate of initial hemostasis, with evidence of only one patient with rebleeding in the follow-up period [47]. Endoscopic band ligation (EBL) is also an effective means of treating DL. Matsui et al. com-

pared band ligation with bipolar electrocautery in patients with acute UGIB. There were 27 patients with DL who underwent endoscopic therapy. Matsui's group demonstrated 100% hemostasis in band ligation with only 86% in the electrocautery group [48]. Park et al. compared band ligation with clip placement for DL and 100% hemostasis was achieved in both groups with one episode of rebleeding in each group. The authors concluded that both band ligation and clip placement were safe and effective therapies for bleeding DL [49]. This seems to be confirmed in a meta-analysis looking at 162 pooled DL UGIB patients from 5 studies, which found similar rates of primary hemostasis and rebleeding in patients who underwent EBL compared to endoclipping [50].

A 2020 study by Nulsen et al., the first and largest cohort study looking at Doppler-guided compared with visually guided treatment of severe UGIB from DL suggests that blood flow-guided treatment may improve patient outcomes. The study retrospectively identified 82 consecutive DL patients from the Centre for Ulcer Research and Education (CURE) hemostasis database and found that rebleeding after a negative post-treatment Doppler signal occurred in 10.5% of patients at 30 days, compared with 33.3% of patients who did not have Doppler-guided treatment. Furthermore, poor 30-day clinical outcomes were noted in 41.3% of the visual-guided versus in 10.5% of the Doppler cohort [51]. Although this study was limited by a small sample size and non-randomized, non-controlled study cohorts, future studies could very well result in revised recommendations to add Doppler guidance for hemostatic control of DL bleeding.

Post-Surgical Acute Bleeding (PSAB)

UGIB after surgery occurs on the order of 0.3–2% depending on the operation performed, and most commonly occurs within 12–24 h post-surgically [44]. It can be categorized as either intralumenal or extralumenal. We will limit our discussion to intralumenal bleeding. The most frequent site of intralumenal bleeding is at the anastomosis or staple lines, for

instance, in such operations as Roux-en-Y gastric bypass, sleeve gastrectomy, or any other upper G.I. reconstruction operation. Early bleeding, if not diagnosed intraoperatively, is usually diagnosed by a decrease in hemoglobin or any of the signs of UGIB as previously discussed. When non-interventional management has failed, careful endoscopy in the early post-operative period is a feasible option with the appropriate precautions of minimal insufflation when a fresh anastomosis is present. CO_2 insufflation should be used when available. Epinephrine injection, thermal therapy, and endoclipping have been documented in this scenario, with such modalities endorsed by the 2016 Japan Gastroenterological Endoscopy Society Guidelines (Table 7.7). TTS clips are an attractive therapeutic modality as there is low probability of tissue injury, whereas thermal therapies have the potential for penetrating tissue injury and perforation. There is insufficient data on the usage of epinephrine injection on anastomotic line ischemia, although this is likely related to the volume injected and the exact clinical scenario.

Bleeding can also occur years after the index operation at or around the gastrointestinal anastomosis in what is known as marginal ulcers. Although the majority of these patients can be treated medically with proton pump inhibitors and cessation of inciting factors, some occasionally do require endoscopic or even surgical intervention. Usage of epinephrine injection in conjunction with thermal therapy or endoclipping has been reported, however, there is a dearth of high-quality evidence recommending any one endoscopic modality.

Tumor Bleeding

Up to 5% of UGIB can be attributed to bleeding from tumors, of which primary gastric cancer (36% to 58%) is the most common etiology [52]. Unfortunately, compared to benign etiologies of UGIB, conventional endoscopic therapeutic modalities are not very effective in this subset of patients. Some of the possible contributory factors resulting in a more challenging endoscopic control of tumor-associated

bleeding are local vessel invasion, neovascularization of tumors, diffuse bleeding with no clear target, and poor tissue quality (either friable or fibrotic). Coagulopathy, either as a sequalae from chemotherapy-induced bone marrow suppression or bone metastasis may also be present. Several small case series demonstrated that conventional thermal therapy (i.e.: heat probe, bipolar electrocautery, APC, or any combination of these with epinephrine injections) can successfully achieve primary hemostasis. However, initial hemostasis success rate is widely variable and overall, 30-day rebleeding rates were uniformly higher than what would be expected in bleeding from benign etiologies—up to 80% rebleeding rate in one retrospective study [53–57].

Hemostatic powders and sprays are a promising modality for usage in tumor-related bleeding. A variety of hemostatic powders and sprays are available, an example being the TC-325 (Hemospray®-Cook Medical), Fig. 7.6. Since the powder does not remain present after 24 h, the most recent 2020

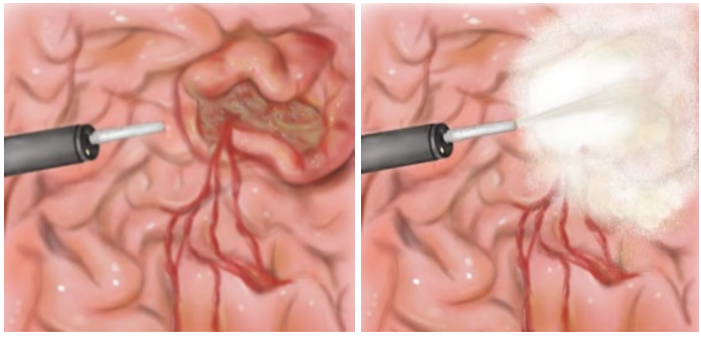


Figure 7.6 Use of hemostatic powder as salvage therapy in tumor-related bleeding. Tumor-associated bleeding can be difficult to control due to local vessel invasion, neovascularization, diffuse bleeding with no clear target, and poor tissue quality (either friable or fibrotic). Hemostatic powders are a promising salvage modality in this scenario to obtain hemostatic control. However, caution should be used, as mucosal surface features become obscured after application, making subsequent treatment with other modalities difficult. Images used with permission, Vimvara Vacharathit, Ph.D. © 2020. All Rights Reserved

AGA guidelines recommend its usage preferentially as a rescue therapy rather than for primary hemostasis, except in malignant or massive bleeding with inability to perform other thermal or mechanical therapy [14]. Pittayanon *et al.* compared the efficacy of Hemospray® to conventional endoscopic hemostasis in GI-related tumor bleeding in 10 patients compared to 10 historical controls matched by G.I. tumor type [58]. Fourteen-day rebleeding rates were lower in the Hemospray® group, but this finding was not statistically significant (10% compared to 30%; $P = 0.60$). More recently, Baracat et al. randomized 39 patients to either Hemospray® or combined TTS and epinephrine injection for hemostatic control of NVUGIB. Primary hemostasis was achieved in 100% of Hemospray® cases compared to 90% of the TTS-epinephrine group ($P = 0.487$); however, five patients in Hemospray® group required an additional hemostatic procedure during second-look endoscopy, compared to none in the TTS-epinephrine group ($p = 0.04$). Rebleeding, emergency surgery, and mortality rates were similar in both groups [59]. Additional high-powered studies are needed to fully define the role of hemostatic powders as salvage or standalone endoscopic therapies, tailored to specific bleed etiologies.

When endoscopic options have been exhausted, surgical management via suture ligation or resection is indicated when bleeding is refractory to non-operative measures. However, not infrequently, these patients are not amenable to surgery, and a possible salvage option for those with uncontrolled gastrointestinal tumor bleeding is targeted radiotherapy. A multidisciplinary approach is often required for this difficult pathology.

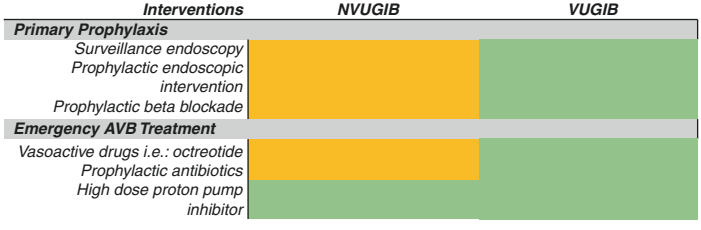
Variceal UGIB (VUGIB)

Acute variceal bleeding (AVB) is a common complication of cirrhosis, with a rate of variceal formation of 5–15% per year in this population. Of patients with varices and cirrhosis, 30–40% will develop variceal hemorrhage [60]. AVB is associated with a mortality rate of 20–25% [61, 62]. The first epi-

sode of variceal bleeding is not only associated with high mortality, but also with a high rate of recurrence. For this reason, management strategies for the endoscopist are slightly different from NVUIB and should be equally focused on primary prophylaxis, emergency treatment of AVB, and the prevention of rebleeding (secondary prophylaxis). We will focus our discussion to the emergency management of AVB.

Like patients with NVUGIB, airway protection and hemodynamic resuscitation with avoidance of over transfusion are of primary importance. Unlike NVUGIB, patients with cirrhosis and suspected VUGIB should also receive prophylactic antibiotics to reduce bacterial infections, mortality, rebleeding events, and length of hospitalization [63]. The American Society for Gastrointestinal Endoscopy (ASGE) 2014 guidelines recommends the use of 7 days of oral or IV quinolone or IV ceftriaxone for this purpose [64] although ultimate selection of therapy should depend on local susceptibility patterns. Vasoactive drugs should be given if VUGIB is suspected. The most common vasoactive drug in the USA is octreotide, with a recommended administration of 50 mcg intravenous bolus followed by a 50 mcg per hour infusion. This should be continued for 3 to 5 days post-endoscopy if VUGIB etiology is confirmed [64, 65]. Table 7.8 shows comparison of management of NVUGIB vs VUGIB

Table 7.8 Comparison of management strategies in nonvariceal upper G.I. bleeds (NVUGIB) vis a vis variceal upper G.I. bleeds (VUGIB)



Green box: recommended; Yellow box: not recommended

Once the patient is optimized as much as possible and the decision is taken to scope the patient, the next important question is the kind (esophageal or gastric) and location of the varices, as this will help the endoscopist best choose their therapeutic modality.

Esophageal Varices (E.V.)

Varices form most commonly from increased pressures in the portal venous system (portal hypertension, defined as hepatic venous pressure gradient greater than 5 mmHg), with enlargement of physiologic collateral plexuses in an attempt to decompress the portal system. They are formed when the gradient between the portal and hepatic veins is greater than 12 mmHg.

Portal hypertension can be categorized based on the location of increased pressure as it relates to the position of the liver. Pre-hepatic causes include portal or splenic vein thrombosis, which elevates the portal venous pressures prior to reaching the liver. When the elevated pressure is caused at the level of the liver, this is termed hepatic portal hypertension and most commonly is caused by cirrhosis. Post-hepatic portal hypertension occurs when the elevated pressures occur distal to the liver, and includes such entities such as inferior vena cava obstruction, or cardiac failure. Cirrhosis is the most common cause of portal hypertension in the Western world, accounting for approximately 90% of cases [66]. Other less common causes of portal hypertension include portal vein or splenic vein thrombosis, nodular regenerative hyperplasia of the liver, congenital hepatic fibrosis, or myeloproliferative disorders.

The main predictors of bleeding are large size of varices, red wale marks, and Child–Pugh C classification [67]. Endoscopic variceal ligation (EVL) is considered the standard therapy for treatment of bleeding esophageal varices,

with a demonstrated lower rate of rebleeding, mortality, and complications than sclerotherapy, which is now second-line [68, 69]. A banding device at the tip of the endoscope is used to apply a rubber band over a varix, causing strangulation and subsequent thrombosis and necrosis. In the acute setting, EVL should be performed on active esophageal variceal hemorrhage and those with stigma of recent hemorrhage [64], as well as in situations where large esophageal varices are present with blood in the stomach and no other probable cause of bleeding [70]. It should be noted that recurrence is the rule rather than the exception to E.V.s and after the management of AVB, multiple subsequent sessions are required for E.V. eradication with even then a high chance of recurrence [71].

A randomized trial by Sarin et al. [72] in 68 patients comparing EVL and no therapy found that EVL was superior in preventing an initial variceal bleed (8.6% vs. 39.4%). Another study by Lay et al. demonstrated decreased incidence and mortality when compared with no therapy [73]. More recently, a meta-analysis including 36 randomized controlled trials with 3593 patients demonstrated that EVL improved bleeding control compared to sclerotherapy, whereas sclerotherapy combined with vasoactive drugs was more efficient than sclerotherapy alone [74].

If these interventions fail, deployment of a self-expanding metal stent (SEMS) is another option, though this use of SEMS would be considered off-label. A randomized controlled trial comparing SEMS and balloon tamponade in refractory AVB demonstrated better control and decreased adverse events with SEMS [75]. Due to its high rate of complications—ranging from esophageal necrosis and perforation to aspiration—balloon tamponade is therefore used as a last resort if endoscopic therapy and pharmacotherapy have failed or as a bridging therapy to transjugular intrahepatic portosystemic shunt (TIPS). Baveno VI guidelines recommend SEMS preferentially to balloon tamponade as a rescue therapy [65].

Gastric Varices (G.V.)

Twenty percent of patients with cirrhosis have G.V.s. Sarin's classification is commonly used to categorize G.V.s. Those in continuity with E.V.s extending to below the cardia into the lesser curvature are classified as type 1 (GOV1) and are the most common type of G.V.s (75%). Type 2 (GOV2) are those in continuity with E.V.s extending into the fundus. Isolated G.V.s type 1 (IGV1) are fundal without E.V. contribution. Finally, isolated G.V.s type 2 (IGV2) are located elsewhere in the stomach. The risk of GV AVB depends on G.V. location (IGV1 > GOV2 > GOV1), increased size, presence of red wale marks, and degree of liver dysfunction [76, 77]. Though bleeding from gastric varices occurs less often than esophageal varices, it can often present more severely and carries with it a high mortality rate (10–30%).

In the acute setting, tissue adhesives can be injected through the endoscope to treat gastric variceal bleeding with good effect. One of the popular tissue adhesives is cyanoacrylate, which is a monomer that rapidly polymerizes when in contact with ionic substances, like blood or tissue fluids. The monomer is injected via a needle in the operating channel. If the procedure is effective, the varix will harden, effectively obliterating it [78]. Sarin et al. compared cyanoacrylate to absolute alcohol in the management of gastric varices. They found cyanoacrylate to be superior in the control of bleeding (89% vs. 62%) and obliteration of the varix (100% vs. 44%) [79]. Additionally, Lo et al. compared cyanoacrylate with EVL and found higher rates of initial hemostasis (45% vs. 87%) and lower rates of rebleeding (54% vs. 31%) in the cyanoacrylate group, demonstrating the superiority of tissue adhesive compared to EVL [80].

Although data on endoscopic treatments of G.V.s are limited compared to those on E.V.s, most guidelines favor cyanoacrylate as a first-line therapy in G.V.s in general. However, the type of G.V. is important in the selection of its first-line endoscopic treatment.

G.V.s continuous with E.V.s (GOV1, GOV2) are more amenable to sclerotherapy than IGVs [64], however, fundal G.V.s (which includes GOV2) require significantly more sclerosant than GOV1 [81]. The reason behind this is higher flow rate through IGVs and fundal G.V.s. Increasing the volume of sclerosant increases the risk of complications such as retrosternal and abdominal pain, perforation, ulceration, and mediastinitis. The 2015 U.K. and Baveno VI guidelines on the management of variceal hemorrhage in cirrhotic patients recommend treating GOV1 endoscopically the same as E.V.s (EVL, tissue adhesive), whereas GOV2 and IGVs should have cyanoacrylate injection as a first-line therapy with possible consideration of thrombin injection [65, 82]. In the practical sense, whether the endoscopist chooses to perform EVL should also be dependent on the G.V. size. EVL works well in smaller G.V.s where both the mucosa and contralateral wall of the vessel can be ligated. However, the insecurely placed band that does not contain these elements will likely fall off in several days, leaving behind an EVL-induced ulcer overlying the vessel, which can result in disastrous rebleeding.

A recent meta-analysis suggests that EUS-guided tissue adhesive or coil placement could improve the rate of vessel obliteration in G.V.s [83]. Nonetheless, should endoscopy fail, transjugular intrahepatic portosystemic shunt (TIPS) should be considered. In cardiofundal varices, endovascular obliteration—such as balloon-occluded retrograde transvenous obliteration (BRTO)—is also an option when large gastro- or splenorenal collaterals are present. Unlike TIPS, BRTO does not divert portal vein liver inflow; however, portal pressure may be increased with increased risk of worsening ascites or bleeding from E.V. Ultimately, management of these complex patients requires multidisciplinary collaboration and rigorous longitudinal care—not only for the acute episode but also for primary and secondary prophylaxis—for best outcomes.

Conclusion

Given the many advances in endoscopy, treatment of G.I. bleeding is increasingly being managed by endoscopic, rather than traditional surgical interventions. Understanding the benefits and limitations of common endoscopic modalities coupled with up-to-date knowledge of current best practices and guidelines will help guide the endoscopist in selection of therapy tailored to a specific patient and clinical scenario.

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Chapter 8
Stricture Management: Interventional Options

Jerry Dang, Noah Jacob Switzer, and Shahzeer Karmali

Esophageal Anastomotic Strictures

Definition

Esophageal anastomotic strictures are typically defined as any form of cervical dysphagia in the anastomotic region requiring endoscopic dilation [1], or failure of passage of a 9-mm endoscope [2]. Post-esophagectomy anastomotic strictures are the most common reason for stricturing disease in the esophagus seen by general surgeons and gastroenterologists [3]. In the pediatric population, strictures from esophageal atresia repairs are the most common etiology [4].

J. Dang (✉)
Division of General Surgery, University of Alberta Hospital, Edmonton, AB, Canada
e-mail: dangj3@ccf.org

N. J. Switzer · S. Karmali
Digestive Disease & Surgery Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: nswitzer@ualberta.ca; shahzeer@ualberta.ca

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_8

Pathophysiology

Benign esophageal strictures are the result of collagen deposition and scar tissue formation from prolonged esophageal inflammation [5]. The majority of benign strictures are the result of peptic disease; however, with the advent of aggressive treatment of reflux, other causes like anastomotic strictures are becoming more common [6]. The exact mechanism behind anastomotic stricturing is yet to be elicited, but a compromised blood supply and reflux of stomach acid are likely involved in the pathophysiology [7, 8].

Incidence and Risk Factors

The incidence of anastomotic esophageal stricturing post-esophagectomy ranges between 5 and 48% [1, 2, 9–11]. Usually appearing between 3 and 6 months post-surgery [12], risk factors for stricture formation can be classified into four categories:

1. Patient factors: smaller esophagus [2, 9], increased preoperative weight [2], preoperative cardiac disease [11], diabetes mellitus [13].
2. Surgical technique: stapled anastomosis [9, 10, 14] with smaller stapler size [12], two-layer hand-sewn anastomosis [1], cervical anastomoses [12, 15], gastroesophageal anastomosis [2].
3. Postoperative complications: conduit ischemia [2], anastomotic leak [2, 11], anastomotic bleed [16], anastomotic infection [16].
4. Treatment factors: postoperative radiation [1].

The incidence of malignant esophageal stricturing post-esophagectomy ranges from 4 to 8% [1, 10]. These strictures usually appear later than benign, fibrotic strictures [12].

In the pediatric population, the incidence of anastomotic esophageal stricture post-esophageal atresia repair ranges

between 18 and 50%[4]. Risk factors for stricture development are classified into three categories:

1. Patient factors: reflux, gap length.
2. Surgical technique: anastomotic tension, anastomosis suture material.
3. Postoperative complications: anastomotic leak, fistula [4].

Symptoms

The most common clinical presentation of esophageal stricturing disease is dysphagia, reported in 83% of patients [5]. The severity of dysphagia does not correlate to the degree of stricture due to patients often adjusting their diet to more tolerable foods [17]. Esophageal complaints of reflux were also quite common (66%), likely due to the strong correlation between reflux and stricture formation [5]. Potential extraesophageal symptoms include chronic cough, weight loss, vomiting, chest pain, hoarseness, and asthma [5, 17].

Treatment

The mainstay of therapy for upper gastrointestinal anastomotic strictures that are associated with a clinically significant functional impairment is mechanical esophageal dilation [18]. The goal of dilation is centered on symptomatic relief of dysphagia [3]. Dilation can be performed with rigid or balloon dilators, with or without a guidewire to help positioning, and with or without endoscopy or fluoroscopy [19]. Esophageal anastomotic strictures generally are considered more complicated than simple peptic strictures, thus often require a number of dilation sessions, with the median ranging between 2 and 9 sessions per patient. Randomized controlled trials have shown no significant difference in efficacy between the rigid versus balloon dilators [20, 21]. Additional therapies like stenting, intralesional corticosteroid injections, and electro-

surgery are generally reserved for refractory strictures after failed dilation, defined as clinical dysphagia despite dilation, in strictures that are unable to be mechanically dilated to 14 mm or to remain at least 14 mm in lumenal size [8, 16].

Dilators

Rigid Dilators

Rigid dilators have been the traditional treatment for esophageal strictures, dating back to the sixteenth century. Significant evolution has occurred since, progressing from initial tools that included whalebones and tapered wax candle dilators [8]. These fixed rigid dilators apply both axial and radial forces as they are advanced through the stricture [22]. Rigid fixed dilators can be quite variable in their appearance and subtleties of action, based on designs of different companies.

The push type dilators (PTD), Hurst and Maloney, are internally weighted with mercury-free tungsten, ranging in sizes from 16 Fr to 60 Fr with their tips being rounded or tapered [19]. These dilators are best suited for simple strictures (straight, symmetric, diameter ≥12 mm) [3].

Wire-guided dilators (WGD) are polyvinyl chloride tapered tubes with a central channel that allow for a guidewire [19]. The Savary-Gilliard and American Dilation System (Conmed, USA) dilators have varied-length tapered tips, radiopaque markings, and external distance markings [19]. These dilators can be used for more complicated strictures (torturous, asymmetric, length >2 cm, diameter <12 mm) [3, 8].

Rigid dilation, as a procedure, begins with an endoscopic or barium study assessment of the stricture; marking diameter, length, and evaluation of any suspicious lesions for cancer-recurrence [3, 23]. A guide-wire is then placed through the

instrument channel into the gastric antrum; this step is omitted for the Hurst and Maloney dilators. The endoscope is then withdrawn and the wire position is maintained [3]. The wire is then grasped at the patient's mouth and its length noted (usually around 60 cm). The initial choice of dilator depends on the estimated diameter of the stricture. A general rule is that a 24 Fr, 30 Fr, and 36 Fr are trialed for strictures ≤6 mm, 7–10 mm, and ≥10 mm, respectively [3]. The dilator is lubricated and loaded onto the guidewire and passed with a fingertip grasp through the stricture and then subsequently removed. The guide-wire length at the patient's mouth is then noted again and further dilation can take place with larger diameter bougies. The first dilator to be used is estimated endoscopically by comparing the lumen with the diameter of the endoscope. The "Rules of Three's" has traditionally been employed, stating that: during any one dilation session, a maximum of three consecutive dilators of progressively increasing size (a total of 3 mm) should be passed after the first one that meets moderate resistance [3]. However, a retrospective analysis by Grooteman et al. found that nonadherence to this rule did not increase the risk of adverse events [24]. Endoscopic evaluation after dilation can be performed to assess any damage to the mucosa. Subsequent dilation sessions can be repeated until the patient has relief of swallowing difficulties [3].

Both PTD and WGD can be passed blindly or under fluoroscopic control. Fluoroscopy is an aid to help determine that the bougie has passed the strictured segment of esophagus and has entered the stomach. This is advantageous in situations where direct visualization with the endoscope cannot be performed [3].

The efficacy of rigid dilators for anastomotic strictures ranges between 78 and 100%[19, 25]. The median number of dilations prior to achieving clinical success ranges between 2 and 9 dilations [25]. 50% of patients will fail initial dilator therapy from rigid dilator therapy [20].

Balloon Dilators

First introduced by London et al. in 1981 for two patients who failed the conventional, bougie rigid dilator technique, this technique has gained widespread popularity in benign esophageal stricturing disease, including anastomotic strictures, for its less traumatic effect on esophageal tissue [7, 26]. Contrary to rigid dilators, balloon dilators exert only radial forces when expanded within a stenosis. There is substantial variability in the type of balloon dilators that exist, such as single-diameter, multi-diameter, and hydrostatic or pneumatic balloons [27].

Through-the-scope (TTS) balloon dilation, as a procedure, begins with an initial evaluation of the stricture via endoscopy or a barium study [23]. The balloon diameter used is once again dependent on the diameter size of the stricture [3]. A general rule is that 10 mm, 12 mm, and 15 mm balloons are used for strictures of ≤6 mm, 7–10 mm, and ≥10 mm, respectively. The endoscope is placed in the stomach, distal to the stricture, and the balloon is passed through the scope to the end of the endoscope. The endoscope is then withdrawn through the stricture and the balloon is then inflated with radiocontrast or water for 30–60 s [3]. The endoscope remains in the esophagus allowing the operator to directly visualize the dilation, an advantage of balloon dilators over most nontransparent bougies [19]. If fluoroscopy is used, the balloon is inflated until the waist deformity from the stricture disappears [23]. Fluoroscopic control has the advantages of visualizing both the proximal and distal ends of the stricture, not merely the entrance as in endoscopy, and allows visual control of the whole balloon catheter [28].

With the advent of controlled radial expansion, the same balloon can be inflated to three consecutive larger diameters rather than one balloon with only one diameter [3]. The rules of three can also be applied for balloon dilators [7]. Once again, the mucosa is then evaluated by the endoscope after dilation for trauma.

The efficacy of balloon dilators for anastomotic strictures ranges between 83 and 100% [7, 11, 13, 19, 29]. The average number of dilations prior to achieving clinical success ranges between 3 and 7 dilations [11, 29]. Studies have shown that restenosis rates after balloon dilation are approximately 50% [7, 13].

Predictive factors that determine the success of dilation include stricture diameter >13 mm [7], stricture length <12 mm [29], and strictures without prior history of leakage [29]. Predictors of failure of dilation include interval from esophageal surgery to the first initial intervention <90 days [7] and balloon dilations to 12 mm or less [7].

Novel Transparent Dilators

Direct visualization throughout the procedure is possible with newer, transparent dilators that fit over a standard endoscope [21]. However, there is limited evidence on the effectiveness of these dilators compared to non-transparent dilators as only small prospective data is available [30, 31].

Complications and Limitations of Dilators

The complexity of anastomotic strictures put them at risk for esophageal perforation or significant hemorrhage with dilation. The incidence of esophageal perforation or significant bleed is reported between 0.1 and 0.5% [3]. There remains a paucity in the literature as to predictive factors associated with decreased or increased dilation attempts prior to clinical success [32]. The drawbacks then of these dilators are the time and expense of repeated, indeterminate therapy sessions, with the potential for adjuvant therapy interruption [32]. Ultimately, the decision to use balloon or rigid dilation is based more on preference, experience, and regional availability [19].

Other Endoscopic Procedures

Stents

Stents are usually considered as a second-line treatment for patients with recurrent dysphagia, failing initial dilation attempts [33]. They have a primary role in patients with unresectable malignancy for palliation and improvement of dysphagia and are used sparingly in benign disease [34, 35].

Metal Stents

Self-expanding metal stents (SEMSs) are metal mesh cylinders usually composed of stainless steel or alloys, which are able to self-expand until they restore the lumen of hollow organs [36]. Traditionally SEMSs have been used as a palliative procedure for patients with stricturing disease from unresectable esophageal cancer, also encompassing recurrences at the anastomotic site [34, 37]. The indications for SEMSs in fibrotic anastomotic strictures are limited. The historical concern with bare metal stents focused on the increased tissue irritation leading to secondary strictures, tissue ingrowth, mucosa ulcerations at contact points, esophageal obstruction, perforation, and tracheoesophageal fistulas [33, 37]. In addition, due to tissue embedding, once placed, metal stents were considered permanent [37]. On the other hand, this tissue embedding does limit possible stent migration, with reported rates by Pennathur et al. to be as low as 8.7%.

Newer, fully-covered metal stents are challenging this non-reversible notion of metal stents, as recent studies have shown that they can be removed successfully [37]. However, the results with anastomotic strictures have only modest efficacy, with studies quoting a dysphagia resolution rate between 29 and 56% [35, 37].

Metal stents and non-metal stents are placed in a similar fashion [38]. The stricture requiring stenting is first visualized with the endoscope [36]. If the stricture is deemed to be too

stenotic for the stent to traverse it, the operator might choose to perform a session of dilation with a rigid or balloon dilator prior to stenting [36]. Most gastrointestinal SEMS require the use of a guidewire for placement [36]. A distal hemoclip is placed approximately 2 cm distal to the stricture and the endoscope is advanced placing a guidewire into the second part of the duodenum. Upon the withdrawal of the endoscope, the guidewire remains and a proximal hemoclip is placed where the stent is planned to start. Under fluoroscopy guidance, using the hemoclips as landmarks, the stent is deployed. The endoscope is then inserted to confirm correct placement. Fully-covered stents are usually left for up to 3 months or less depending on the endoscopist's discretion, prior to being endoscopically retrieved. Partially covered self-expanding metal stents are left in place for a shorter duration, owing to more significant tissue ingrowth making retrieval after a longer period of time more challenging. This same characteristic likely decreases the migration rates of partially covered metal stents. Retrieval involves using foreign body forceps with a longitudinally directed force that narrows the stent for removal [33].

Non-Metal Stents

Self-expanding plastic stents (SEPS) were developed to correct for some short-comings of metals stents and they have been shown to be a successful treatment tool for benign anastomotic strictures [33]. Usually made of a combination of polyester and silicone, where the silicone prevents hyperplastic tissue growth and the polyester helps with anchoring, these stents are able to be removed easily due to the lack of tissue embedding [33, 37]. As a second-line treatment modality for recurrent dysphagia post initial dilation, plastic stent placement has been associated with decreased median numbers of subsequent dilatations, improved dysphagia scores, and improved cost-effectiveness at 15 months of follow-up. Recurrent dysphagia rates after plastic stenting ranges

between 5 and 36% [32, 33, 38]. Long-term resolution of dysphagia symptoms after SEPS removal is poor, with high associated dysphagia recurrence rates [6]. Evrard et al. stressed that SEPS should not be used as initial therapy for anastomotic strictures but should be considered in patients with cervical anastomotic stenosis and patients with refractory dysphagia to dilations [39].

There are a few other important drawbacks of SEPS. As a result of poor mucosa embedding, SEPS migration rates are high, ranging between 6 and 69% [40]. SEPS are also less effective than metal stents in managing esophageal perforations and leaks [40]. Lastly, they require a larger applicator compared to metal stents, therefore requiring pre-dilation of the stricture more often [33].

Biodegradable Stents

Biodegradable stents (BDS) are not widely available yet with only small case series speaking to their efficacy [41]. BDS potentially solve the problem with stent extraction and migration, as most stents are dissolved by 6 weeks. However, dedicated trials with larger patient populations are needed. In one small randomized trial, after three months, patients with strictures who had BDS stents required fewer dilations compared to dilation alone. However, by six months, the number of dilations was similar[42]. Other small studies have shown that dysphagia clinically improved in 33–100% of patients, but stent migration rates continued to be quite high ranging from 8 to 77% [43].

Corticosteroid (Triamcinolone acetonide) Injection

Intralesional injection of corticosteroids has been used for refractory esophageal strictures for the last 50 years. Used as an adjunct to dilation, intralesional steroids interfere with

collagen synthesis and fibrosis, thereby inhibiting stricture formation. Triamcinolone, specifically, inhibits fibronectin and pro-collagen synthesis, reduces inhibition of collagenase, and prevents scar contracture. In addition to triamcinolone, betamethasone solutions are also commonly used. The procedure itself involves radial injections of the steroid using a sclerotherapy injection needle. Optimally, injections are given prior to dilation and radial injections in 4–6 quadrants just proximal to the stricture and then distally. Studies have shown that intralesional injection of corticosteroids in conjunction with dilation for anastomotic fibrotic strictures significantly reduces stricture recurrence, the number of periodic dilations required for recurrent strictures and increases the maximum dilation diameter achieved [8, 44–46].

Mitomycin C

Mitomycin C, a chemotherapeutic agent, has demonstrated success for the treatment of refractory esophageal strictures in small case series. In these case series, endoscopic application is performed via injection or rubbing with soaked gauze. These case series demonstrate decreased frequency of dilations and improvement in dysphagia [47]. One randomized controlled trial has been conducted in pediatric caustic esophageal strictures which demonstrated significantly higher rates of stricture resolution and decreased number of dilations needed in the mitomycin C group [48].

Electrosurgical Needle Knife

Limited, small case series have described the use of electrosurgery to treat esophageal surgical anastomotic strictures [16, 49]. A sphincterotome or endoscopic knife, under direct endoscope visualization, supplies an electrosurgical current to cut several longitudinal incisions (usually 6–12) with variable length and depth circumferentially around a stricture

[16, 25, 49]. The limited literature available is favorable toward electrosurgery as success rates are as high as 100% for dysphagia resolution with recurrence rates of 12.5% and without major complications [3, 49]. A randomized controlled trial comparing dilation versus electrosurgical needle knife as a primary therapy for esophageal anastomotic stricturing showed no significant difference between the two groups. The authors concluded that an electrosurgical needle knife can be used as primary therapy in the hands of an experienced endoscopist, but in less experienced hands it should be used as second-line therapy [25].

Medical Management

Based on the theory that benign strictures can be affected by the exposure of the surgical anastomosis by the reflux of acidic stomach contents, proton pump inhibitors (PPIs) have been shown to independently reduce fibrotic stricture formation 32% [12].

Gastric Anastomotic Strictures

Definition

Gastric anastomotic strictures are diagnosed clinically in patients with persistent vomiting and dysphagia with a history of a gastric anastomosis and endoscopically as a failure of passage of a 9-mm [50] or 9.5-mm [51] endoscope through the anastomosis [51]. Post Roux-en-Y gastric bypass, gastrojejunostomy strictures are the most common gastric anastomotic strictures seen by general surgeons and gastroenterologists and will become more common with the increasing number of bariatric surgical procedures performed worldwide [3, 51]. Other possible surgical etiologies include pancreaticoduodenectomy and gastrojejunostomy reconstructions, as well other gastric resections [3].

Pathophysiology

The mechanism behind gastrojejunal anastomotic stricturing is not completely understood [52]. Benign gastrojejunostomy anastomotic strictures are the result of fibrosis and the inflammation response secondary to a number of factors including gastric acid secretion from the neo-pouch, anastomotic ischemia or leak, technical problems, marginal ulcerations, NSAIDS, alcohol, or smoking [52–54].

Incidence and Risk Factors

The incidence of anastomotic gastrojejunostomy stricturing post-gastric bypass ranges between 0.6 and 27%, with no difference between open versus laparoscopic approaches [3, 51, 54].

Usually appearing as a late complication, risk factors for stricture formation can be classified into three categories:

1. Patient factors: female gender [3], healing capacity [51].
2. Surgical technique: stapled anastomosis [51] with a circular stapler [3, 51, 52], 21-mm stapler size [51, 54], anastomotic tension [51], large volume gastric pouch [54], surgeon inexperience [55].
3. Postoperative complications: anastomotic ischemia [3, 51].

Treatment

The mainstay of therapy for a post-gastric bypass anastomotic stricture that is associated with a clinically significant functional impairment is mechanical gastrojejunostomy dilation using balloon dilation [51]. Considered the gold standard treatment, these strictures respond favorably to dilation with efficacy rates reaching 100% and require less dilation sessions compared to esophageal anastomotic strictures, with 55–90% of patients requiring only one session [50, 51, 56, 57]. TTS balloon dilation has a low overall complication rate and

an acceptable perforation rate under 2% [50]. The role for other treatments, like surgical revision and to a lesser extent endolumenal stenting and Savary-Gilliard bougies are usually reserved for refractory strictures, defined as recurrence of stenosis despite 3–5 balloon dilation attempts [50, 53].

Balloon Dilators

As described earlier, balloon dilation can be performed under endoscopic or fluoroscopic guidance [51]. TTS dilation has the advantage of assessing the stricture visually. The procedure is as described earlier. Briefly, the stricture is visualized by gastroscopy, 6–18 mm balloon catheter is inserted through a side channel and through the stricture [51, 56]. Fluoroscopy then confirms that the balloon is traversing the waist of the stricture and the balloon is inflated until the waist disappears on fluoroscopy [51]. After 30–60 s, the balloon is deflated, withdrawn and the endoscope is advanced through the dilated anastomosis [51]. The goal of dilation is to achieve a diameter at least 2.5 times the original strictured diameter or at least 12-mm, with repeated dilations as necessary with progressively larger balloon sizes and repeated sessions for recurrences [3, 50]. For strictures post-gastric bypass, dilation above 15mm is discouraged as it can impair postoperative weight loss.

Other Endoscopic Procedures

Endolumenal Stents

The role of endolumenal stents in the treatment of refractory gastrojejunal anastomotic strictures is controversial [53]. Small case series have shown varying success with management of refractory strictures causing continued feeding intolerances, with success rates ranging from 0 to 80% [53, 54, 58]. Eubanks et al. reported significant abdominal pain associated

with all patients in their anastomotic stricture subgroup, requiring most stents to be removed after only one week [58]. Stent migration from the gastrojejunostomy is the most common complication, reported in almost 50% of patients, likely from small bowel peristalsis and the unique stricture formation of these particular strictures [53, 58]. Distal migration may be less with partially covered stents. Securing the stent with endoscopic sutures is a promising technique that was able to decrease stent migration to less than 20% in a small case series [59].

Savary-Gilliard Dilators

Bougie dilators have been reported to be successful in treating gastric anastomotic strictures [50, 60]. The procedure is the same as described previously and often involves fluoroscopy [3]. While rigid dilators have been reported to be successful, TTS balloon dilation is the preferred method due to the long distance from the mouth to the anastomosis and the presence of a potentially difficult and variable curvature of the Roux limb [3, 50].

Colorectal Anastomotic Strictures

Definition

Colorectal strictures can be defined clinically as a significant intestinal obstruction causing either defecation difficulties, pain with passing flatus or stool, and abdominal distention in a patient with a history of a colorectal surgery [61]. Endoscopically, it is the inability to pass a 12-mm [62] endoscope through the anastomotic stricture [61, 62]. This is an extremely heterogeneous group of stricturing disease from a number of different colorectal surgeries, including low anterior resection, sigmoidectomy, and ileal-anal pouch creation [61].

Pathophysiology

Similar to the previously aforementioned esophageal and gastric anastomotic strictures, colorectal anastomotic strictures are not fully understood but important factors include continued inflammation with ischemia, leakage, and in some cases, radiotherapy [62]. For unclear reasons, it is reported that the rectum is the most common site for stricturing disease [61]. Other possible proposed factors include discrepancies in size between the two ends of the anastomosis and an abnormal collagen synthetic reaction [63].

Incidence and Risk Factors

The incidence of benign colorectal anastomotic strictures ranges between 3 and 30%, yet only 5% of patients become symptomatic [28, 61, 62, 64]. Risk factors can be separated into four categories: patient factors, surgical technique (stapled anastomosis [62], smaller stapler diameter [62], temporary diverting loop ileostomy [62]), and complications (anastomotic ischemia and leak [61], pelvic sepsis [3, 61]) and adjuvant therapy (radiation [3, 61]).

Treatment

The mainstay of therapy is endoscopic balloon dilation. Dilation is favored over bougienage for the simple fact that it causes less traumatic injury [65]. While dilation is generally successful, frequently repeated dilation sessions are usually required. Stents, steroids, and incisional therapy with electrosurgery, laser, or argon are less commonly implemented and are reserved for combination treatment adjuncts or for dilation failures.

Balloon Dilators

The TTS balloon dilation is as described previously. For narrow lumen stenotic strictures or angulated intestines a technique called over-the-wire (OTW) dilation is preferred over TTS, which uses an endoscopically placed guidewire to allow for more successful proximal placement of the balloon [27, 62]. OTW uses the Seldinger technique for balloon insertion and generally has larger diameter balloons than the TTS type. Balloon dilation, including both TTS and OTW, has been shown to be efficacious with medium-term success rates reported between 33 and 86%, however, recurrence rates after initial dilation are reported to be quite high at 30–88% [61, 62, 65]. The large disparity in success rates speaks to the high heterogeneity amongst the results of the studies; this is likely in keeping with difference in technique, especially in the diameter of the balloon used for dilation.

Di et al. reported improved results for the use of second, simultaneous balloon dilation for colorectal strictures [28]. In double balloon dilation, two guidewires are employed, each passed separately through the endoscope. The first balloon, usually a 20-mm, is used for initial stricture dilation under fluoroscopic surveillance for 1–3 min [65]. Then a second guidewire is passed alongside with a smaller balloon, usually 10–15-mm, and then the two balloons are inflated simultaneously [28]. At the end of the procedure, water-soluble contrast medium is injected into the rectum to rule out perforation [65]. 71–100% of patients reported long-term success in the management of symptomatic colorectal anastomotic strictures post-double balloon dilation [65]. This reported improvement with double balloon dilation could be explained by the fact that balloon size appears to be the most important factor regarding dilation efficacy for colorectal anastomotic stricturing disease [3]. Therefore, the additional benefit in diameter from the second balloon accounts for its success

[65]. The largest balloon diameter reported in the literature for this population is 40-mm. Increased balloon diameter appears not to be correlated with an increased complication rate [65]. The balloon dilation procedure is relatively safe with minimal morbidity and complications [3, 62].

Other Endoscopic Procedures

Rigid Dilators

The Savary-Gilliard bougies have been shown to have similar success rates, approximately 80%, to balloon dilators with the added advantage of being less expensive, as the bougies are reusable [66].

Stents

Stents for colorectal strictures are reserved for patients with recurrent symptoms after failed initial dilation treatment. Success rates range between 70 and 80% [63, 67].

SEMSs' role in malignant colonic unresectable strictures is well established but in benign disease its role is yet to be defined [63]. SEMS, once again, can be covered or uncovered, with the uncovered stents promoting tissue hyperplasia and embedding and therefore are harder to remove. This characteristic can lead to possible re-occlusion but have lower migration rates as a result, with uncovered stents being the opposite [63, 64].

Biodegradable stents have gained popularity of late as a management option for colorectal anastomotic strictures. Building upon the limitations of SEMS and SEPS, avoiding a second endoscopic removal procedure and its gradual expansion and dilatory effect gives these stents inherit advantages over both [64, 67]. Repici et al. reported suboptimal efficacy of these stents with stricture resolution in only 45% of patients and surprisingly high stent migration rates of 36%. The authors attributed these poor results to the fact that

colorectal specific biodegradable stents are not yet available; therefore, the stents, originally meant for esophageal strictures, were too small in diameter to be adequate for colonic strictures [64]. At this time, clinical availability of biodegradable stents is dependent on varying regulatory approvals throughout the world.

Electrosurgical Coagulation

Electrosurgical coagulation and other less commonly described incisional procedures like laser stricturotomy, microwave coagulation therapy, and argon plasma coagulation can be performed independent or in conjunction with balloon dilation [62]. These adjunct therapies involve radial incisions at multiple locations around the stricture just prior to the planned dilation. These procedures have shown synergistic results when combined with balloon dilation, especially for high-grade stenosis (<7-mm lumenal diameter) [68].

Endoscopic stricturotomy (ES) using the needle knife is a promising novel treatment for treating of anastomotic strictures in inflammatory bowel disease (IBD)[69]. In a case series by Lan and Shen, ES resulted in lower rates of subsequent surgery when compared to balloon dilation (9.5 vs 33.5%) in Crohn's patients [70]. However, there were much higher rates of bleeding requiring transfusion in the ES cohort (8.8 vs 0%). In another case series, ES appeared equally efficacious for non-IBD related strictures [71].

Endoscopic Transanal Resection of Strictures (ETAR)

ETAR entails resecting the anastomotic stricture. The procedure involves the insertion of a urologic resectoscope into the rectum and using a loop-cutting electrode to resect the lesion superficial to the muscular wall [72]. The incision by the loop-cutting electrode is in the posterior part of the stricture, where the peri-rectal fat and fibrosis limit the morbidity of

intraperitoneal wall perforation [68]. The incision into the posterior wall opens up the stricture, allowing a channel to be created by the incision [68]. The site is then sealed using a Foley balloon catheter, which is removed the following day. A limited, small case series on its use in anastomotic strictures report success rates ranging from 84 to 100% [68, 72, 73]. This procedure is reserved for distal, low-lying strictures, up to 15 cm, that are accessible with a resectoscope [73].

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Chapter 9
Upper Gastrointestinal Tract Leaks

Xane Peters, Patrick Sweigert, and Bipan Chand

Introduction

Anastomotic leaks represent one of the most dangerous complications after gastrointestinal (GI) surgery. The incidence and severity of leaks vary widely among different disease processes, surgical anastomoses, and locations within the GI tract. Although GI leaks are rare complications, results can be devastating particularly when a delay in diagnosis or treatment exists. Upper GI leaks, as emphasized in this chapter, represent a particular challenge to surgeons due to their significant morbidity and anatomic complexity. However, novel therapeutic strategies employing upper endoscopy have revolutionized the management of patients with leaks. Herein, we describe the approach to early diagnosis and

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X. Peters · P. Sweigert · B. Chand (✉)
Department of Surgery, Loyola University Medical Center, Maywood, IL, USA
e-mail: Patrick.sweigert@lumc.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_9

management of upper GI leaks, including novel endoscopic treatment strategies like endoluminal stenting, suturing, clipping, and drainage.

Early Diagnosis of GI Leaks

Postoperative care following upper GI surgery is characterized by cautious monitoring of resumption of GI function in the setting of altered anatomy. The astute clinician observes the patient's progress with an understanding of an expected course to have optimal recognition of a significant deviation from the typical progression. Upper GI leaks may result in a severe systemic inflammatory response including septicemia; however, it may also have a more subtle clinical onset. In Fig. 9.1, we summarize some hallmarks to diagnosis and management, once a heightened suspicion for upper GI leak is present.

If the surgeon suspects upper GI leak, the diagnostic approach may include:

1. Complete history and physical examination, with review of the operative approach details and anastomotic techniques employed, as well as risk factors for leakage. Such risk factors account for nutritional, vascular, and technical aspects of the case affecting wound healing and anastomoses.
2. Laboratory: A full set of blood work including a complete blood count, complete metabolic panel, coagulation profile, serum amylase, and lactic acid may have utility in the appropriate setting.
3. Drain fluid analysis such as fluid amylase, Gram stain, and culture. Some have even reported utility of oral ingestion of a colored fluid to potentially observe its migration into the drain fluid.

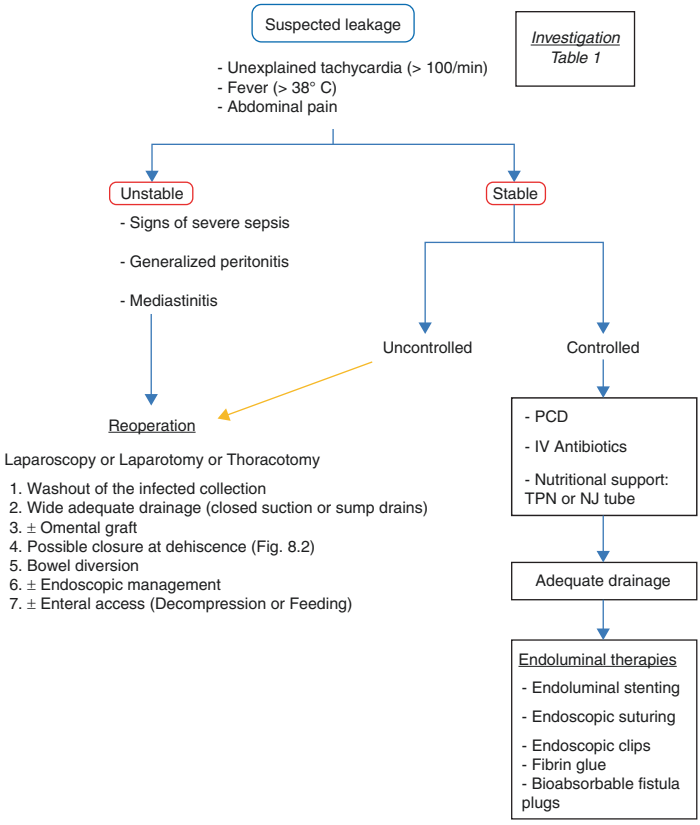

FIGURE 9.1 Algorithm for management of anastomotic leak

4. Diagnostic imaging:

- Acute abdominal X-ray series can alert the surgeon of severe findings of pneumoperitoneum, or more subtle findings such as enteric distension.
- Upper gastrointestinal (UGI) contrast study including water soluble or barium-based contrast material. In general, water soluble contrast is preferred, however, barium may increase the sensitivity of the exam. UGI studies are helpful due to the dynamic nature of the

evaluation and give the surgeon information unavailable from static studies. A detailed understanding of the post-surgical anatomy can increase the utility of the study in identifying and characterizing subtle leakage of contrast. An UGI may also be continued as a small bowel follow-through to further evaluate distal bowel.

- Abdominal ultrasound (US) may be useful particularly when evaluating for alternative diagnoses. However, in the setting of upper GI leakage, abdominal US has limited diagnostic utility.
- Computed tomography (CT) is considered by most to be the diagnostic test of choice, when performed optimally. The ideal study evaluates the chest, abdomen, and pelvis with well-timed IV contrast and oral contrast. Unique to a suspected upper GI leakage is the attention paid to administration of some quantity of oral contrast just prior to the cross-sectional imaging to optimize the sensitivity of the study. CT allows for a static characterization of the leak and its local severity, chronicity, size, and effect on surrounding structures.

5. Diagnostic endoscopy to evaluate the post-surgical anatomy for signs of wound breakdown, inflammation, foreign body, distal obstruction, and/or for directed fluoroscopic evaluation using injected enteral contrast.

Management of Gastrointestinal Leaks in Esophagogastric Surgery

The management of the leak depends on the patient's clinical condition (Fig. 9.1). The surgeon managing this complication must develop a clear treatment strategy based on the patient's status, the duration of the leak, and the resources available. When an upper GI leak is highly suspected or confirmed, the management strategy must begin with optimal bundled sepsis resuscitation and supportive care including the following [1]:

1. Airway management, supplemental oxygen therapy.
2. Broad-spectrum antimicrobial coverage including antifungal agents after appropriate cultures have been obtained.
3. Intravenous fluid resuscitation begins with a 30 cc/kg rapid administration of resuscitative crystalloid solution if hypotensive or lactate is >4 mmol/L of using markers of end organ perfusion to guide response (including whole blood lactate).
4. Intravenous vasopressor support to maintain mean arterial pressure >65 mmHg.

A complete diagnostic workup can at times be unavailable in the setting of severe sepsis, generalized peritonitis/mediastinitis, and signs of end organ failure. If the patient's condition contraindicates further diagnostic workup, reoperation should be performed. In the case of reoperation, a surgeon must understand the morbidity associated with a repeat intervention on altered and inflamed tissues with respect to the post-surgical timeframe. Early re-intervention within 72 h is generally felt to yield optimal results in relationship to more delayed approaches.

After diagnosis, clinical improvement results after addressing the three "D"s:

1. Drainage: obtain source control of leaked enteric contents (ideally enteral drainage if possible).
2. Diversion: modify the flow of enteric contents away from the site of leakage.
3. Distal enteral access: obtain a safe method of enteric feeding distal to the site of leakage.

Interventional options include radiological procedures, endoscopic procedures, or surgical exploration. In general, interventional radiological procedures are well tolerated and preferred in many cases over surgical exploration due to reduced peri-procedural morbidity. The efficacy of this minimally invasive approach is highly related to how orga-

nized the collection is, the character of the leakage, and the location. A percutaneous pigtail type catheter may be inserted into the collection near the site of upper GI leakage using a Seldinger technique under image guidance (e.g., ultrasound, CT) and only local anesthesia or MAC/sedation. This approach may be more challenging when collections are located in the mediastinum or subphrenic space, particularly when the pleural space has not been surgically violated or the risk of entry into the pleural space on drain entry is significant.

Traditional open or minimally invasive approaches to the chest or abdomen may be used for re-operative exploration. In general, the goals remain the same—source control/washout, wide drainage, identification/repair of site of leakage with tissue buttress if available or anastomotic revision, and possible distal enteral access.

Endoscopic management of upper GI leaks, the focus of this chapter, includes a wide variety of techniques that seek to accomplish the same clinical goals using a multitude of available technologies and platforms, including endoscopic clips, pigtail drains, stents, and suturing devices.

Endoscopic Stent and Suturing Management of Anastomotic Leakage after Esophagogastric Surgery

Management of an esophageal anastomotic dehiscence is challenging and is associated with high morbidity and mortality. Treatment is often selected based on patients' symptoms, site of leak, extent of leak, and systemic manifestations. The incidence of a leak and its outcome is dependent on the site of anastomosis (cervical or intrathoracic anastomosis). Cervical anastomoses are associated with a higher leakage rate of 10–20%, but with associated lower mortality [2]. In contrast, intrathoracic leak rates have been reported at 7.9%, resulting in a 3-month mortality rate of 18.2% (OR 3.0) [2]. If treatment is delayed beyond the first 24 h, a mortality rate has been reported at up to 50–60% [3, 4].

Successful management of an esophageal leak requires early recognition, prompt control of sepsis, and elimination of ongoing contamination of the mediastinum. For large esophageal anastomotic leaks with significant contamination of the pleural cavity, treatment includes a thoracotomy or thoracoscopic approach, surgical drainage and repair, and gastrointestinal diversion, while small-contained leaks are treated with conservative management including percutaneous drainage alone, abstinence of oral intake, parenteral nutrition, and intravenous antibiotics. Mortality associated with nonoperative treatment of esophageal leak ranges from 8.5% to as high as 46.2% in selected case series with successful management being between 40 and 96.3% [5–8].

Endoscopic management of GI leaks has gained great importance as it avoids the morbidity and mortality of surgical intervention. For over a decade, covered self-expanding stents (SEPS: Self-Expanding Plastic Stents; FSEMS: Fully covered Self-expanding Metal Stents; PSEMS: Partially covered Self-Expanding Metal Stents) were the mainstay of endoscopic therapy for anastomotic dehiscence after esophagogastric surgery. These stents were initially designed for use in the setting of malignant strictures; however, they have been used successfully in an off-label setting for the treatment of leaks.

Inherent to their design, the main limitations of these stent types include stent migration and hyperplasic tissue in- and/or overgrowth, especially with prolonged indwelling of stents. The emergence of partially covered stents has the theoretical advantage of increase in tissue ingrowth (at the proximal and distal portion of the stent) in comparison with fully covered stents and therefore a reduced risk for distal migration.

A major advantage of endoscopic stenting in the treatment of anastomotic leak is that a surgical intervention can often be avoided. When conventional approaches are used to manage anastomotic leaks, surgical reoperation is often required in 23–74% of these cases [5–8], compared to the use of esophageal covered stents where the rate of reoperation is 0–22.2% [9–13]. The mortality associated with an intrathoracic leak following esophagectomy has decreased in the

modern era. The leak-associated mortality between 1970 and 1986 was 43%, which decreased to 3.3% in 1987–2004 [5]. Presently, a leak-associated mortality is closer to 0% with a variety of multidisciplinary approaches available. Endoscopic treatments (SEMS, endoscopic suturing, clips and biological glue), percutaneous drainage, broad-spectrum intravenous antibiotic, and nutritional support are all employed in leak management [14, 15]. Compared to the non-interventional treatment group, patients who were treated with endoscopic stents had earlier oral intake, a less extensive intensive care course, and shorter hospital stay. Given these findings, it is highly likely that esophageal covered stents would be associated with significant cost savings over conventional treatments.

Treatment success of stent placement is defined as control of the leak, healing of the leak site, and cessation of mediastinal contamination or sepsis. Clinical success in the treatment of benign esophageal ruptures and anastomotic leaks with temporary stent placement has been demonstrated, and previously shown not to be significantly different across the above-mentioned stent types in systematic review [16] and cohort studies [14]. Notable complications reported in these studies related to stent use include tissue in or overgrowth, stent migration, ruptured stent cover, food obstruction, severe pain, esophageal rupture, hemorrhage, and, rarely, stent related death. Despite their demonstrated comparable effectiveness in sealing esophageal anastomotic leaks, the different stent types each have advantages and disadvantages. While plastic stents are less expensive than their metallic counterparts, drawbacks of plastic stents include their larger diameter and higher rigidity, which led to a higher incidence of complications (e.g., perforation, hemorrhage) as shown in a randomized prospective comparison between SEPS (9%) vs. PSEMS (3%) [17].

Historically, endoscopic stent management of esophageal anastomotic leaks was developed using the only self-expandable plastic stent (Polyflex®, Boston Scientific) with diameters ranging from 16 to 21 mm and lengths from 90 to

150 mm. The stent was made from silicone, entirely covered with a polyester film and flared at the proximal end. The polyester film helped decrease the risk of ingrowth into the esophageal mucosa and facilitated stent removal; however, it also enhanced the risk of migration. This migration has been demonstrated more commonly with fully covered stents [16]. Of note, the majority of patients in the cited study had no obstructive lesion keeping the stent in place.

Currently, self-expanding metal stents (partially covered or completely covered) are used in the treatment of complications of esophagogastric surgery (Fig. 9.2). Even though their cost is higher than previously used plastic stents, their

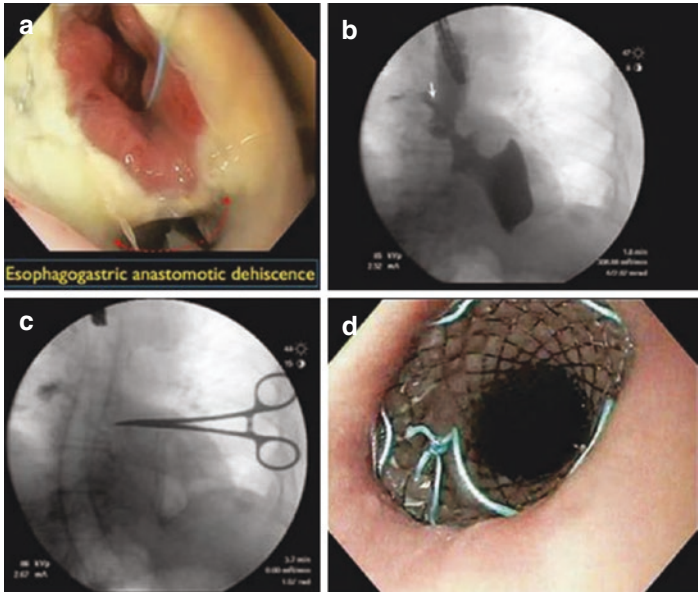

FIGURE 9.2 (**a**) Esophagogastric anastomotic dehiscence (*arrow* sign). (**b**) Contrast leak at the Esophagogastric (EG) anastomosis after Ivor-Lewis esophagectomy (*white arrow*). (**c**) Intraoperative fluoroscopy demonstrated PSEMS insertion in order to bypass the leak site with cutaneous landmarking (Hemostat). (**d**) Endoscopic view demonstrating completed PSEMS deployment

utilization is easier (more flexible and pre-assembled) and the risk of complications associated with their use—namely, perforation, hemorrhage, and migration—is less than SEPS. As evidence of this transition, there are currently no self-expanding plastic stents with market availability in the USA.

Self-expanding metal stents are composed of one or several braided strands of a metal with high shape memory, most made of nickel titanium, also known as "Nitinol." They are contained within a tight sheath placed on a carrier tube. The caliber of the assembled system ranges from 18 to 24 Fr, which is not compatible with the passage of the stent through the operating channel of an endoscope (over-the-wire, OTW, system). However, there are novel models with a thinner delivery diameter (10 Fr) that can be passed through a 3.7 mm operating channel referred to as a "through-the-scope" system, (TTS). The self-expandable metal stents vary according to the alloy used, the length (70–170 cm and even longer), the diameter (18–23 mm or greater), the delivery system, as well as the coating material. The proximal and sometimes the distal ends are flared (approximately 5 mm larger than the shaft) in an attempt to limit the risk of migration. Several options (anti-reflux valve, anti-migration systems, or proximal deployment) are available. The choice of the stent is crucial in case of proximal esophageal leaks or fistulas, especially after the Lewis-Santy operation where the low radial force of the Ultraflex® (Boston Scientific) stent is most appropriate. Proximal deployment systems allow adjustment of the position of the stent between the high-riding fistula and upper esophageal sphincter.

Esophageal self-expanding stents are placed under endoscopic and radiologic guidance typically with sedation or general anesthesia. The initial step consists of visualizing and marking the leak site endoscopically and by contrast opacification, as well as estimating the extent of the leak in order to choose a stent of appropriate length. Radiopaque objects (e.g., paper clip or hemostats) are used for cutaneous marking if patient movements can be limited, or more rarely

internal markings (submucosal injection of contrast or clip placement) are used. After placement of a guide-wire, the endoscope is withdrawn and the stent deployment system placed over the wire under fluoroscopic guidance. A rigid guide-wire (Savary type) is preferred. An endoscope can be inserted alongside the deployment system for visualization. The distal end of the stent is placed in the stomach, duodenum or jejunum, according to the preceding procedure. Small adjustments can be made at the beginning of delivery. Contact between the stent and the endoscope must be avoided immediately after delivery as it can increase the risk of migration. Contrast medium is often injected within the stent itself after deployment to check for extravasation and proper sealing. A plain X-ray after the procedure can help evaluate the degree of expansion of the stent and the exact location. This image can be used to establish for stent migration. Patients can resume oral intake if there is no evidence of ongoing leak on contrast imaging. Recommendations to avoid the risk of food impaction within the stent include eating while in the seated position, avoiding thick, dense aliments (meat), avoiding stringy aliments (leeks, for example), avoiding karaya gum gastric demulcents, and drinking sparkling water at the end of the meal. Stent surveillance protocols should be in place with weekly X-ray to look for migration. There are currently select stents with on-label status outside of the USA for the management of gastrointestinal leak.

Tissue overgrowth involving endoluminal stents mostly occurs at the uncovered part of PSEMS. It is caused by the proliferation of granulation tissue and/or local fibrotic reaction (Fig. 9.3) that can clinically manifest as early as 2 weeks after stent deployment. This can lead to difficult stent removal, which may result in a secondary esophageal perforation [18]. On the other hand, the hyperplasic epithelium growing into the stent meshes may reduce the risk of stent migration, providing a better watertight barrier to saliva and fluids, and ultimately favoring fistula healing [19]. The mean healing time varies and has been reported to be 7 weeks

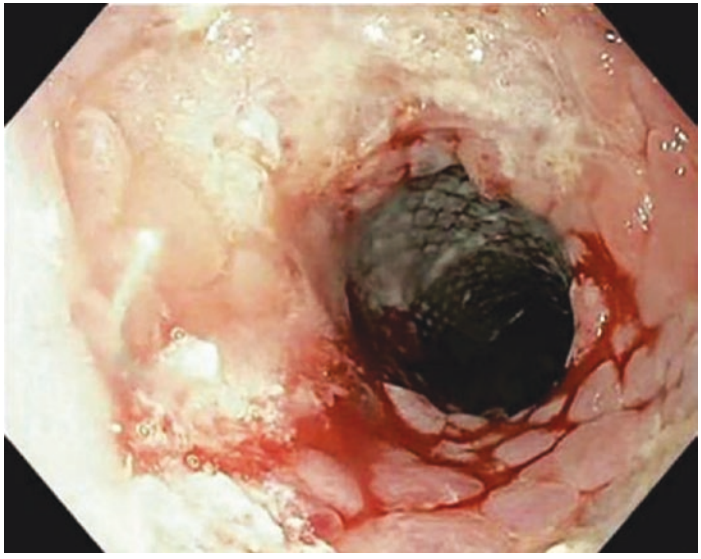

FIGURE 9.3 The proliferation of granulation tissue (tissue overgrowth)

(range: 6–8 weeks) in some series. Six to eight weeks have been suggested as the optimal time for stent removal (this may require two separate stent intervals). A shorter interval may lead to incomplete closure of the fistula or the leak site, while a longer interval may cause either stent migration or excessive mucosal overgrowth within the stent with subsequent dysphagia or difficulty in stent removal. Stent extraction can be done simply by pulling on the suture attached to the proximal end of the stent, either with a toothed forceps or polypectomy snare (Fig. 9.4). In more difficult cases, particularly extraction of partially covered metallic stents with epithelial ingrowths into the mesh, grasping the stent at two points via the two channels of a double-channel endoscope can be helpful. When the proximal extremity of the stent is close to the upper esophageal sphincter area, placing an overtube can be useful for extraction. A useful technique to remove an embedded PSEMS is to place a fully covered stent of the same diameter inside the first one. This so-called stent-

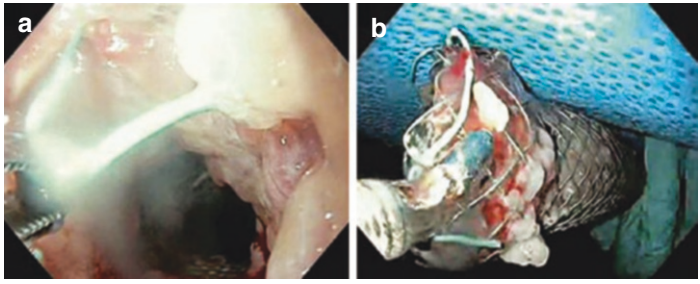

FIGURE 9.4 (**a**) Stent extraction with rat toothed forcep. (**b**) PSEMS after removing

in-stent technique causes necrosis of the hyperplastic epithelium and both stents can be more easily removed after 7–14 days [19, 20]. Biodegradable stents have recently emerged, which may provide the additional benefit of not needed extraction. However, their use in esophageal leaks is limited and has not yet emerged in the US market.

Esophageal stenting is often performed with simultaneous endoscopic or percutaneous drainage of mediastinal fluid collections. The success rate for control of anastomotic leak with covered stenting appears to be similar or better than that of conservative treatments, ranging between 77.3 and 100% [9–13].

Endoscopic Suturing of Esophageal Leaks

Literature describing endoscopic suturing of esophageal leaks is limited to a few case reports. A 77-year-old man with a Boerhaave's disease, who had undergone emergent surgical repair and later esophageal diversion procedure along with jejunal feeding, developed an esophagopleural fistula. The fistula was closed by using a combination of fistula tract coagulation and endoscopic suturing (Endocinch, CR Bard Interventional, Murray Hill, New Jersey) [21]. Bonin et al. reported a case involving endoscopic suturing to close a chronic esophagopleural fistula in a 66-year-old woman. A

10-mm fistula (for which thoracostomy was unsuccessful) was successfully closed after two sessions of endoscopic suturing [22]. In another study, Kurian et al. described closure of an inadvertent full-thickness esophagostomy while performing mucosotomy during peroral endoscopic myotomy. With the use of the OverStitch suturing device (Apollo Endosurgery, Austin, TX), the defect was successfully closed and laparoscopy was prevented. In this particular case, the esophagus was dilated from achalasia disease, which precluded adequate apposition, making an esophageal cover stent a less than ideal option. The patient had an uneventful postoperative course. At 9-month follow-up, the patient had excellent palliation of dysphagia without reflux [23].

Endoscopic Vacuum-Assisted Closure in Esophageal Anastomotic Leaks

Most recently, endoscopic vacuum-assisted closure (E-VAC) has been described to treat anastomotic leaks after rectal and esophageal resections. Conceptually similar to the established usage of vacuum-assisted closure for extensive cutaneous infected wounds, accessible upper gastrointestinal leakages have been treated by endoscopically placing sponges that have been connected with a drainage tube in the necrotic cavities. The favorable outcomes of this treatment may be a result of the reduction in the intraluminal pressure and the induction of marked growth of granulation tissue.

E-VAC therapy is applied by endoscopic insertion of the EndoSPONGE system (B. Braun Melsungen AG, Melsungen, Germany) through the esophageal defect and into the cavity. The EndoSPONGE is composed of an open-pored polyurethane sponge cut to fit into the paraesophageal cavity. The sponge is positioned via an over-tube in the vicinity of the leak and then inserted with the grasper forceps into the paraesophageal cavity (intracavitary vacuum therapy). In case of a small orifice, the polyurethane sponge can be placed at the level of the esophageal wall defect (intraluminal vacuum therapy). The sponge is then connected with a nasogastric tube, and suction is applied via a portable pump. Secretions

are continuously evacuated using a negative pressure of 100 mmHg. After 2–3 days of continuous suction, the pump is inactivated, and the sponge is removed by pulling at the nasogastric tube or using an endoscopic forceps if the sponge is adherent to adjacent tissues. Persisting leakage can be adequately managed using a self-expanding metal stent placed for a period of 4–6 weeks. This hybrid therapy treatment strategy for esophageal wall defects has been described in case series with complete restoration of the esophageal defect [24]. A further study comparing stent therapy with EVAC for intrathoracic esophageal leaks demonstrated significantly favorable closure rates in the EVAC group at 84.4%, compared with the SEMS/SEPS group at 53.8%. No difference was found for either hospitalization or hospital mortality. They reported significantly more strictures occurring in the stent group at 28.2% versus 9.4% with EVAC [25]. A recent cross-national systematic review and meta-analysis demonstrated significantly favorable success rates in healing esophageal leaks, lower rates of major complications, and in-hospital mortality compared to SEMS [26].

Endoscopic Internal Drainage in Esophageal Anastomotic Leaks

Endoscopic internal drainage with double pigtail stents (DPS) has been described as an effective means of managing esophageal leaks. The principle involves placement of a double-sided pigtail drain through the defect into the area of leak or abscess, where the extraluminal pigtail preferentially drains through to the luminal pigtail into the enteric tract, facilitating resolution and defect closure. The essential principle of this methodology was initially utilized in the management of pancreatic pseudocysts, though is currently becoming more widespread in the management of gastrointestinal leaks. Its use is largely confined to small, contained leaks and is performed under fluoroscopy with over-the-wire placement. In the American market, there are two available products: Boston Scientific's Advanix™ with a 7–10 Fr diam-

eter and center bend and varying length from 3 to 15 cm, and the Solus™ from Cook Medical with a 10 Fr diameter and varying length from 1 to 15 cm. Recently, this modality has surfaced in the literature as an acceptable form of managing gastrointestinal anastomotic leaks. Endoscopic evaluation of the leak prior to placement of the stent to characterize the size and extent of the cavity requiring drainage is an important step. Limitations include the small caliber of pigtail drainage and the resultant propensity to become clogged [27]. Further data regarding the relationship between internal drainage and concomitant or initial external drainage have yet to be clearly delineated in the literature.

Endoscopic Stent and Suturing Management of Gastrointestinal Leak After Gastric Bypass and Sleeve Gastrectomy

Most existing data on post-bariatric surgery leaks are related to the management of the two most common bariatric procedures: laparoscopic Roux-en-Y Gastric Bypass (RYGB) and laparoscopic sleeve gastrectomy (LSG). Endoscopic treatment strategies may attempt to bypass a leak (stenting) or occlude it (clips, plugs, glues, or suture) or allow for internal drainage and closure by secondary intention (double-pigtail plastic biliary stents). Control of abdominal contamination, use of systemic antimicrobials, and nutritional support are all required as well. Gastrointestinal leak after bariatric surgery has also been described in terms of time to diagnosis: early onset within postoperative day 1–7; or delayed onset, after postoperative day 8 [28]. They have been further described by the site of leakage, listed below.

- Site of leakage: Identification of the gastric leak site based on:
  - LSG: anatomic thirds (upper, middle, or distal third of the remaining stomach)
  - RYGB: there are seven potential sites for a leak [29], described from proximal to distal:

- Type 1 Gastric pouch
- Type 2 Gastrojejunal (GJ) anastomosis
- Type 3 Jejunal stump
- Type 4 Jejuno-jejunal (JJ) anastomosis
- Type 5 Excluded stomach
- Type 6 Duodenal stump (in resectional bypass)
- Type 7 Blind end biliary jejunal limb

The most frequent location of leaks is the GJ anastomosis (49–53%). The highest mortality is associated with leak at the JJ anastomosis.

A systematic review and meta-analysis reviewing safety and efficacy of self-expandable stents (SES) for the management of post-bariatric surgery leaks demonstrated successful leak closure using SES, reported at 87.77% (95% CI, 79.39–94.19%). Successful endoscopic stent removal was reported at 91.57% (95% CI, 84.22–96.77%) and stent migration was noted in 16.94% (95% CI, 9.32–26.27%) [30].

Early Gastrointestinal Leak After Gastric Bypass

Patients manifesting signs of sepsis or instability are most commonly found to have type 2 (GJ anastomosis) leaks, and rarely, type 4 (JJ anastomosis) leaks. Early onset leaks in this setting should be managed operatively with laparoscopy or laparotomy with washout of the infected collection and wide drainage of the area. Direct primary closure of the defect with or without sealants should be reserved for cases diagnosed early (within 24–48 h) and with good tissue viability. Closed suction or sump drains should be placed in close vicinity and omentum sewn over the defect to help contain contamination. If the patient is stable during the case, a feeding jejunostomy should be placed for long-term enteral access (Fig. 9.1).

Endoscopic therapy is an alternative in this situation and is associated with acceptable risk in selected patients (Fig. 9.5). Stent placement in these patients allows them to resume oral

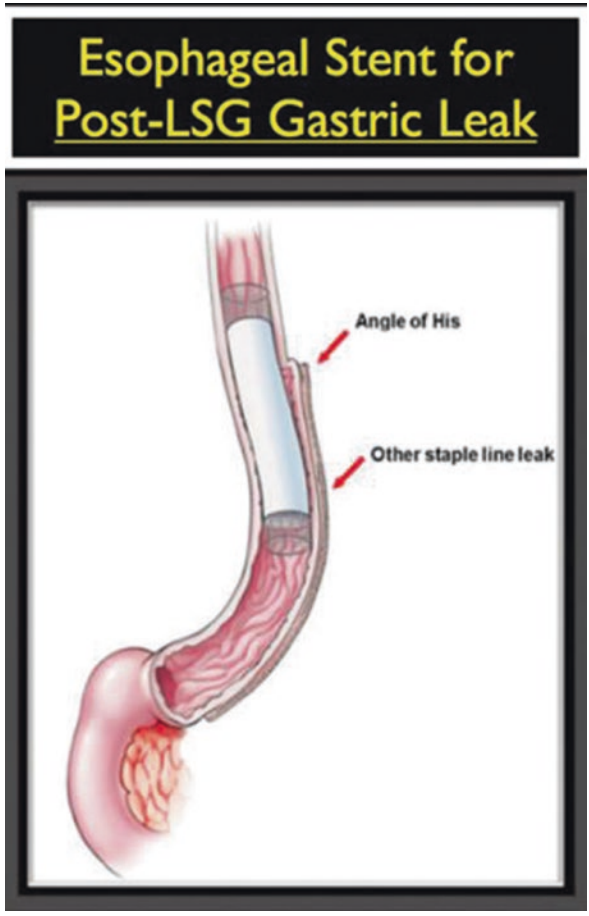

FIGURE 9.5 Schematic illustration of gastric anatomy after sleeve gastrectomy (LSG) with stent in situ

intake while the leak heals. Stenting also accelerates and promotes closure when a leak test is positive after primary or omental closure. Endoscopic stent placement for anastomotic complications has been demonstrated to be effective at definitive management with symptomatic improvement, and allowing for early oral intake; with complicating stent migration often amenable to endoscopic intervention [31].

Delayed Leak with Abscess

A leak may also present as a well-defined abscess several days or weeks after surgery. In such cases, percutaneous image-guided drainage or pigtail drainage, intravenous antibiotics, and nutritional support (intravenously or through an enteral access) is appropriate. If drainage is adequate, endoluminal therapies can be used to facilitate closure of the leak. This process often includes placement of endoluminal stents, endoscopic clips, suturing, fibrin glue, or bioabsorbable fistula plugs across the leak. Before attempting to stent, the extraluminal collection must be adequately addressed in all cases and placement of drains with washout of the infected field is often warranted to promote closure of the leak.

Early Gastrointestinal Leak after Sleeve Gastrectomy (LSG)

Compared to post-RYGBP leaks, LSG leaks are more difficult to manage. Proximal fluid collections often contain saliva and gastric acid while distal leaks may additionally drain bile. In proximal leaks, the use of drains (surgical or percutaneous) plus alimentary support should be initiated. In addition to adequate drainage, the application of endoscopic agents like fibrin sealants in combination with somatostatin and placement of endoluminal stents have yielded promising results. Stenting has been shown to be effective in selected cases, but results can be variable depending on the size and duration of the leak [31]. Although placement of self-expanding covered, or partially covered stents (Polyflex or Wallflex stents, Boston Scientific, Natick, Massachusetts) may be beneficial, the current stent technology is not ideal for this anatomy. The difficulty is in the two different lumen diameters and the curvature of the gastric lumen (Fig. 9.5).

Several principles should be followed when an esophageal stent is considered for management of a gastric leak after sleeve gastrectomy. First, an upper GI endoscopy must be

performed to evaluate the site and size of the leak, as well as the viability of the conduit. Gastric leaks at the proximal and mid-aspect of the gastric sleeve are the only leaks amenable to endoscopic stenting. A leak at the distal staple line of the gastric sleeve near the gastric antrum will not be amenable to endoscopic stenting, owing to the stent's smaller diameter, and inability to provide appropriate sealing of the defect. The selection of stent size is based on evaluation of the gastric sleeve diameter and the ability to deploy the stent. Another strategy to minimize stent migration is to use a longer stent or two stents whereby the distal aspect of the stent is rested along the wall of the gastric antrum, preventing luminal migration. Many studies have suggested routine stent removal no later than 6 weeks in order to avoid tissue hyperplasia and difficult extraction. Tolerance to stents is variable. Some patients report nausea, vomiting, drooling, and retrosternal discomfort, which tends to improve after the first days typically. Covered SEMS also present morbidity and rarely mortality, with migration being one of the main concerns. The high migration rate has been explained by the "abnormal" placement of the stent along the last portion of the esophagus and the gastric pouch. The type of stent used may also lead to higher rates of migration. Fully covered stents will have the greatest degree of migration while less covered stents will have a greater degree of tissue ingrowths. Overall, the success rate for stent treatment ranges between 50 and 100% with a migration rate between 8 and 58% [31–36].

Treatment success is defined as the absence of contrast agent leakage in CT and endoscopic evaluations after placement of covered SEMS, T-tube, or pigtail drains and their subsequent removal. In contrast, "treatment failure" is defined as the need for surgery for persistent GL (total gastrectomy or Roux-en-Y gastroenterostomy at the site of GL).

There are fewer reports on the management of distal leaks; however, the same principles as previously described should be applied. Court et al. presented a case report with distal and proximal disruptions of the staple line. A T-tube gastrostomy with a large proximal and distal limb was placed into the most

distal area of disruption. After thorough over sewing and drainage of the proximal site and T-tube (distal), a feeding jejunostomy was placed. Four weeks postoperatively, the T-tube was removed after the patient had a negative Gastrografin study and tolerated oral fluids with a clamped T-tube [37]. Persistent leaks (both proximal and distal) may require conversion to a low-pressure system, unlike sleeve gastrectomy. In this circumstance, the alternative treatment could be to conversion to an RYGB.

Another important factor when treating proximal or distal leaks is to rule out distal obstruction, in particular at the incisura angularis. If present, an upper endoscopy and endoscopic deployment of a covered stent across the leak site and obstruction will both cover the leak but more importantly decrease the pressure in the gastric lumen.

Endoscopic Clips and Suturing in Gastrotomy Closure

While endoscopic clips were initially described with promising outcomes for the closure of gastrostomy in porcine models, particularly after NOTES procedures [38, 39], they are less useful for larger defects owing to the limited opening distance between their jaws, reduced closure force, and the inability to adequately capture deeper tissue. Through-the-scope (TTS) clips, primarily used in the management of hemostasis due to their smaller purchase on tissue, may have applicability in the management of leaks and have recently come available with increased diameters. Over-the-scope clips (OTSCs) have demonstrated long-term success for the management of GI perforations, leaks, and fistulas in a multicenter report. This methodology may have higher long-term success when applied as initial therapy versus rescue therapy [40]. The Padlock Clip (STERIS, Mentor, OH) has recently emerged with an over-the-scope delivery method, attaching to the outside of the endoscope and thus freeing an instrument channel.

Alternatively, a number of endoscopic tissue approximation suturing devices have emerged with early studies showing superior withstanding of high endoluminal pneumatic bursting pressure than endoclips [41]. Only a few have been used in human subjects, including the OverStitch Endoscopic Suturing System (Apollo, Austin, TX) (Fig. 9.6), the G-Prox (USGI Medical, San Capistrano, CA), and the NDO Surgical Plicator (Mansfield, MA), which is no longer commercially available. While the original Overstitch device required a double-channel therapeutic endoscope, the Overstitch SX (Apollo, Austin, TX) allows alongside-mounting, thereby allowing for the use of a single-channel endoscope [42].

The deficiencies of endoscopic clips make endoscopic suturing more appropriate in the setting of the inflamed, indurated, and fibrotic tissue. This was readily demonstrated in case reports that described endoscopic suturing techniques involving the repair of late fistulas with good success by incorporating healthy, less-inflamed tissue adjacent to the site of leak [43, 44]. Trials of innovative new endoscopic suturing devices have included the Double-arm-bar Suturing System: DBSS [45], the master and slave transluminal endoscopic robot: MASTER and closure by Apollo OverStitch device [46], and Eagle Claw VIII [41]. These have been used in live and ex vivo porcine experimental studies and are undergoing studies to compare conventional endoscopic closure devices (such as endoclips) in efficacy and safety.

Liu et al. (2014) compared the safety and feasibility of closure of a 2-cm linear gastrotomy in 51 ex vivo porcine stomach models using endoclips, an Eagle Claw VIII suturing device, and surgical suturing [41]. Median pneumatic bursting pressures varied with endoclips being at 19 mmHg, compared to the Eagle Claw VIII (56 mmHg) and surgical suturing (78 mmHg). While median scores for technical difficulties were not significantly different between endoclips and the Eagle Claw, closure time of the latter was significantly the

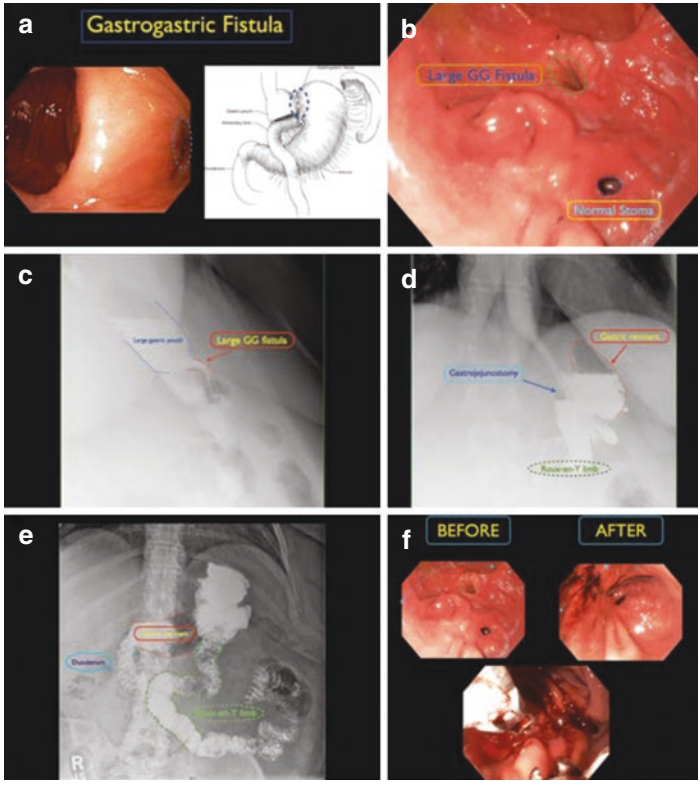

FIGURE 9.6 (**a**) Endoscopic view and schematic illustration of gastrogastric (GG) fistula after LRYGB. (**b**) Endoscopic view of a GG fistula and normal gastrojejunostomy (GJ) stoma. (**c**) Lateral view of upper gastrointestinal contrast radiograph shows large GG fistula. (**d**) Anterior-posterior view of upper gastrointestinal contrast radiograph shows abnormal contrast pass to the gastric remnant from gastrojejunostomy. (**e**) Contrast medium in both gastric remnant and Roux-en-Y limb. (**f**) Endoscopic suturing technique for closuring GG fistula and pouch reduction

longest of the three. The Apollo OverStitch, with its ability to create full-thickness plications, achieved durable gastrogastric fistula closure in three of seven cases in series presented by Watson and Thompson with no procedural complications reported [47]. As endoscopic suturing technology improves, this procedure may find greater application.

Endoscopic Internal Drainage and Endoscopic Vacuum Therapy After Sleeve Leak

The principle is the same endoscopic internal drainage with double pigtail stenting previously noted and involved placement of the stent through the defect into the cavity where the leak is contained, while the other pigtail remains in the stomach causing internal drainage. A recent systematic analysis of English-published papers in patients with imaging-confirmed gastric leaks demonstrated favorable outcomes with DPS as a first-line treatment. All patients with deemed success were without residual fluid collection or contrast extravasation on CT, were discharged on a normal diet, and were without recurrence after 6 months [48]. Though primarily noted for its use in esophageal leak management, EVT has become an emerging therapy modality in leaks after Sleeve Gastrectomy, with purported benefit of avoiding additional operations. Therapy length is variable but typically longer, extending to 84 days in one study [49]. This method has limited benefit in patients with multiple perforation sites, though may represent an additional option in management of these leaks and avoidance of further surgery [49].

Summary

The use of endoscopic therapies continues to play a vital role in the management of surgical complications throughout the gastrointestinal tract. Upper endoscopy, in particular, allows

for unique delivery of advanced and novel diagnostic and therapeutic modalities. The most common therapies include stents, large clips, and suturing devices. As device technology evolves, the technical skill set of the endoscopist will also need to evolve in order to achieve both initial technical repair and durable treatment of the presented complication.

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Chapter 10
Endoscopic Treatment of Gastrointestinal Leaks

Natan Zundel, Manoel Galvão Neto, Luiz Gustavo de Quadros, Nicole Pena Sadhala, and Fernanda Oliveira Azor

N. Zundel (✉)
University at Buffalo, Buffalo, NY, USA

ABC University, Sao Paolo, Brazil

Jackson North Medical Center, Miami, FL, USA

M. G. Neto
Sri Aurobindo Medical College, Indore, India

L. G. de Quadros
Faculdade de Medicina de São José do Rio Preto (FAMERP), São José do Rio Preto, Brazil

Hospital Estadual Mario Covas, Santo André, Brazil

Hospital Beneficencia Portuguesa de Sao Jose do Rio Preto, Sao Jose do Rio Preto, SP, Brazil

Kaiser Day Hospital, Sao Jose do Rio Preto, SP, Brazil

N. P. Sadhala
Universidad Nacional Pedro Henriquez Urena, Santo Domingo, Dominican Republic

F. O. Azor
Kaiser Day Hospital, Sao Jose do Rio Preto, SP, Brazil

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_10

Introduction

Gastrointestinal fistulas are abnormal communications between two epithelialized surfaces, typically between the gastrointestinal tract and another organ, including skin, abdominal cavity, or another organ in the body. Gastrointestinal leaks are serious complications, mainly related to postoperative anastomotic defects with substantial morbidity and mortality. When they become chronic, leaks and postoperative collections can evolve into fistulas [1, 2].

When the fistula is communicating with the airways, tracheoesophageal, bronchoesophageal, or bronchogastric fistulas may be due to malignant diseases, prolonged use of mechanical ventilation, or chronic leak after sleeve gastrectomy, for example. Due to the risk of recurrent aspiration pneumonia infection, these fistulas should be closed. Other types of fistulas are gastroduodenal, gastrocutaneous (for example, after removal of an endoscopic gastrostomy tube), and colonic fistulas. The latter can communicate with the vagina, bladder, and skin due to inflammatory pathologies, trauma, or a previous radiotherapy history [3]. After esophageal surgery, an anastomotic leak is a severe complication with an incidence ranging from 3% to 25% after esophagectomy or proximal gastrectomy. It can develop severe mediastinitis and sepsis with a mortality rate of 3–10% [4].

The process of managing fistulas and leaks is to identify their location, drain excess luminal content, prevent further leakage by diverting the flow of secretions or closing the originated defect. Surgical interventions can be complicated with high morbidity and mortality. In cases of leakage and fistulas in the postoperative period of a Gastric Bypass and Sleeve Gastrectomy, measures include surgical or percutaneous drainage, antibiotic therapy, and nutritional support. Surgical drainage can be indicated when there is peritonitis or perigastric abscess. Conservative management can be an option in stable cases with functioning and correctly located drain. Abscesses can be drained percutaneously or endoscopically [5]. Endoscopic management aims to

resolve the three main causes of leakage: distal gastric stenosis, increased intragastric pressure, and the persistence of the fistulous path. Specifically, there may be a deviation of the sleeve gastrectomy gastric axis with increased intragastric pressure [5, 6].

Endoscopy is becoming the first line in treating fistulas due to the endoscopic arsenal for closing and covering the leaks and draining collections; this arsenal includes clips and self-expanding metallic prostheses, tissue sealants, in addition to "pigtail" prostheses and negative pressure therapy [1]. Treatment requires an individualized and multidisciplinary approach. Patient clinical stability, defect chronicity, defect characteristics (location and size of the fistula), and resource availability are essential aspects to be considered before the treatment [2]. Endoscopy is a tool that allows direct analysis of the leak orifice and visualization of complications such as strictures.

Classification

Fistulas can be classified according to anatomy, output volume, and etiology. Anatomically they can be internal or external, the latter being communication with the skin. Internal fistulae communicate between the GI tract and another organ, peritoneal space, or thorax. As for the throughput, they can be of high or low output [7].

Diagnosis

Fistulas diagnosis must be made through a good clinical history, physical examination, radiological findings, and endoscopic examination. A thorough clinical history should include recent surgical history, history of radiation therapy, and clinical signs of obstruction, infection, or abscess. The clinical evolution can lead to diarrhea, dehydration, weight loss due to nutrient malabsorption, fever, hypotension, and

sepsis with leukocytosis. Tachycardia is usually the first signal of the clinical significance of a fistula causing infection and sepsis.

A physical exam is particularly helpful for external fistulae. The external fistula manifests itself with the discharge of secretion through the skin, abdominal pain, fever, obstruction, and leukocytosis. Enterocutaneous fistulas have a cure rate after surgery of 75–85%, with a mortality rate of 5–20% [8]. Adequate evaluation is critical to study the feasibility of endoscopic treatment. The affected tissue characteristics should be analyzed—whether macroscopically healthy, inflamed, or with a chronic or ischemic aspect. Fistulae can be further assessed using a combination of radiologic contrast imaging and endoscopic examination [2]. The fistula's origin and path must be identified to adequately treat the problem. Simple abdominal radiography can identify the presence of surgical clips and drains. Although barium is a standard contrast, its leakage can induce inflammation in the thoracic or peritoneal cavity. Therefore, water-soluble contrast is preferred when esophageal, stomach, or intestinal perforation is suspected. Fistulography can be performed with the injection of contrast into the cutaneous orifice in cases of external fistulas [7].

Ultrasonography and computed tomography with enterography can further evaluate the intestinal fistula and the presence of abscesses. Magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) is useful in biliopancreatic fistulas. Through ERCP, therapy can be performed—such as dilation of stenoses, sphincterotomy, or stent placement [8].

Endoscopic Treatment of Fistulae

Initially, clinical support is performed with venous hydration and control of hydroelectrolytic and acid-base disorders, antibiotic therapy, nutritional support, skin protection in enterocutaneous fistulas, and meeting each type's particularities of

fistula [8]. It is critical to treat septic patients expediently, which may include surgical intervention in addition to endoscopic therapies as indicated.

Endoscopic treatment options for fistulae depend on the time of onset of the condition. For example, in cases of bariatric fistulas and leaks, chronicity is defined as:

- Acute phase: <7 days—stent or EVT
- Early phase: 1–6 weeks—stent + balloon dilation (rarely with associated septotomy) or EVT or PigTail drain
- Late phase: from 6 to 12 weeks: septotomy + balloon dilation and in some cases, stent placement or PigTail drain
- Chronic phase:> 12 weeks: septotomy + balloon dilation or Pigtail drain

There are several options for endoscopic treatment, which are outlined below.

Balloon Dilation

Distal obstruction is one factor that contributes to fistula formation. This is particularly true in cases of bariatric leaks. Distal obstruction increases luminal pressure, maintains patency of the fistula, and lengthens the time to healing. Thus, endoscopic dilation is a part of the therapeutic strategy. The dilations can be performed with hydrostatic or pneumatic balloons, the choice being dependent on the surgical technique that caused the intraluminal pressure change and the fistula. The dilations can be repeated until therapeutic success and must be individualized according to the patient's situation and the endoscopist experience.

Roux-En-Y Gastric Bypass (RYGB): Dilation with TTS-CRE balloons up to 15 mm for periods of 3 min [8]. Overdilation of a gastrojejunostomy can lead to weight gain, and so dilation past 15 mm is discouraged. For banded RYGB: If not previously removed, the narrowing caused by the external ring should be dilated with an achalasia balloon up to 30 mm because the CRE balloon is not strong enough

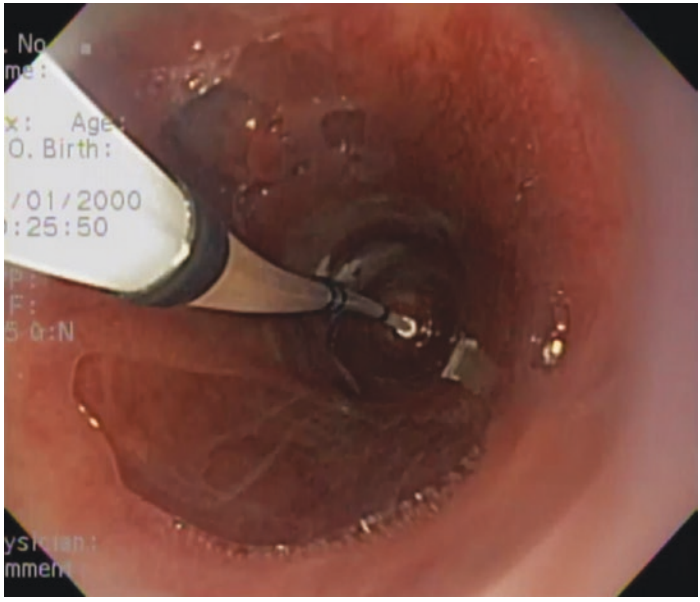

Figure 10.1 Endoscopic view with the achalasia balloon

to break the external ring or mesh. Endotracheal intubation and radiological guidance during dilation are advised [9]. Sleeve gastrectomy: the narrowing or corkscrew lumen should be dilated with a pneumatic achalasia balloon, beginning with 30 mm up to 35 mm. Endotracheal intubation and radiological guidance is advised [8] (Fig. 10.1).

Stricturotomy

This procedure is indicated for fistulas located at the angle of His. There is often a perigastric cavity with a septum and stenosis of the distal pouch. This cavity can contain pus and secretions and drains placed previously and must be washed and cleaned previously. The septum between the perigastric cavity and the proximal gastric pouch is then incised with a Needle Knife™ or similar or using argon plasma, then com-

municating the two cavities. In a gastric bypass, the gastrojejunal anastomosis stenosis is dilated with a hydrostatic balloon for about 3 min [9]. In sleeve gastrectomy cases in which the pouch's diameter is smaller than the esophagus and stenosis is present, a pneumatic dilation of up to 30 mm can be added [8].

Endoclips

Endoclips have been used effectively to close acute perforations, with a controversial role when it comes to closing fistulas/leaks. Over-the-scope (OTS) and Through-the-scope (TTS) clips are available on the market. The TTS clip has several sizes and models, inserted through the endoscope channel, and can be reloadable or single fire clips. The single-use allows reopening and repositioning several times before the final release. However, these clips limit the pressure applied to chronic wounds, so, in tissue with necrosis or inflammation, the closure may not be adequate [2].

The OTS, on the other hand, is a clip in the shape of a "bear trap" mounted on the endoscope tip, closing the defect thickness up to 2 cm. Some of those available are OTSC (Ovesco Endoscopy AG, Tuebingen, Germany) and Padlock (US Endoscopy/Steris, Mentor, Ohio). However, despite performing a mechanical compression with full-thickness closure, they pose a challenge in cases of removal in the event of a technical failure in placement, with a high recurrence rate of fistula—which could interfere in a future surgical procedure. Some professionals use argon in the edges of the fistula and the surrounding mucosa to ensure a more efficient grip of the clip [2].

Unfortunately, part of the studies showed a failure of the OTS clip system in treating fistulas in an average period of 2 weeks (ranging from 5 days to 4 weeks) after treatment. This fact may reflect the lesions' chronicity and suggest that merely closing the fistulous orifice without treating the underlying cause may not be sufficient for therapeutic suc-

cess. Thus, the OTS proved to be promising in immediate closings of iatrogenic perforations, close larger defects of up to 3 cm, with a higher clinical success rate compared to closing the fistulas [3].

A systematic review of the OTS clip's use analyzed the effectiveness and safety of this method in closing fistulas and leaks after vertical gastrectomy. After selecting ten studies, 195 patients with fistula/leak after sleeve were included. 65.3% of patients needed a clip to close the lesion. From complications, leakage was reported in five patients (9.3%), and migration, stenosis, and loosening of the OTS clip in one patient. 86.3% of patients ($n = 63$) had successful wound closure, showing that the system is a promising treatment. Studies with a larger sample are necessary [10].

Self-Expanding Luminal Stent

The endoscopic stent comes as an alternative to occlude the defect and deflect the luminal content, aiding in the mucosa's healing, allowing an early oral diet, and reducing the risk of stenosis [2]. The use of the stent avoids the morbidity of reoperation and the need for long-term parenteral nutrition [11]. Before its use, it is necessary to drain collections for successful closure and avoid sepsis risk. Traditional esophageal stents are designed for esophageal strictures secondary to malignancy and are used off-label for bariatric leaks and stenoses. They have a diameter ranging from 16 to 23 mm and a length of 6–15 cm. New bariatric stents have been developed and customized for vertical gastrectomy, which can reach 240–280 mm in length, with a maximum diameter of 30 mm and promising results [6]. Stents can be plastic or metallic, fully or partially covered. Fully covered stents are removed easily but have more chance of migration, especially when there is no associated stenosis. Although more challenging to be removed, already partially covered stents have less chance of migration,

with mucosal hyperplasia occurring in the uncovered extremities, which favors its fixation [2, 12]. This removal difficulty may be associated with complications such as perforation. The technique of placing a fully covered prosthesis on top of the partially covered one causes tissue necrosis, allowing its removal less traumatically 1 week later.

After the initial leak control, the stent is removed in post-bariatric complications even if complete orifice closure is not achieved. When necessary, endoscopic treatment continues through septotomy, stenotomy, and balloon dilations, which will lead to complete closure of the fistula. Internal drainage with pigtail drains has been successfully described in some initial cases, especially in smaller leaks (<10 mm) with associated perigastric abscess [5]. Most post-bariatric studies have a success rate of 70–85%, in many cases, part of a strategy that is not limited to the placement of a single stent [12].

In a multicenter study by Neto et al. [6] in which 87 patients in the postoperative period of bariatric surgery underwent stent implantation, only 19.5% of patients had stent migration, mainly in the vertical gastrectomy, and these were repositioned or replaced; only 3.4% (n = 3) of the patients had their stents removed due to intolerance. 80.5% of the cases were resolved without additional procedure, demonstrating the usefulness of stents in post-bariatric complications [13]. Another study of luminal stenting after bariatric leak evaluated 58 patients (50 with leak and 8 with stenosis and obstruction after bariatric surgery). They found success in treating 72% with failure in 16 patients, 14 of which were treated endoscopically with other procedures and two with surgery. Stent migration occurred in 19% of cases. Luminal self-expanding stenting is one of the early treatment options of post-bariatric fistulas, leaks, and strictures [14] (Figs. 10.2, 10.3, 10.4, 10.5, 10.6 and 10.7).

In parallel, another promise in the treatment using prostheses is the cardiac septal defect occluder (CSOs)—

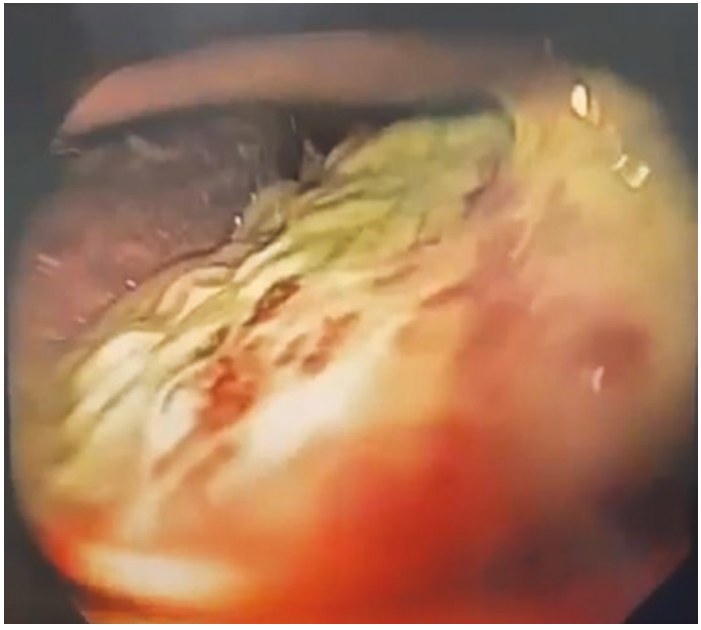

Figure 10.2 Endoscopic image in the abdominal cavity

Amplatzer™—a double disk-shaped prosthesis that promotes occlusion of the fistulous orifice and tissue growth, which can be recaptured and repositioned during its placement. The device allows addressing irregular fistulas with edema, less susceptible to suture or cut. The disk has a variable diameter (9–54 mm), a variable waist (4–38 mm), and close ventricular septal defects and other defects such as aortic pseudoaneurysms. Reports demonstrate its use in closing bronchopleural and gastrointestinal fistulas [1]. There are two types of CSOs, both of which can be used in gastrointestinal defects. However, the system has a maximum length of 80 cm, which cannot be used by most endo-

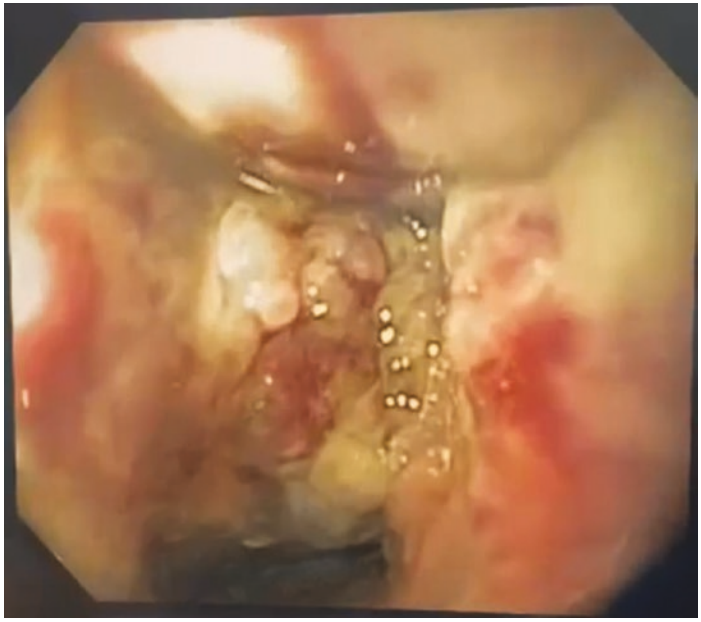

Figure 10.3 Fistulae orifice

scopes. One possible technique is to separate the CSO from its delivery system and use it with an adapted bile catheter long enough to be used through a therapeutic endoscope with a pediatric biopsy forceps aid [1]. In a systematic review by De Moura et al. [1], out of 19 selected studies, technical success was achieved in all cases. The authors considered the closure successful in 77.27% of the fistulas, with disagreement in two cases considered successful by the authors of the selected articles [1]. Due to the scarce literature composed of case reports, this review draws attention to the potential use of these CSO devices successfully in gastrointestinal fistulas.

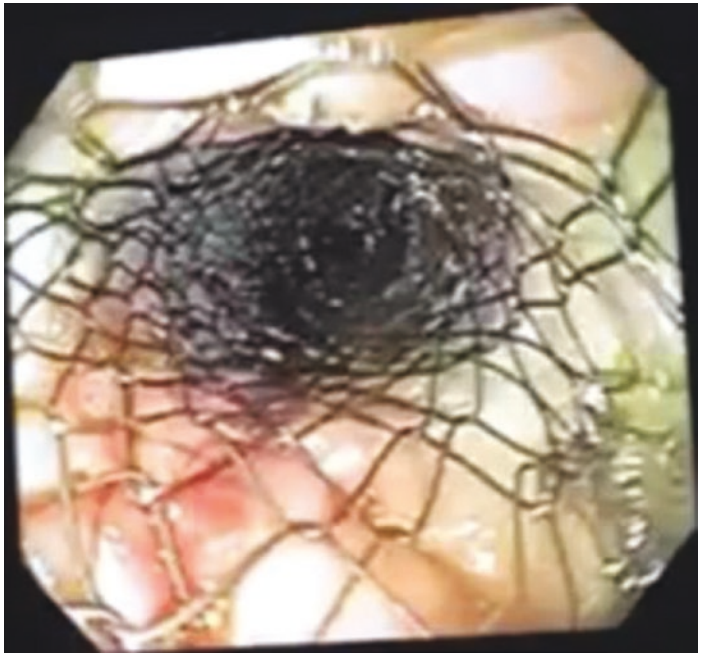

Figure 10.4 Stent placement

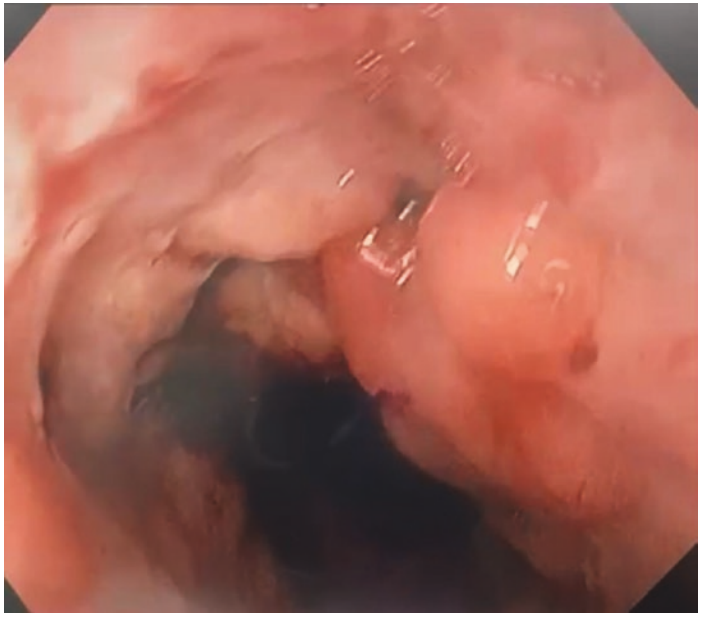

Figure 10.5 Leak healing after mega stent removal

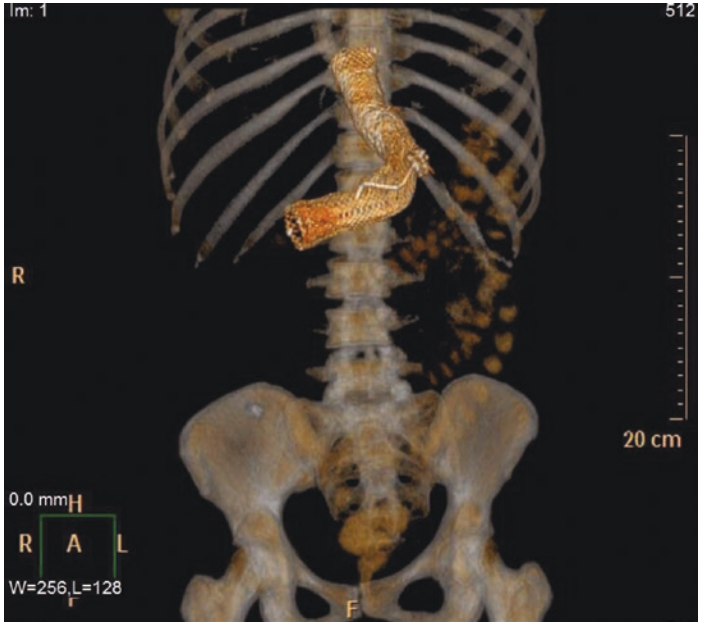

Figure 10.6 Mega stent in CT 3D view

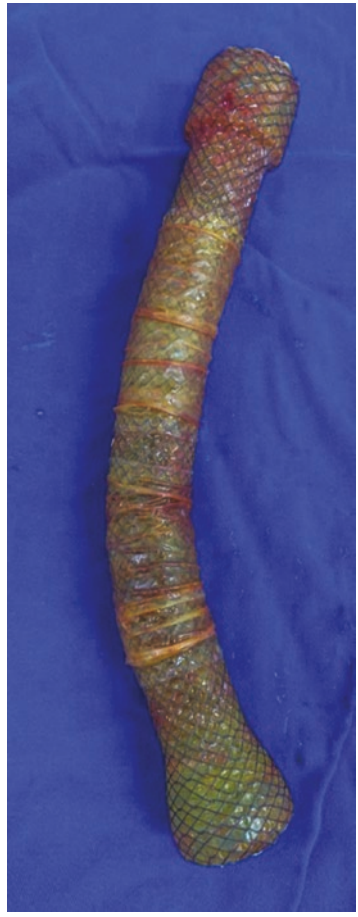

FIGURE 10.7 Mega stent after endoscopic removal

Endoscopic Internal Drainage

Internal endoscopic drainage is performed with the implantation of one or more pigtail plastic stents placed through the leak orifice to drain collections and occlude the leak orifice, thus draining the collection internally and allowing an early oral diet with subsequent re-epithelialization of the fistula. It is essential in deciding the size and model of the stent to

evaluate with a study of contrast and orifice and the cavity, including with endoscopic exploration [2]. This type of treatment is useful in late fistulas and can be a bridge to other endoscopic treatments and a unique modality [12] (Fig. 10.8).

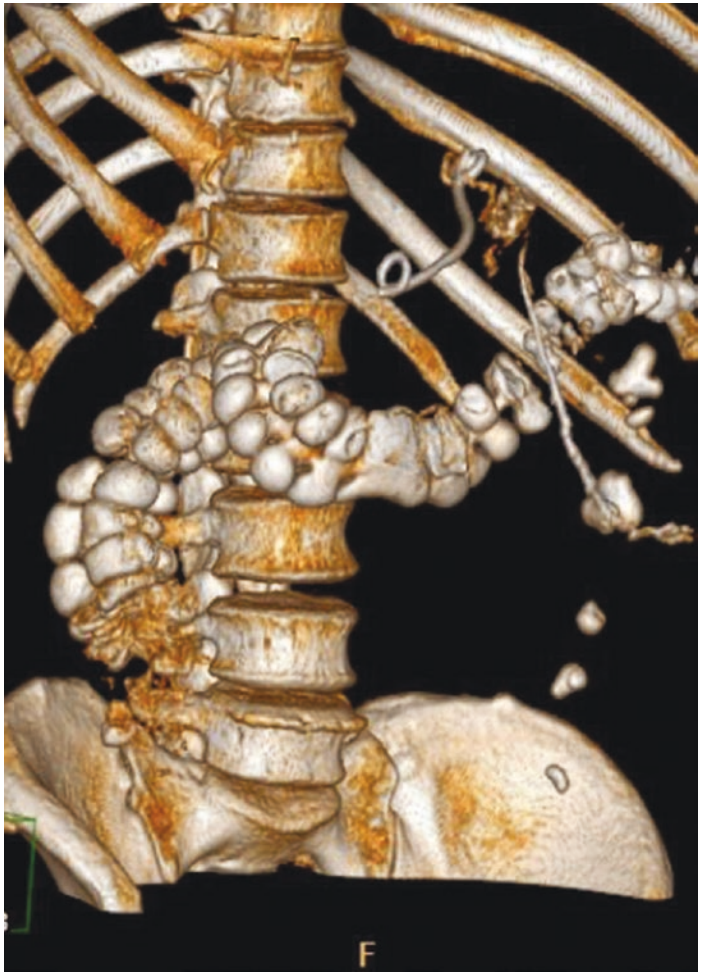

Figure 10.8 Pigtail drainage

Endoscopic Suture

The OverStitch endoscopic suturing system (Apollo Endosurgery, USA) is an endoscopic suture platform that performs full-thickness closure of gastrointestinal tract defects with non-absorbable or resorbable sutures. It requires technical experience and specific training. It has been used for defect closure in acute and chronic leaks, as well as stent fixation to prevent migration [2]. It allows the closing of larger defects as a compared endoscopic clip (more than 2 cm). The device allows the performance of continuous or intermittent suture patterns without the need to remove the endoscope between sutures. In a series of post-bariatric fistulas, 9% of cases were total closure using the technique; however, reopening has been observed in up to 65% of cases [15]. Its usefulness in perforations and fistulas still needs further studies.

A systematic review using endoscopic suturing in different contexts evaluated the use in 24 patients with fistulas or leaks, most of them female patients and without risk factors for poor wound healing. All defects were less than 5 cm in diameter. There was a technical failure in closing the coloanal fistula, and most of the closures were fistulas in endoscopic revisions of gastric anastomosis, with moderately high clinical success. Failures occurred in fistulas with cutaneous or bladder involvement, and all esophageal closures were successful. When compared to other studies, slightly lower success rates may be due to the complexity of some treated fistulas, such as enterocutaneous fistulas [16].

Endoscopic Vacuum Therapy (EVT)

It is a minimally invasive technique and can be used in rectal and esophageal surgery, such as anastomotic defects. It consists of polyurethane foam that can drain secretions when connected to a suction system, producing a continuous vacuum therapy. With continuous drainage, granulation tissue is

formed and re-epithelialization with consequent closure by the second intention. Mechanical cleaning of the site occurs through the effect caused by negative pressure, reducing microorganisms and interstitial edema, with improved microcirculation. In the colon and rectum, it may favor early closure. Other uses include leaks in bariatric, pancreatic, and duodenal perforations after retrograde cholangiopancreatography (ERCP) [2]. Foam replacement is performed every 2–4 days, with promising results in major gastroesophageal surgeries, requiring further studies in cases of post-bariatric complications [12].

To assemble the device for placement, a nasogastric tube is inserted through the nose and removed through the mouth. Then, the distal end with holes is trimmed. The polyurethane sponge is sutured in the remaining tube, made slightly smaller than the fistulous orifice, promoting collapse and closure of the fistula. After its placement, continuous negative pressure of 100–180 mmHg is performed with a vacuum pump aid. The sponge is changed every 3–4 days, depending on the injury. Some authors suggest exchanges every 1–2 weeks, and further studies should be carried out to define the ideal time interval between exchanges [17].

Endoscopic negative pressure therapy can be performed in two ways: intracavitary and intraluminal. If it is intracavitary, the sponge is inserted through the defect into the extraluminal wound's cavity. This cavity is emptied continuously and drained under negative pressure. If it is intraluminal, the sponge is placed directly over the lumen [18].

Leeds et al., in a study with E-Vac therapy performed in nine patients with leaks after sleeve gastrectomy, found a success rate of 89%. The listed limitations of therapy included the need for multiple interventions to change the vacuum sponge (10.5 procedures on average) and the use of jejunostomy or total parenteral nutrition during treatment. E-Vac is an option in severe ICU or defects with no possibility of stent placement or internal drainage [11, 19].

A retrospective study by Min et al. [17] analyzed 20 patients with esophageal leak after esophagectomy treated

with EVAC. Treatment failure was defined as no improvement of the anastomotic defect after treatment with EVAC, requiring additional therapeutic modalities, or death due to the leak. Overall there was a 95% success rate. There was a 35% rate of stenosis of successful treatments, with associated dysphagia and treated with dilation. There was an average of 5 interventions per patient. Limitations include small sample size and no comparison with other therapeutic modalities [17].

Tissue Sealant

Glues have been used successfully in low-flow leaks and fistulas. The most common are fibrin and cyanoacrylate. The fibrin glue is utilized in a double-lumen catheter and forms a flexible and absorbable tissue, simulating an initial stage of blood clotting and healing, acting better in dry areas. In that case, it is recommended to eliminate purulent material or perform mucosal ablation before use. On the other hand, cyanoacrylate is a synthetic glue that polymerizes after contact with moisture, necrosing the tissue and causing an inflammatory reaction, thus acting as a foreign body, helping in the healing of the tissue [2].

De-epithelialization of the tissue around the fistula should be performed before applying the sealant. This can be done using a biliary cytology brush or through low potency argon plasma coagulation. To apply the sealant, a double-lumen catheter is inserted to avoid the adhesion of the sealant to the endoscope [15].

Conclusion

Endoscopic treatment for leaks and fistulas is safe and efficacious. It is commonly the first line of treatment in post-bariatric surgeries when a bariatric endoscopist is available.

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Chapter 11
Lower Gastrointestinal Tract Bleeding

Robert F. Cubas, Anupam K. Gupta, and Jose M. Martinez

Introduction

Lower gastrointestinal bleed (LGIB) is defined as blood loss originating in the alimentary tract distal to the ligament of Treitz [1]. Lower GI bleeding can be classified according to the duration as acute or chronic. Acute lower GI bleeding may present as hematochezia (classically described as a maroon-colored stool when coming from the right colon or bright red blood or clots per rectum when the source is the left colon) associated with normocytic anemia, conversely chronic GI bleeding usually presents as microcytic anemia with a positive fecal occult blood test or, less commonly, as melena.

LGIB accounts for approximately 20%–25% of all gastrointestinal hemorrhages, with a reported annual incidence of 21–27 per 100,000 populations and a mortality rate of 2–4% in North America. The incidence rises with increasing age and

R. F. Cubas (✉) · A. K. Gupta · J. M. Martinez
Division of General Surgery, Section of Laparoendoscopic and Minimally Invasive Surgery, University of Miami, Miller School of Medicine, Miami, FL, USA
e-mail: rcubas@miami.edu; anupamkumar.gupta@jhsmiami.org; jmartinez4@miami.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_11

the frequent use of antithrombotic agents in the elderly population. There is an occurrence of 13–19% of rebleeding after 1 year [2].

Thankfully, the vast majority of lower GI bleeds (80–85%) stop spontaneously [3].

Etiology

In most series, diverticulosis is the most common etiology, 15–55% of the cases [4]. Fortunately, it stops spontaneously in more than 80% of patients. In one series, surgery was unlikely if <4 U red cell transfusion was given in 24 h but required in 60% of patients receiving >4 U in 24 h [5] (Fig. 11.1), whereas angiodysplasia may be the most frequent cause in patients over the age of 65 years, 2–30% of the cases. Acute bleeding appears to occur more frequently due to lesions in the proximal colon [6] (Fig. 11.2).

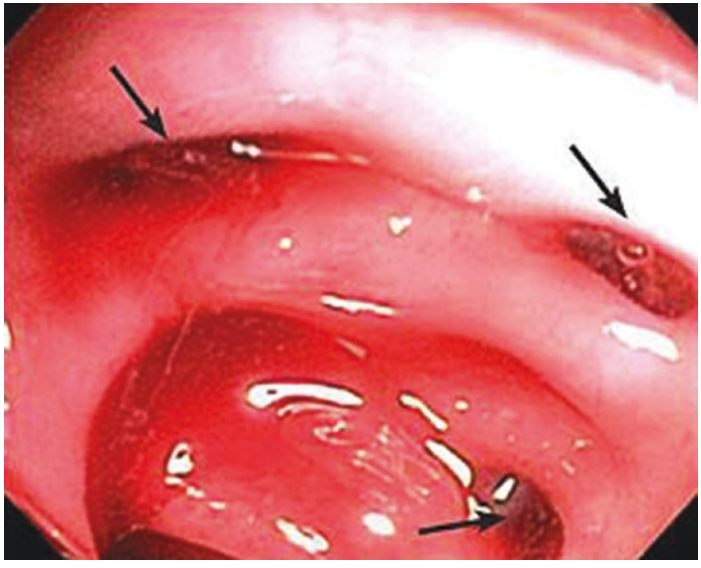

Figure 11.1 Diverticular bleeding

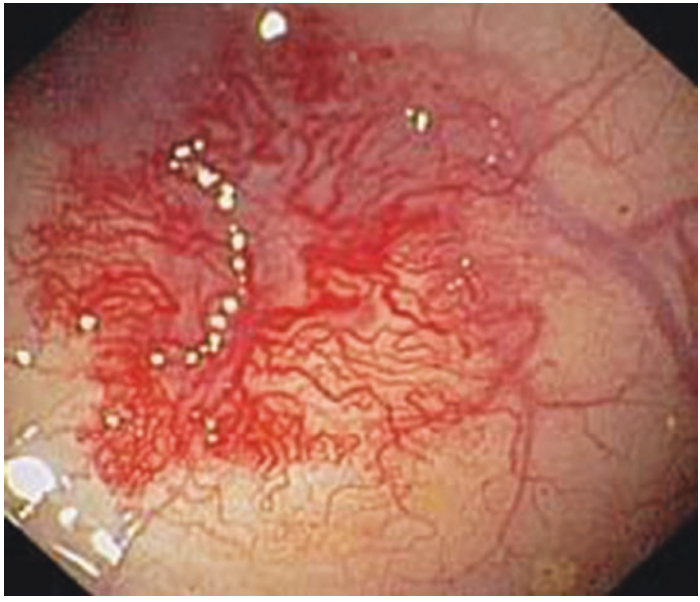

Figure 11.2 Angiodysplasia

Colitis is a manifestation of different etiologies that can be grouped as ischemic, infectious, and inflammatory bowel disease, all of which account for 9–21% of the cases. When ischemic, it often presents with pain and self-limited hematochezia. Colitis is segmental, most often affecting the splenic flexure [7]. When bloody diarrhea is present, infectious colitis or inflammatory bowel disease should be suspected. A routine stool culture will identify Salmonella, Campylobacter, and Shigella, the three most common causes of bacterial diarrhea in the USA [8] (Fig. 11.3).

Post-polypectomy bleeding, occurring less than 2 weeks after polypectomy, and colonic neoplasia account for 11–14% of the cases [9] (Fig. 11.4).

Anorectal causes, including hemorrhoids and fissures, account for 4–10% of the cases. An anoscopy should be included in the initial evaluation of these patients [10].

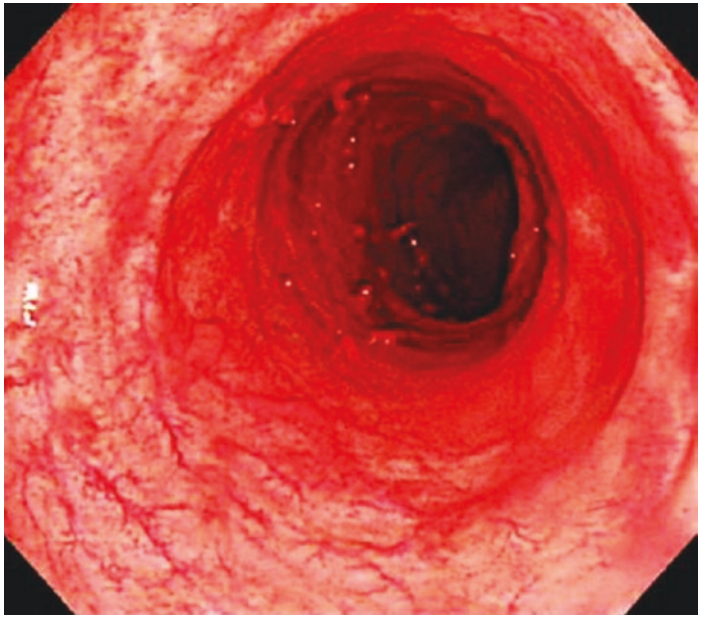

Figure 11.3 Colitis

Up to 11% of the patients presenting with lower GI bleed have an upper GI etiology. Patients with clear indicators of upper GI bleeding should have an upper GI endoscopy before a colonoscopy. Even in patients that do not have blood in the nasogastric tube but present with lower GI bleeding and hypotension, an upper GI endoscopy should be considered [11].

Two to nine percent of cases present with etiology in the small bowel, including Crohn's ileitis, Meckel's diverticula, tumors, and vascular ectasia [12].

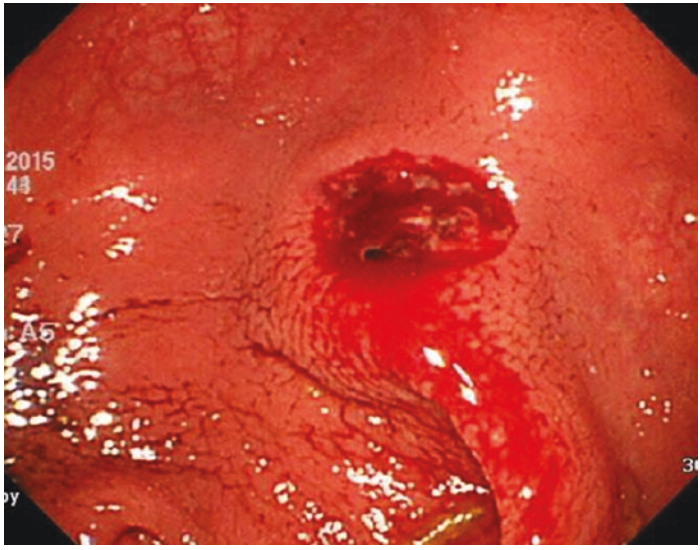

Figure 11.4 Post-polypectomy bleeding

Initial Assessment and Management

Initial evaluation for LGIB includes history and physical, labs, and nasogastric tube lavage. In some instances, upper endoscopy may be needed. Depending on the hemodynamic status, simultaneous fluid resuscitation or blood transfusion needs to be considered. The three initial goals are to assess the severity of the bleed, identify potential sources, and determine if other disorders are present that could affect the management [13].

Hematochezia associated with hemodynamic instability, orthostatic hypotension, or a BUN/Cr ratio > 30:1 should raise the suspicion of an upper GI source, whereas blood clots in the stool point more toward an LGIB [14].

A thorough history can help determine the cause and possible location of the bleeding. The patient may give an account of prior episodes of LGIB, painless hematochezia with diverticular bleeding, change in bowel habits with colon cancer, and abdominal pain with colitis.

History of prior interventions or surgeries could reveal the current pathology. For example, a history of previous abdominal aortic aneurysm repair could be suggestive of an aortoenteric fistula, which is usually associated with the third or fourth portion of the duodenum (upper GI bleed). However, it can be an unusual but potential catastrophic cause of lower GI bleed when associated with the jejunum/ileum.

A review of comorbid conditions such as liver disease, renal failure, and coagulopathies, as well as the use of anticoagulant and antiplatelet agents, may influence the management.

A physical examination should include vitals to assess for hemodynamic instability. An abdominal examination can reveal abdominal growth or masses. A perineal and digital rectal examination can reveal potential anorectal sources of bleeding. A nasogastric tube placed in the emergency room aids in ruling out upper GI causes of bleeding and can be used to perform gastric lavage and to administer mechanical bowel preparation for a potential colonoscopy [15].

When managing patients with GI bleeding of any source, it is important to triage them according to their hemodynamic status. If unstable or with signs of active bleeding, they should be placed in a monitored setting like an Intensive Care Unit. Two large-bore IVs or a central line should be placed. Due to their shortage of O2 transportation carriers in the blood (low Hgb), oxygen via nasal cannula or mask should be initiated. Close monitoring of fluid balance, central venous pressure, hemoglobin, hematocrit, and urine output are essential for patients with suspected shock. They should remain NPO for potential surgical or endoscopic interventions. If unstable, stuporous, or there is a concern for airway protection, endotracheal intubation must be considered [16].

Resuscitative intravenous fluids, such as lactate ringer or normal saline, should be started, a type and cross, coagulation profile and complete blood count collected, and blood transfusions must be individualized, but consider if Hgb drops below 7 mg/dl for most patients. Patients should have frequent blood draws every 4–6 h, depending on the situation, to correct for losses [17].

Anticoagulants and antiplatelet agents must be held when the risk of ongoing bleeding is deemed higher than the risk of thromboembolic events, and transfusion of fresh frozen plasma and platelets given as needed. A gastroenterologist with training in advanced therapeutic endoscopy or a surgical endoscopist should be consulted as well as interventional radiology and general surgery for the presence of massive hematochezia [18, 19].

Coagulopathy should be corrected as much as possible. An INR close to 1.5 is desirable; platelet transfusion should be done to maintain a platelet count of over 50,000/ml. Transfusion of packed red cells, platelets, and plasma in a ratio of 1:1:1 is the preferred approach during resuscitation [20].

When reinitiating anticoagulation is necessary, intravenous heparin is the favored agent to be used at most centers, as this can be rapidly reversed due to its short half-life.

In patients with prior use of anticoagulants, some centers are using thromboelastography to direct the reversal agents. However, this has not been universally accepted. When reversal agents are available, they should be used with caution, keeping in mind potential complications like thrombosis. Good initial management and resuscitation help to control bleeding in approximately 80% of the patients [21].

Diagnostic and Treatment Options

Treatment options in a patient with a lower GI bleed have to be tailored to the patient-specific situation. A colonoscopy should be the initial exam of choice; however, if upper GI bleeding is suspected, an esophagogastroduodenoscopy

should be performed initially. Push enteroscopy is seldom used to identify lower GI bleeding. Radionuclide imaging, computed tomography angiography, and mesenteric angiography all need active bleeding at the time of exam [22].

Esophagogastroduodenoscopy

Patients presenting with a lower GI bleed and hemodynamic compromise with evidence of bleeding from the nasogastric tube, a blood urea nitrogen to creatinine ratio over 30 is suggestive of an upper GI bleed. They should undergo an upper GI endoscopy. It should be kept in mind that approximately 10–15% of the patients presenting with acute lower GI bleed have an upper GI source (Fig. 11.5).

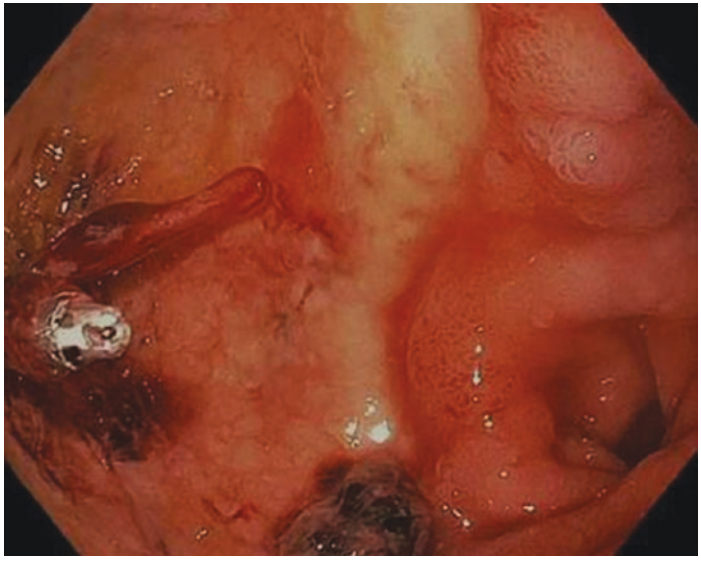

Figure 11.5 Duodenal bleeding

Colonoscopy

Colonoscopy has both diagnostic and therapeutic roles in acute LGIB. The goal of a colonoscopy is to identify the site of bleeding and achieve hemostasis if indicated. The diagnostic yield of colonoscopy in this patient population ranges from 48% to 90% [23].

Once stable, the patient can undergo a bowel preparation with 4–6 L of polyethylene glycol solution for 3–4 h until the rectal effluent is clear of blood and stool. A nasogastric tube could be used to provide bowel prep in patients that are intolerant to oral intake [24].

A poorly-prepped colon can make colonoscopy and the localization of a bleeding source difficult. And patients with diverticular disease may also increase the risk of perforation. Colonoscopy performed within 24 h of presentation after adequate colon preparation is shown to improve diagnostic and therapeutic yield [25].

Colonoscopic guided control of bleeding can be done with the help of diluted epinephrine (1–2 mL aliquots, dilution 1:20,000), contact thermal therapy like a bipolar/monopolar/heat probe (using 10–15 W with moderate appositional pressure applied in 1-s intervals until vessel flattening was achieved), noncontact thermal treatment like argon plasma coagulation, use of through the scope (TTS) or over the scope clips, topical sprays, and powders. The choice of the agent can be used as a monotherapy or in combination to control bleeding. After endoscopic treatment, an Indian ink tattoo or clip (if not already used for hemostasis) should be placed adjacent to the culprit lesion to assist in re-localization should rebleed occur [26] (Fig. 11.6).

Endoscopic therapy should be provided in patients with active bleed, visible blood vessels, or an adherent clot. Clips are considered safer than contacting thermal treatment for the management of diverticular bleed. Angiodysplasia bleed-

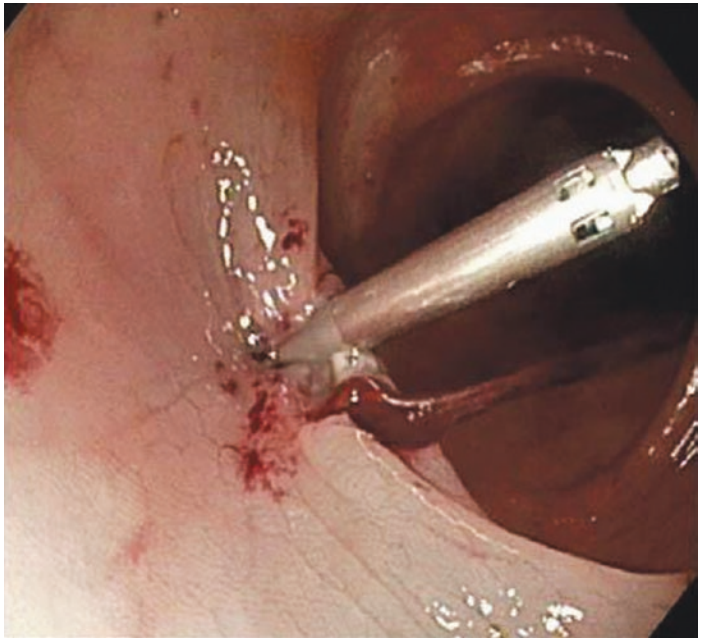

Figure 11.6 Post-polypectomy bleeding treated with TTS clip

ing can be controlled using argon plasma coagulation. Post-polypectomy bleed can be managed by a mechanical clip or contact thermal therapy. Epinephrine injection diluted with saline can control active bleed and improve visualization so that the endoscopist can provide adjunct with other modes like clipping [27–29].

Computed Tomography Angiography

Computed tomography angiography (CTA) has shown a sensitivity of 85.2% and a specificity of 92.21% to diagnose acute gastrointestinal bleed. CT angiography is an appealing diagnostic modality because it is fast, broadly available, and minimally invasive. Furthermore, it provides anatomic detail

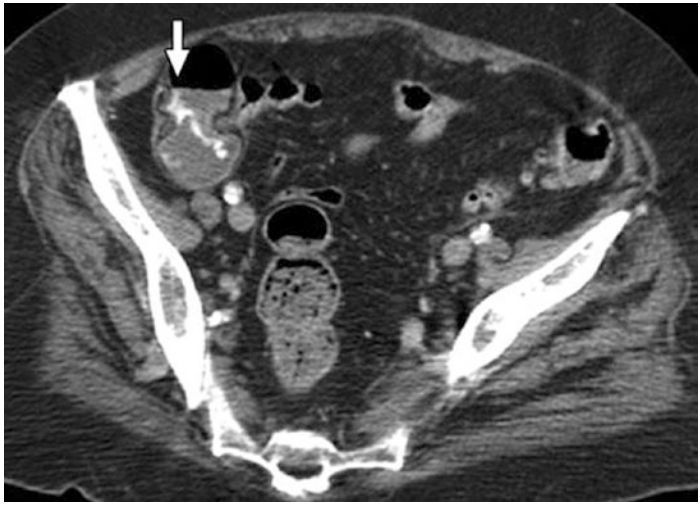

FIGURE 11.7 CTA of the abdomen showing active cecal intraluminal extravasation (arrow)

that may be useful for subsequent interventions such as angiography [30].

Bleeding at a rate of 0.3–0.5 mL/min can be detected with CT angiography [31]. The scans are performed without oral contrast, and a positive study displays intraluminal extravasation. Computed tomography angiography can sometimes fail to show the source when bleeding is intermittent in nature as it is, for example, with diverticular bleed (Fig. 11.7).

Therapeutic Mesenteric Angiography

Once a suspicious area of blush or extravasation has been identified, therapeutic mesenteric angiography can be undertaken. Most authors state that the bleeding rate should be at least 0.5 mL/min in order to detect extravasation (Fig. 11.8).

Selective embolization or vasopressin injection into the feeding vessels can be utilized with a targeted catheter. There

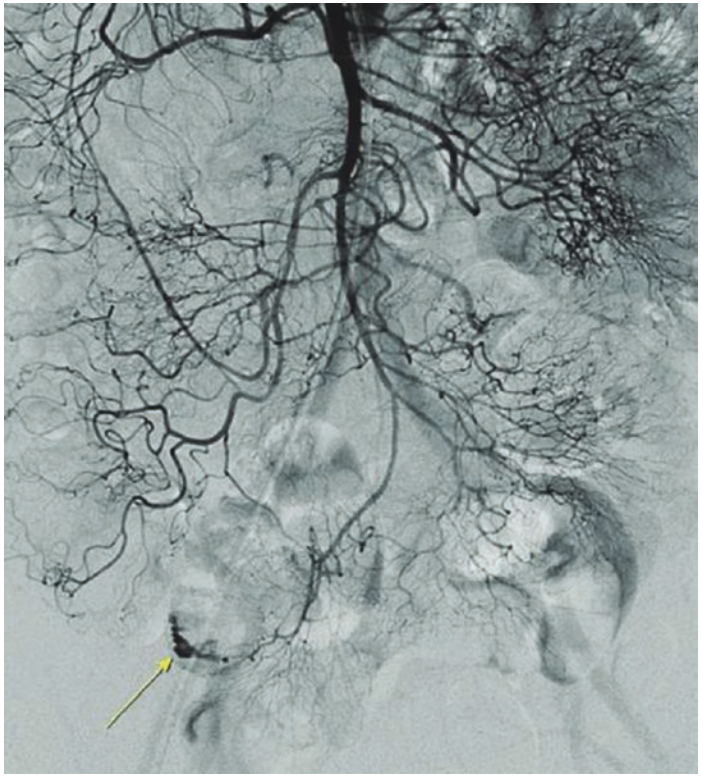

Figure 11.8 Superior mesenteric angiogram showing extravasation in a branch of the distal ileal artery (arrow)

have been reported incidences of rebleeding in up to 50% of the patient and bowel ischemia in about 20% [32, 33]. This procedure cannot be utilized in patients with dye allergy or chronic kidney disease and is best suited for patients with massive hematochezia who cannot be stabilized for a colonoscopy.

Radionuclide Imaging

This involves labeling erythrocytes with technetium 99 and performing serial scintigraphy, also known as tagged red blood scans. Radionuclide imaging is a diagnostic modality that can help confine the general bleeding area only to use further therapeutic measures, accordingly, later on. The bleeding rate must be of at least 0.1 mL/min, and overall there is a 65–80% accuracy in localizing the bleeding site (Fig. 11.9).

In approximately 25% of the scans, the site of bleeding can be inaccurate due to the transit of extravasated blood in the gut [34]. However, one benefit of tagged red blood cell scintigraphy is the ability to perform repeated scans after the initial injection of tagged cells. This makes this study most suitable for the evaluation of intermittent, obscure-overt GI bleeding [35].

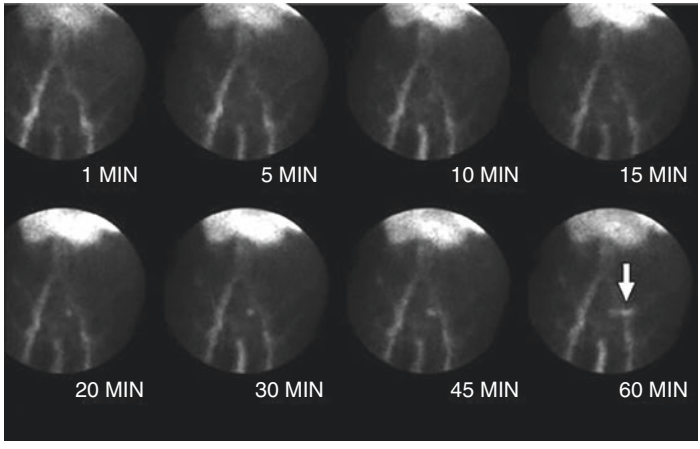

FIGURE 11.9 99mTc-labeled RBC scan show focus of increased radiotracer activity in left lower quadrant (arrow)

Surgery

Surgery in patients with lower gastrointestinal bleeding should be reserved as a last resort when other options mentioned above have failed. It is helpful to have localization of the bleeding source before surgery. Emergency surgery carries a mortality of up to 27%. Lower GI bleeding is considered massive when a patient has required more than four units of blood transfusion in a 24-h period and continues to show evidence of hemorrhage [35–37].

Commonly, these patients are approached via a midline laparotomy. The GI tract filled with blood helps localize the area of bleeding. If the small bowel is found to be full of blood, an intraoperative enteroscopy may be necessary. Intraoperative colonoscopy can also be performed with intraoperative lavage; however, this may be difficult and time-consuming in most situations with an unstable patient (Fig. 11.10).

If preoperative localization of the culprit of lower GI bleeding has been obtained, segmental resection is ideal. However, in cases where preoperative localization has not been obtained, and there is a reasonable suspicion that the colon is the source of bleeding, a subtotal colectomy must be performed. Since this is typically performed in an emergent fashion, an anastomosis is usually not recommended. In addition, an ostomy permits the surgeon to perform an ileoscopy in situations of rebleeding.

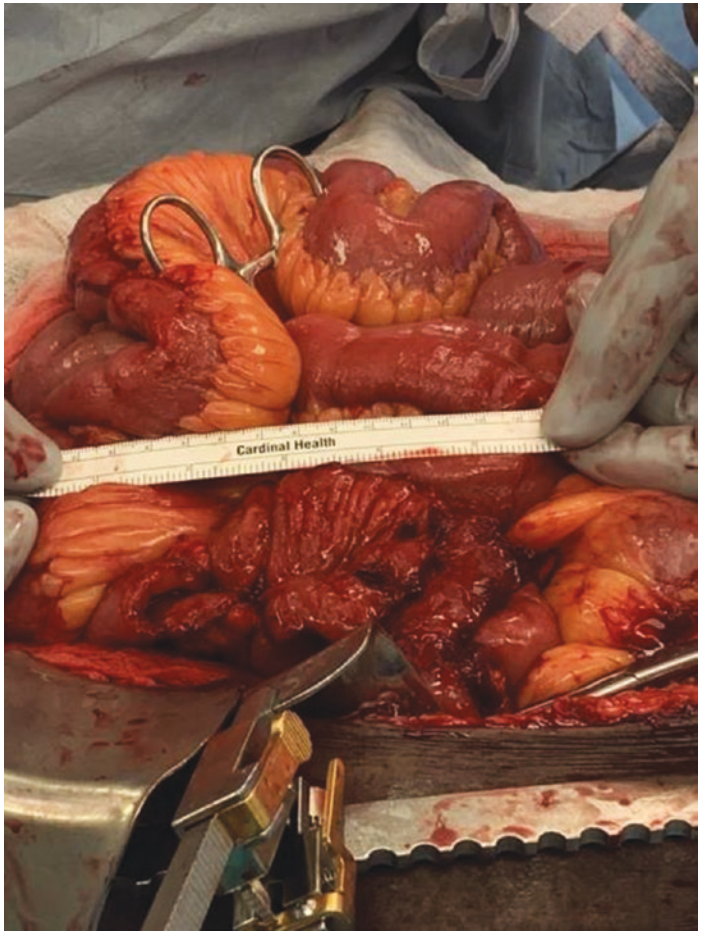

Figure 11.10 Exploratory laparotomy for a bleeding ileal ulcer

Conclusion

Lower gastrointestinal bleeding beyond the ligament of Treitz emanates from a variety of sources and etiologies. Initial resuscitation followed by endoscopic and/or radiographic imaging set the stage for management which often includes medical support, endoscopic treatment, and in rare occasions surgical resection.

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Chapter 12
Endoscopic Stenting for Malignant Colorectal Obstruction

Arielle Kanters, Michael Valente, and Scott R. Steele

Background

Management of obstructing colorectal masses carries a high risk of perioperative morbidity and mortality [1]. As such, malignant large bowel obstructions (LBO) are widely recognized as surgical emergencies. With rates of obstruction at initial presentation in colorectal cancer patients ranging from 8% to 30% [2–5] it is imperative that we consider all management options when determining the next steps in care. While historically, these cases were emergently taken to the operating room for resection and/or diversion, physicians have long sought alternative management strategies that allow for clinical and oncologic optimization prior to pursuing definitive surgery and reduce the risk of permanent (or even temporary) stomas.

The use of stents for palliation of malignant large bowel obstruction was first introduced in 1991, and 3 years later, Tejero et al. reported the use of stents as a bridge to surgery

A. Kanters (✉) · M. Valente · S. R. Steele
Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA
e-mail: kantera@ccf.org; valentem2@ccf.org; steeles3@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_12

in the setting of an LBO [6]. Historically, these stents served as a palliative management option for patients with left-sided colonic or rectal obstructions when trying to avoid a diverting ostomy. However, with continued advancements in this technology, stents can now also be used to relieve right-sided obstructions either temporarily or as a bridge to surgery [7, 8].

Technical success in the context of stent placement is defined as the ability to safely deploy and position the stent across the stricture without any immediate complications. Clinical success is defined as colonic decompression and resolution of obstructive symptoms. Comparing the randomized controlled trials to date on endoscopically placed stents as a bridge to surgery, a total of 201 patients were randomized to stent placement versus emergency surgery, and the overall technical success rate ranged from 46.7% to 100% (average across all studies: 81.1%), and the overall clinical success rate ranged from 40% to 100% (average across all studies: 76.1%) [9]. This is in comparison with stents placed for palliation, which have both a technical and clinical success rate of 93% [10, 11]. In this chapter, we will discuss the indications and outcomes associated with endoscopic stent placement for malignant obstruction in the colon and rectum.

Indication for Stenting (Table 12.1)

Bridge to Surgery

Large bowel obstructions present a problematic situation for the patient and surgeon alike. Often presenting in the setting of locally advanced primary or metastatic disease, patients are typically dehydrated, malnourished, and the bowel is often massively dilated, filled with stool, and difficult to handle. Given the increased risk of emergency surgery in the setting of large bowel obstruction, a non-surgical intervention allowing for decompression and an eventual semi-elective operation for a resectable malignancy carries significant ben-

Table 12.1 Stenting for malignant bowel obstruction overview

Indication	*Advantages*	*Disadvantages*
Bridge to surgery	– Opportunity for staging and decompression – Shorter hospital course – Lower stoma rate – Higher rate of primary anastomosis	– Concern for worse oncologic outcomes
Palliation	– Shorter hospital stay – Lower stoma rate – Earlier return to chemotherapy – Lower rate of short-term complications	– Risk of perforation (particularly with bevacizumab treatment)
Contraindications	*Absolute*	*Relative*
	1. Perforation 2. Ischemia 3. Necrosis	1. Long stricture 2. Low-lying tumor (<5 cm from anal verge) 3. Carcinomatosis (extrinsic tumor compression)
Complications	*Management*	
Major		
Perforation	Emergency surgery	
Migration	Replacement of endoscopic stent	
Re-obstruction	Replacement of endoscopic stent or additional stent placement	
Minor		
Pain, bleeding	Symptom control	

efit for the patient [12]. Colonic stenting offers one such option. Previous work has shown that stents serve to reduce the need for emergent operations, allow time for appropriate staging, minimize the risk of bacterial translocation, and provide a reduction in stool burden prior to intervention. This effectively provides a stopgap for oncologic optimization and may provide a potentially resectable patient with the opportunity to make it to curative surgery [13]. In some instances, it can also temporize an obstruction allowing for delivery of neoadjuvant therapy.

Early work on this subject demonstrated that stenting is associated with a shorter hospital course and ICU stay, as well as a lower rate of ostomy formation [14, 15]. More recent randomized controlled trials, however, have not shown a clear benefit to stenting over emergency surgery aside from lower rates of stoma creation during initial intervention [16–20], and overall lower rates of permanent ostomy (8.7% vs 20.0%, $p = 0.002$) [21].

Recent studies assessing the long-term outcomes comparing stent placement for bridging with emergency surgery suggest no difference in overall survival, time to progression, or disease-free survival [22]. That said, some argue that the available RCTs are underpowered to assess differences in survival. The most recent meta-analysis of pooled data from both RCTs and high-quality retrospective analyses notes that when a stent is placed as a bridge to curative surgery, there is a lower 30-day mortality rate (RR 0.65, $p = 0.01$), lower complication rate (RR 0.65, $p < 0.001$), and higher lymph node harvest at the time of surgery (mean difference 2.51, $p = 0.005$) [23]. Length of hospital stay was also shorter for patients stented for both bridging and palliation (mean difference = 7.24, $p < 0.001$). Of note, in this particular study, there was no difference in terms of 3-year and 5-year disease-free and overall survival [23, 24]. Taken together, it appears that the risks of surgery can be mitigated while still preserving some of the oncological benefits.

Palliative

In contrast to stenting as a bridge to surgery, palliative stent placement for patients presenting with a large bowel obstruction in the setting of metastatic disease has demonstrated significant improvement in outcomes compared to those undergoing emergent decompressive surgery [25, 26]. This is particularly true when the patient has factors making them a poor operative candidate, including severe malnutrition or carcinomatosis.

Studies have demonstrated shorter hospital stays (9.5 vs 18.8 days, $p < 0.001$) and lower stoma creation rates (12.7% vs 54.0%, $p < 0.001$) with endoscopic stent placement [10, 27]. Furthermore, relieving the acute obstruction nonoperatively allows for earlier return to chemotherapy, which is the mainstay treatment for patients in these circumstances [10]. Finally, palliative stenting has been shown to be more cost-effective compared to surgical intervention [28] and can offer a meaningful improvement in quality of life [29].

When comparing relief of obstruction between surgical and stenting intervention, previous meta-analyses have demonstrated higher success with surgery compared to stent placement (99.8% versus 93.1%, $p < 0.001$). However, there is a higher rate of 30-day mortality within the surgery group as well (10.5% versus 4.2, $p = 0.01$) [10].

Overall, there is a lower rate of short-term complications associated with stent placement compared to palliative surgery, which makes it an ideal option for patients with unresectable disease. That said, there is concern about long-term patency given the risk of continued tumor growth occluding the stent, and patients must be counseled on the fact that stent occlusion requires additional interventions, both endoscopic and surgical. Some suggest that a multidisciplinary discussion should be held prior to palliative stenting in order to determine goals of care and the anticipated chemotherapy course.

Contraindications to Stenting

Absolute contraindications to stent placement include acute perforation, ischemia, or necrosis [30]. Relative contraindications include the presence of a long stricture, low-lying lesions, and diffuse carcinomatosis—especially given the high failure rate. Additionally, stent placement is not recommended in patients being treated with bevacizumab given the significantly increased risk of perforation [31]. Finally, obstructions that exist at tortuous portions of the colon, such as the flexures or an angulated sigmoid colon, can be technically challenging and have a relatively high failure rate [32]. As for patient tolerance of a stent, low stent placement (within 5 cm of the anal verge) puts the patient at risk of pain, tenesmus, and incontinence. Yet, improvements in stent offerings, ease of deployment, and removability have all contributed to better tolerance with lower morbidity.

Types of Stents

The majority of stents used for the management of malignant large bowel obstructions are radiopaque, self-expandable tubes comprised of metallic mesh. Once placed, they take approximately 2–3 days to fully expand and are anchored by forces opposing the colonic wall.

The metal used for the stents includes stainless steel, elgiloy (a cobalt alloy), and nitinol (an alloy of nickel and titanium), and each has a different flexibility and possible interaction with MRI. Stainless steel tends to be the stiffest, while nitinol is the most flexible. Stainless steel also causes MRI interference, while elgiloy and nitinol do not. Nitinol is

the most commonly used stent material worldwide, given its flexibility, ability to hold its original shape, and MRI compatibility [33].

When selecting a stent, it's important to consider diameter and length. There is a decreased risk of migration with a larger body diameter (≥24 mm). Additionally, the length of the lesion must be measured on imaging, and the stent length should allow for at least 2 cm of landing space on either size of the obstruction [34].

Covered Versus Uncovered Stents

Stents are available as uncovered, partially covered, and completely covered. Covered stents have a lower rate of tumor ingrowth, but a higher rate of migration. Uncovered stents are able to anchor more securely to the lumen wall and therefore have a lower rate of migration but also a higher rate of tumor ingrowth. The partially covered stent has been proposed as an option that maintains both the benefits of a covered and an uncovered stent. It has exposed architecture at either end of the stent, which improves anchoring while the covered mid-portion limits tumor ingrowth. Even with this potential benefit, comparison studies continue to demonstrate improved outcomes with the use of uncovered stents [35, 36]. In a recent meta-analysis by Mashar et al., pooled data demonstrated superior outcomes with uncovered stents, including lower risks of complications, stent migration, and lower need for stent reinsertion (Fig. 12.1) [36].

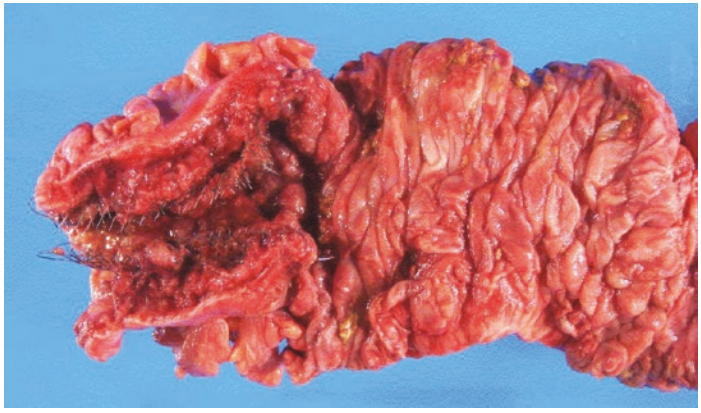

Figure 12.1 Stent in situ at the time of cancer resection

Placement of the Stent

Most stents are placed endoscopically with fluoroscopic guidance. Endoscopic placement has a higher rate of success compared to fluoroscopic alone, but the highest success rates are achieved with the use of combined image guidance [37–40]. This is reinforced by the European Society of Gastrointestinal Endoscopy (ESGE) Guidelines, which have been reviewed and endorsed by the American Society of Gastrointestinal Endoscopy (ASGE) [25]. Early work investigating the learning curve associated with stent placement suggested that physicians required a minimum of 20 stent placements in order to improve technical and clinical success. However, to date, no formal recommendations exist to support a minimum case requirement. Rather, the ESGE states that stents should be placed or supervised by an operator who has expertise in both endoscopic and fluoroscopic stent placement and performs the procedure regularly [25].

Colorectal stent placement is warranted in patients with symptoms of obstruction and imaging consistent with a malignant large bowel obstruction. Stents are not recommended for prophylactic placement, even if there is a concern for impending obstruction. Prior to stent placement, patients should undergo enema to improve endoscopic visualization [25].

Following positioning of the patient and initiation of sedation, the endoscope is advanced to the point of obstruction. A catheter containing a hydrophilic tip guidewire is introduced into the endoscope, and the catheter tip is placed at the site of the obstructing lesion. Importantly, the catheter should be introduced in parallel to the direction of the bowel to allow for unobstructed advancement of the guidewire. The guidewire is then used to gently cannulate the lumen. If resistance is encountered, the guidewire is retracted and repositioned for another attempt. Once the wire has successfully been passed, its location is confirmed using fluoroscopy. Next, the catheter is advanced over the guidewire using the Seldinger technique, and water-soluble contrast is injected to confirm the length of obstruction and identify any possible perforation during cannulation. Once this is confirmed, the catheter is withdrawn, leaving the guidewire in place, and the stent is passed over the wire and through the obstruction. Frequent confirmation of the location of the guidewire using fluoroscopy is required (Fig. 12.2). Finally, the stent is deployed under both endoscopic and fluoroscopic visualization. Stent placement and deployment are confirmed with an injection of water-soluble contrast. Upon completion of the procedure, an abdominal X-ray is obtained to document the location of the stent and to rule out perforation [34, 40].

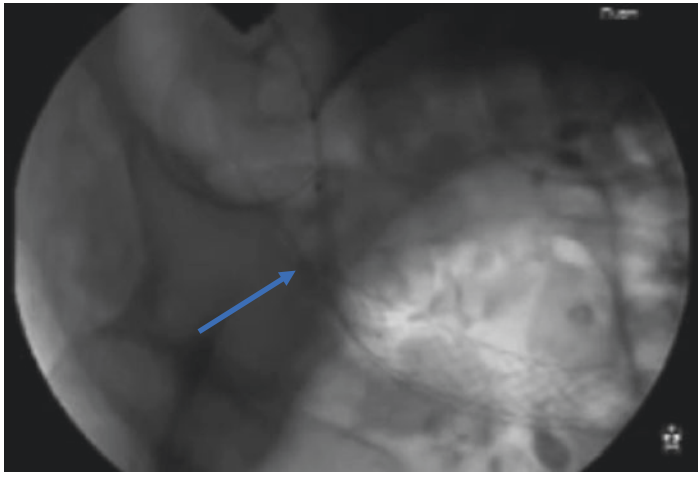

Figure 12.2 Fluoroscopy demonstrating stent deployment. Arrow indicates narrowing of the stent at the site of the tumor

Post-Stenting Follow-up

Following stent placement, the patient is generally monitored overnight, and a repeat abdominal X-ray is obtained within 24 h to confirm the position of the stent. The patient is monitored for signs of perforation, including worsening abdominal pain and clinical instability. Oral intake is resumed once obstructive symptoms resolve, and patients are usually maintained on a bowel regimen in conjunction with a low residue diet.

The ESGE recommends early surgical intervention within 2 weeks of stent placement in potentially resectable patients where stenting is being used as a bridge to surgery. The risk of stent-related complications is minimized by a short interval between stent and definitive surgery though it is also important to let sufficient time pass to optimize surgical status (e.g., staging, decompression, and nutritional optimization) [25].

Complications after Stent Placement

The most common complications following colonic stenting include perforation (Fig. 12.3), stent migration, re-obstruction, pain, and bleeding. Complications are divided into early (≤30 days) and late (>30 days) complications. Rates of colonic perforation are reported to range from 4% to 13% [16, 39]. Acute perforation often requires emergency surgery and is associated with higher rates of recurrence [41]. Migration of the stent can occur both as an early or late-stage complication and generally requires replacement of the stent. The ESGE recommends early surgery rather than repeat colonic stenting in the setting of an obstruction or migration, both of which have reported rates of occurrence between 3% and 10% [25, 34]. The use of covered stents, small stent diameter (<24 cm), and tumor shrinkage are associated with stent migration [34, 40]. Tumor ingrowth is considered a late complication and is more prevalent in the setting of palliative stenting. As for post-stent bleeding, it is usually minor and can be managed conservatively.

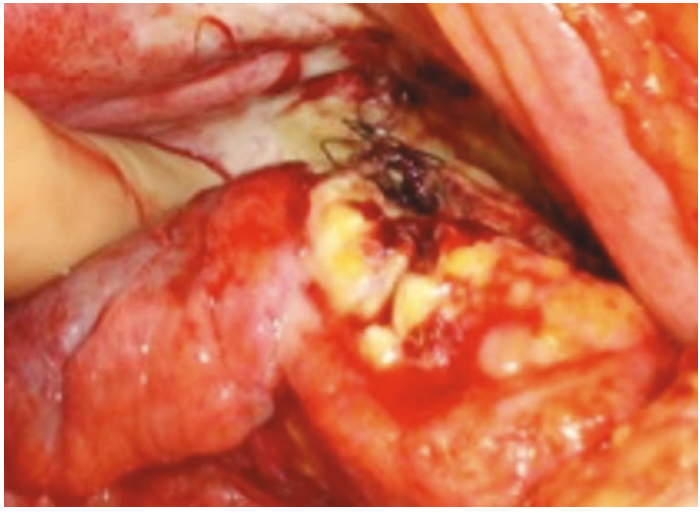

Figure 12.3 Stent erosion and perforation

When counseling patients, it's important to acknowledge that there is a hypothetical risk of hematologic spread through manipulation of the mass during endoscopic procedures as well as a risk of peritoneal seeding in the event of a perforation. Retrospective analyses have demonstrated a higher risk of local recurrence in patients who underwent stent placement compared to emergency surgery (32% vs. 8%, $p = 0.038$) [42]. This has been supported by long-term outcomes in the Dutch Stent-In 2 Trial, which demonstrated significantly lower rates of disease-free survival in patients who suffered a perforation in the setting of stenting as a bridge to surgery [41]. There is also evidence of worse tumor biology in patients who have previously undergone stenting, including increased rates of perineural invasion [43].

As mentioned above, there is also a significantly higher rate of perforation in the setting of higher risk chemotherapy agents, particularly bevacizumab, and warrants discussion with both the patient and oncologist before pursuing stent placement if there are plans for use. Bevacizumab is associated with an increase in stent-related perforation at a rate of 12.5%, which is significantly higher than chemotherapy without bevacizumab (7.0%) or without chemotherapy (9.0%) [31].

The risks of spread and worse oncologic outcomes have led the European Society of Gastrointestinal Endoscopy and the Governing Board of the American Society of Gastrointestinal Endoscopy to recommend stent placement as a bridge to surgery to be conducted primarily within a shared decision-making process. Specifically, they encourage a discussion with patients regarding the increased risk of stent-related perforation and higher recurrence rates of the tumor, while still providing similar overall survival and mortality rates when compared to emergency surgery. The benefits of stent placement include lower overall complication rates and rates of permanent ostomy, along with increased rates of successful laparoscopic surgery [25]. It's also important to prepare patients for the potential failure of the stent and the need for surgical intervention. An individual's priorities will influence their preferences and help guide the next steps in decision making.

Conclusion

Endoscopic stent placement for the management of malignant large bowel obstructions is an effective option in colorectal cancer patients as both a bridge to definitive resection and as palliative therapy. Palliative stenting, in particular, offers lower morbidity and mortality rates when compared to emergency surgery and may be considered as a first-line treatment in patients without contraindication to stent placement. Colonic stenting as a bridge to surgery also offers some advantages, for example opportunity for staging and lower rates of stoma formation, but this must be weighed against the potential for worse oncologic outcomes. Importantly, stent placement provides an alternative treatment modality for high-risk patients who would otherwise require emergency surgical intervention and should be considered when confronted with a malignant large bowel obstruction.

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Chapter 13
Interventional Procedures for Inflammatory Bowel Disease

Sara El Ouali and Florian Rieder

Abbreviations

CRC	Colorectal cancer
CD	Crohn's disease
DCE	Dye spray chromoendoscopy
EBD	Endoscopic balloon dilation
HDWLE	High-definition white light endoscopy
IBD	Inflammatory bowel disease
PSC	Primary sclerosing cholangitis
RCT	Randomized controlled trial
SDWLE	Standard-definition white light endoscopy
UC	Ulcerative colitis
VCE	Virtual chromoendoscopy

S. El Ouali (✉)
Digestive Disease Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE
e-mail: Elouals2@clevelandclinicabudhabi.ae

F. Rieder
Department of Gastroenterology, Hepatology and Nutrition, Digestive Diseases and Surgery Institute, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: riederf@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_13

Introduction

Inflammatory bowel diseases (IBD), comprised of ulcerative colitis (UC) and Crohn's disease (CD), are chronic immune-mediated inflammatory diseases of the gastrointestinal tract leading to significant morbidity in affected patients. More than two million North Americans are estimated to have IBD, with worldwide incidence rates increasing significantly over the last few years [1]. Endoscopy plays a crucial role in the diagnosis and management of inflammatory bowel diseases [2]. In addition to its well-established role in the diagnosis of IBD, endoscopy has been shown to be fundamental during follow-up through monitoring of response to therapy and assessment of mucosal healing, which has been associated with improved long-term outcomes [3]. However, despite advances in medical and surgical treatments, many patients with IBD go on to develop disease complications such as strictures, penetrating disease or malignancy, highlighting the need for additional therapeutic options. In recent years, the role of endoscopy has therefore expanded to add a variety of non-invasive techniques to our therapeutic armamentarium in IBD. In the following chapter we will discuss the different types of endoscopic techniques used in the treatment of IBD, with a focus on the management of stricturing complications and dysplasia.

Endoscopic Management of Strictures

About 20% of patients with Crohn's disease have a stricture at the time of diagnosis, and up to half of patients may develop strictures over the course of their disease [4]. Strictures most commonly occur in the small bowel, but can be found anywhere throughout the gastrointestinal tract, including the colon [5]. In patients with UC, colonic strictures are usually managed surgically given the risk of underlying malignancy. In Crohn's disease, strictures in the colon are associated with an increased risk of malignancy and

surgery is therefore considered earlier in the management algorithm, particularly in the setting of medically refractory disease [6, 7].

Several modalities are available for the management of small bowel CD strictures, including medical therapy, endoscopic techniques, and surgery. A multidisciplinary team approach to discussing these patients is therefore important in order to help decision-making and optimize outcomes [8].

Endoscopic Balloon Dilation

Although multiple endoscopic modalities have been described in the treatment of strictures, endoscopic balloon dilation (EBD) remains the cornerstone of endoscopic stricture management [5]. In a large meta-analysis including individual patient level data, EBD was found to have a clinical efficacy rate of 80.8% with an immediate technical success rate of up to 89.1% [9]. EBD can be used in both naïve and anastomotic strictures and is an option for straight and short (<5 cm) strictures that can be reached endoscopically. There should not be an associated abscess, internal fistula, or suspected malignancy [5].

Stricture biopsies are recommended prior to dilation in order to rule out cancer, although this is rare in the small bowel [10]. EBD is performed with the use of a through-the-scope balloon and can be done in the setting of both standard endoscopy and balloon-assisted enteroscopy [11]. Complications associated with EBD can occur in up to 4% of patients and include infection, perforation, bleeding, or/and hospitalization [9].

Stricturotomy

Stricturotomy using a needle-knife has been described in the management of anal and small bowel strictures [2]. In a cohort of 85 patients, needle-knife stricturotomy led to pas-

sage of the scope in all patients immediately after treatment [12]. However, 60.6% of patients required additional endoscopic stricture therapy (dilation or stricturotomy) during follow-up. Although stricturotomy appears promising, additional efficacy and safety data are needed to better understand long-term outcomes.

Stent Placement

Stents have been used in the management of CD-associated strictures [2, 13]. However, stent placement can be complicated by perforation or stent migration and is consequently not recommended in the routine treatment of strictures, pending further data on its efficacy and safety in this setting. Emerging data on removable temporary or biodegradable stents are promising [2].

Intralesional Injection

Injection of corticosteroids or infliximab into a stricture has been described but has shown controversial data. In a recent systematic review, intralesional injection was not found to be beneficial and is therefore not recommended [14].

Dysplasia Diagnosis and Management

Endoscopy plays a crucial role in the evaluation and management of IBD-associated dysplasia.

The incidence of colorectal neoplasia in patients with IBD is estimated to be 60% higher than in the general population and increases over the disease course [15]. The risk of colorectal cancer (CRC) is estimated at 2%, 8%, and 18% at 10, 20, and 30 years of disease, respectively [16].

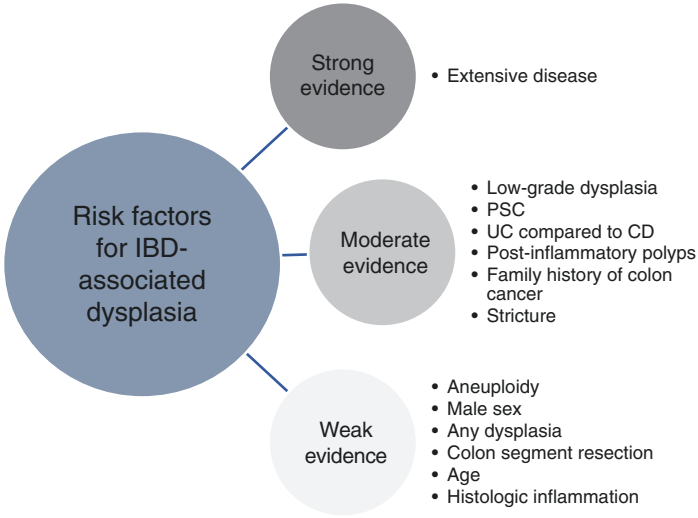

Figure 13.1 Risk factors for IBD-associated neoplasia [17]; *CD* Crohn's disease, *PSC* primary sclerosing cholangitis, *UC* ulcerative colitis

In addition to disease duration, several other factors are associated with an increased risk of IBD-associated neoplasia [17] and are listed in Fig. 13.1.

Society guidelines recommend initiating colorectal neoplasia surveillance 8 years after diagnosis in patients with UC with extent greater than the rectum and in CD patients with at least 30% of colon involvement [18, 19]. Surveillance in patients with concurrent primary sclerosing cholangitis (PSC) should be performed at the time of PSC diagnosis and annually thereafter [18].

Diagnosing IBD-Associated Dysplasia

Different modalities and techniques are available for CRC surveillance and are summarized in Table 13.1. In order to optimize dysplasia detection, a good bowel preparation and minimal mucosal inflammation on endoscopy are important, regardless of the modality used for surveillance [20].

Table 13.1 Endoscopic techniques used for evaluation and management of IBD-associated dysplasia

Diagnostic techniques
White-light endoscopy - supplemented by segmental random biopsies if standard-definition endoscopy is used
Virtual chromoendoscopy (eg: NBI, FICE, I-scan)
Dye-spray chromoendoscopy
Biopsies - Targeted biopsies - Random biopsies (4 quadrant every 10cm)
Therapeutic techniques
EMR
ESD
Hybrid ESD

NBI narrow band imaging, *FICE* flexible spectral imaging color enhancement

Dye spray chromoendoscopy (DCE) involves the application of dye (generally methylene blue or indigo carmine) during colonoscopy to enhance visualization of the mucosa and improve dysplasia detection [21]. On the other hand, virtual chromoendoscopy (VCE) uses image-enhancement technology to improve mucosal visualization Fig. 13.2. White light endoscopy is used as well, supplemented with 4-quadrant biopsies every 10 cm in order to sample for possible invisible dysplasia particularly in the setting of standard-definition endoscopy [22].

Although both high-definition white light endoscopy (HDWLE) and chromoendoscopy have been shown to be superior to standard-definition white light endoscopy (SDWLE) in the diagnosis of dysplasia [20], it is still unclear how HDWLE compares to chromoendoscopy. Although the SCENIC consensus statements recommended dye spray

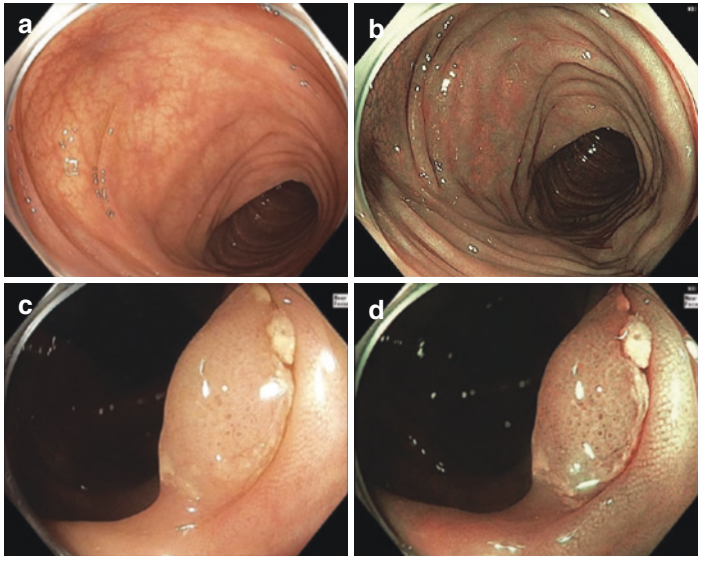

Figure 13.2 Virtual chromoendoscopy in a patient with Crohn's disease undergoing colon cancer surveillance. (**a**), colon mucosa visualized using high-definition white light; (**b**), colon mucosa visualized using narrow-band imaging; (**c**), polyp visualized using high-definition white light; (**d**), polyp visualized using narrow-band imaging. Courtesy Dr. Ammar Kheir

chromoendoscopy over white light endoscopy (particularly if only standard-definition endoscopy is available) in 2015 [22], several practice-changing studies have been published since. Meta-analyses of prior observational studies indeed show a superiority of chromoendoscopy in the detection of dysplasia over SDWLE and HDWLE, but this does not hold true for HDWLE in randomized controlled trials (RCTs) [23]. In two recent RCTs, VCE [24] and HDWLE [24, 25] were not inferior to dye spray chromoendoscopy.

Current ACG guidelines recommend dye spray chromoendoscopy, particularly if standard-definition endoscopy is used. In the setting of high-definition endoscopy, either DCE or VCE with narrow-band imaging (NBI) can be used.

Our approach to dysplasia screening is however likely to evolve over the next few years as we gather additional data on the current techniques and as more modalities possibly become available, such as artificial intelligence-based detection methods [26].

Endoscopic Management of IBD-Associated Dysplasia

The first step in managing IBD-associated dysplasia is determining whether it is resectable endoscopically. According to the SCENIC consensus statements, an endoscopically resectable lesion should have the following features: (1) distinct margins (2) complete removal on visual inspection after resection (3) complete removal on histology (4) dysplasia-free biopsies from the adjacent mucosa [22]. There should not be concurrent multifocal or high-grade dysplasia. Resection of these lesions should be undertaken by endoscopists skilled to perform such techniques.

Several techniques can be used and are summarized in Table 13.1. Endoscopic mucosal resection (EMR) is the most common method and generally involves the use of lifting the lesion. However, for lesions larger than 2 cm, piecemeal resection is required. Lifting can also be challenging in the setting of submucosal fibrosis. Endoscopic submucosal dissection can allow the lesion to be resected *en bloc* and circumvents the need for lifting. However, ESD is not easily accessible and many centers may lack the adequate expertise [21]. Hybrid ESD has also been described, in which a lesion is resected using a snare after limited submucosal dissection [21].

Tattooing the lesion after resection is recommended in addition to sampling the mucosa adjacent to the resected lesion for dysplasia [22].

However, it is important to emphasize that patients with IBD-associated dysplasia should ideally be discussed in a multidisciplinary team approach to discuss endoscopic or surgical options in order to determine the optimal management [27].

Other Therapeutic Endoscopic Procedures

In addition to its important role in strictures and dysplasia management, endoscopy has also been used in the treatment of fistulas, post-operative complications or in the management of complex pouch disorders.

Management of IBD Post-Operative Complications

Endoscopic treatment of various post-operative acute and chronic complications such as anastomotic strictures, leaks, or sinuses has been described [2]. Several techniques have been reported in the endoscopic management of anastomotic leaks, including clips, suturing, or stent placement [2]. In addition, several endoscopic modalities have been used in the management of J-pouch complications, such as closure of "tip of the J" leaks using over-the-scope clips in a case series of 12 patients [28]. In addition, endoscopic management of chronic presacral sinuses using needle-knife sinusotomy has been described [29, 30].

Fistulas

Endoscopy has been used in the treatment of fistulas. In a case series of 29 patients with fistulas in a variety of locations (including perianal, pouch-pouch, and entero-enteric fistulas), successful endoscopic fistulotomy using a needle-knife was reported in 89.6% of patients [31]. Endoscopic closure of fistulas has also been described using over-the-scope clips [32]. Although promising, further safety and long-term efficacy data are needed before these techniques can be used in routine clinical practice.

Conclusion

In recent years, the role of endoscopy has expanded to include a variety of non-invasive techniques to address gaps in IBD care. In addition to its important function in the management of strictures and dysplasia, recent advances in endoscopy have allowed alternative options in the management of disease or surgical complications such as fistulas, leaks, and sinuses. As endoscopic technologies continue to develop, such as through additional and artificial intelligence-based detection methods, IBD care is likely to evolve, with endoscopy gradually filling important gaps in IBD management.DisclosureFR is a consultant to or on the advisory board of Adnovate, Agomab, Allergan, AbbVie, Arena, Boehringer-Ingelheim, Celgene/BMS, CDISC, Cowen, Galmed, Genentech, Gilead, Gossamer, Guidepoint, Helmsley, Index Pharma, Jannsen, Koutif, Mestag, Metacrine, Morphic, Organovo, Origo, Pfizer, Pliant, Prometheus Biosciences, Receptos, RedX, Roche, Samsung, Surmodics, Surrozen, Takeda, Techlab, Theravance, Thetis, UCB, Ysios, 89Bio.

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Chapter 14
Enteral Access: Percutaneous Endoscopic Gastrostomy, Gastrostomy-Jejunostomy, and Jejunostomy

Kelli Ifuku and Shawn Tsuda

Abbreviations

PEG	Percutaneous endoscopic gastrostomy
PEG-J	Percutaneous endoscopic gastrostomy-jejunostomy
PEJ	Percutaneous endoscopic jejunostomy

Introduction

Enteral access is artificial access to the gastrointestinal tract to provide a means of nutritional support and gastrointestinal decompression. Enteral nutrition allows patients with a func-

K. Ifuku · S. Tsuda (✉)
Valley Health System General Surgery Residency Program, Las Vegas, NV, USA
e-mail: Kelli.Ifuku@uhsinc.com; drshawntsuda@vipsurg.com

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_14

tional gastrointestinal tract and who have difficulty with oral intake of food to maintain nutritional status. Enteral feeding allows for more physiologic digestion and preserves gastrointestinal integrity and local defense. Enteral feeding is increasingly recognized as therapeutic for critically ill patients, attenuating severity and reducing complications of their underlying conditions.

Access for enteral feeding is established by placement of tubes through natural orifices or directly by percutaneous or surgical approaches. For short-term use (<4 weeks), enteral tubes are temporarily placed through the nasal or oral passage. However, prolonged use of oral or nasal enteral tubes is poorly tolerated and may create local complications; thus, direct access to the stomach or small intestine is recommended for the use of enteral tubes longer than 4 weeks. The percutaneous approach is a popular alternative to surgically-created stomas, albeit each has its own advantages and disadvantages.

Percutaneous endoscopic gastrostomy (PEG) was introduced in 1980 by Michael Gauderer, MD, and Jeffrey Ponsky, MD [1]. The procedure was performed on a 4 month-old infant with the intent to create a sutureless opposition of the stomach to the peritoneum and abdominal wall without laparotomy [2]. Although originally intended for children, PEG is now widely performed across all age groups. In the USA, more than 200,000 PEG procedures are performed annually by surgeons and gastroenterologists. The advantages of PEG include convenience and the use of moderate, conscious sedation compared to general anesthesia. Compared to the standard open Stamm gastrostomy, PEG is associated with reduced operative time, expense, the incidence of complications, and less recovery time [3]. The PEG procedure has also undergone several modifications and has led to the other modalities of enteral access, such as percutaneous endoscopic gastrojejunostomy (PEG-J) and percutaneous endoscopic jejunostomy (PEJ) [2].

Patient Selection

The suitability for enteral access should be assessed and confirmed by a multidisciplinary team, including an endoscopist and nutritional support team. Patients should be evaluated by history, physical examination, and risk factors prior to performing the operation. Proper patient selection is a key to achieving successful outcomes.

Gastric Feeding and Decompression

Gastrostomy is the most common route of prolonged enteral feeding (>4 weeks). Patients must have normal gastrointestinal motility and adequate stomach anatomy for gastric access. Patients selected for PEG often have impaired swallowing, contraindications to oral intake, metastatic disease, or neurologic impairment.

Patients with upper GI malignancy are candidates for PEG due to obstruction and side effects of tumor radiation impeding swallowing abilities. Up to 64% of patients with head and neck carcinoma have dysphagia and associated malnutrition. Malignancies in the upper gastrointestinal tract can cause gastric outlet or intestinal obstruction. PEG is performed in these patients for decompression of abdominal pressure, to alleviate nausea and vomiting, and to provide supplemental nutrition. However, PEG should not be performed if the patient has esophageal cancer and may require gastric conduit reconstruction.

Inability or difficulty to swallow due to neurologic disorders, such as stroke and ALS, are indicators for enteral feeding [4]. Indicators of prolonged dysphagia may include aspiration, pneumonia, and lesions of the frontal and insular cortex of the brain [5]. Because under-nutrition is associated with poor prognosis, stroke patients should be initiated for enteral feeding early as most require prolonged nutrition

support [6]. However, one study did show that placement within seven days of a stroke may increase the risk of death [7]. Compared to NG tube feeding, PEG -tube feeding for neurologic disorders is associated with fewer treatment failures and GI bleeding and has higher feed delivery and albumin concentration. However, the placement of PEG in patients with advanced dementia or Alzheimer's disease may not be useful. Although these patients have poor nutritional intake, PEG -tube feeding does not appear to prolong survival, according to seven observational studies [8, 9].

Patients with severe cerebral injury or trauma may also require enteral nutrition. Although recovery time and the expected duration of nutrition support are unclear, some studies suggest that PEG placement can be performed in 14 days to restore physiological digestive function [10].

PEG also allows patients with chronic inflammatory intestinal disorders, such as Crohn's disease and cystic fibrosis, to meet their nutritional needs. Crohn's disease was initially believed to be a contraindication due to disease occurrence within the gastrostomy tract. However, PEG placement is now commonly performed to improve weight and growth in children with Crohn's disease. Similarly, patients with cystic fibrosis experience a greater improvement in nutritional status and pulmonary function with early intervention from PEG [11].

Jejunal Feeding

Jejunal feeding is achieved through percutaneous endoscopic gastrostomy-jejunostomy (PEG-J) or percutaneous endoscopic jejunostomy (PEJ). Although there is no difference in mortality between gastric feeding and jejunal feeding, jejunal feeding is considered in situations when the placement of a conventional PEG tube is unsuitable. Several meta-analyses show that there is no difference in mortality between jejunal feeding and gastric feeding. Both procedures are acceptable; however, jejunal feeding may be preferred due to anatomical

factors and intolerance to PEG. Insufficient amount of stomach due to gastrectomy and gastrojejunostomy allows more proximal access to the jejunum by a standard endoscope. A common scenario for this is patients with a Roux-en-Y gastrojejunostomy, where the endoscope can access the roux limb in an ante-colic position. Thus, PEJ is often preferable compared to PEG-J or PEG in patients with previous upper gastrointestinal surgeries for nutrition support.

Jejunal feeding is also recommended in patients with recurrent aspiration, gastric outlet obstruction, altered gastric motility, or who had gastric feeding intolerance. Delivery of nutrients to the small bowel can attenuate problems with aspiration, vomiting, or reflux due to gastroparesis, GERD, or recurrent aspiration. If a PEG is already present, PEG can be converted to PEG-J. A PEG-J is also beneficial for simultaneous jejunal feeding and gastric decompression in the presence of gastric outlet obstruction.

Jejunal feeding may be physiologically beneficial for patients with severe chronic pancreatitis. Nutritional management for pancreatitis should include minimal stimulation of the exopancreas, while providing optimal nutrition. Oral or gastric feeding stimulates the cephalic, gastric, and intestinal phases of pancreatic secretion and thus leads to significant pancreatic secretions. Conversely, jejunal feeding has less disturbance or impact on normal gut hormone and exocrine pancreas secretions. Several case reports have reported successful outcomes from PEJ therapy in this subset of patients [12].

Special Considerations

Obesity With the emergence of the worldwide obesity epidemic over the last few decades, an increasing number of patients with obesity require enteral nutrition support. Obese patients can present a challenge due to increased difficulty of transillumination or digital palpation with a thicker abdomen and additional adipose tissue. However, recent studies report an 89.6–97% success rate and 0% mortality rate for PEG in overweight and obese patients [13–15].

Pregnancy Special precautions must be taken when performing PEG in pregnant women. PEG insertion may pose a risk of injury to uterus and fetus. However, PEG has been performed successfully in pregnant women without any major complications.

Absolute Contraindications

Prior to the placement of the natural access tube, the overall patients' prognosis and ability to recover are important considerations. Although increasing studies suggest earlier initiation is acceptable, the consensus remains that enteral feeding is reserved for long-term feeding (>4 weeks). PEG, PEG-J, or PEJ tubes should not routinely be offered if life expectancy is <4 weeks or cannot improve the patient's quality of life. Other contraindications are severe ascites, discontinuous esophagus, hemodynamic instability, septic shock, and coagulopathy (INR >1.4).

Preoperative Considerations

Antibiotic Prophylaxis

Wound infection is the most common complication associated with trans-abdominal enteral access. In addition, many patients who require enteral nutrition are inherently at high-risk for infection, such as old age, malnutrition, and immunosuppression, further emphasizing the need for prophylactic antibiotics. The risk for infection indicates the need for prophylactic antibiotics with broad-spectrum coverage, such as cefazolin. According to a meta-analysis of ten randomized clinical trials, cephalosporin and penicillin-based antibiotics have a similar relative risk reduction (64% and 62%) and absolute risk reduction (10% vs. 13%, respectively) [16]. Systemic antibiotics should be administered as prophylaxis 30 min prior to the procedure, unless the patient is already

receiving broad-spectrum antibiotics. Decolonization of equipment prior to the procedure may also decrease risks of MRSA infection.

Sedation

Moderate or conscious sedation is frequently used for endoscopic procedures. However, comorbid conditions, such as obesity, seizure disorder, neurologically impaired consciousness, may indicate the need for anesthesia-assisted sedation. Accordingly, sedation is associated with the risk of cardiopulmonary complications. Patients should be carefully assessed for these risks preoperatively, and interventional equipment should be present during the procedure. Alternatively, a method for unsedated PEG placement has been described for highly select patients whose risk of anesthesia outweighs the benefit. Woodward et al. describe the nasal unsedated seated PEG using nasal endoscopes in patients with progressive neurodegenerative disorders that employ only the use of local anesthetic with acceptable success and complication rates [17].

Anticoagulation and Antiplatelet

Anticoagulation and antiplatelet therapy increase risk of hemorrhage during and after the procedure. In a prospective study of patients undergoing upper endoscopy, cessation of antiplatelet therapy 10–14 days prior to procedure was associated with less procedural bleeding. While the use of aspirin can be continued, discontinuation of warfarin and clopidrogrel is recommended. The concomitant use of heparin is contingent on the risk for thromboembolism. Cardiac consultation is recommended for patients with severe cardiac conditions or at high risk for cardiac occurrences.

Consent

Consent should be obtained from the patient, or family members or representative if the patient is unable. The concept of tube feeding, including nutritional benefits and the burden of tube placement and feeding in addition to complications, must be acceptable to the patient and family or caregivers. Although the goal of enteral tube placement is to improve nutritional status and prolong survival, tube feeding may have major implications on quality of life.

Techniques

Percutaneous Endoscopic Gastrostomy

In principle, PEG can be placed by thre methods: pull, push, or introducer techniques. The original method, referred to as the "pull" technique, was first described in 1980 by Ponsky and Guaderer and is the most frequently used method today. Prior to the procedure, feeding is suspended for 8 h and systemic antibiotic prophylaxis is administered. Patients undergo conscious sedation, often with topical sprays for posterior pharyngeal topical anesthesia. The procedure begins with a diagnostic upper endoscopy. The gastroscope is introduced trans-orally under direct vision and advanced through the esophagus and into the stomach and duodenum. The stomach anatomy is evaluated and its contents are aspirated. The abdomen is insufflated to ensure that the stomach is in close apposition to the abdominal wall.

Next, an access site in the mid-epigastrium region, where the stomach and abdominal wall are in closest apposition, is chosen for PEG placement. This is marked by the area with maximal transillumination in the mid-epigastrium region and is ascertained with indentation of the anterior gastric wall by external digital pressure (Fig. 14.1). This position on the anterior gastric wall typically is the midway point between the greater and lesser curvatures, thus avoiding the associated vascular structures.

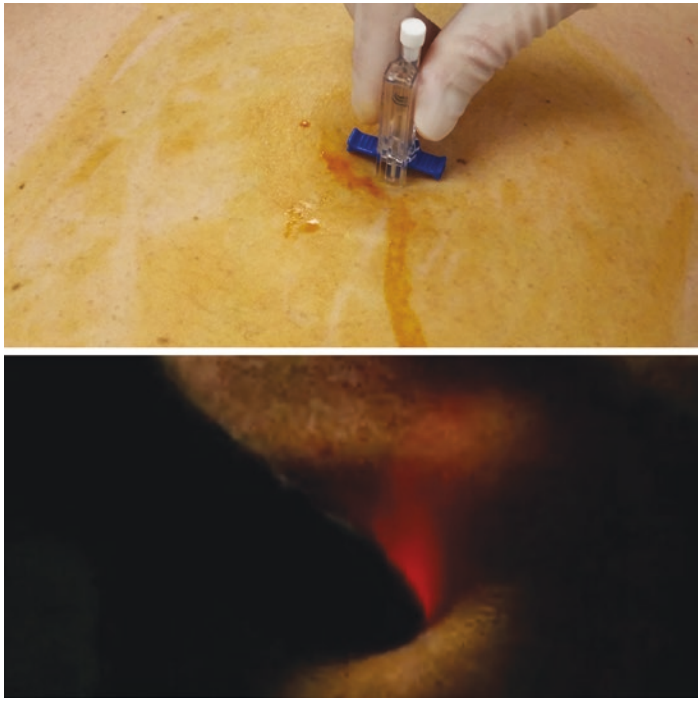

FIGURE 14.1 Transillumination of abdominal wall during initial needle access during PEG

At the site of gastric indentation, a small incision, approximately 0.5 cm in length is made. Under endoscopic visualization, the trocar and/or guidewire are inserted via puncture needle through the abdomen and grasped by the endoscope snare. As a unit, endoscope and snared guide wire are withdrawn through the mouth. The gastrostomy tube is connected to the guidewire from the mouth end and "pulled" back into the stomach via the guidewire from the abdominal end. An internal bumper is placed for fixation against the gastric wall, as well as an external bumper to secure the PEG tube in place (Fig. 14.2). An upper endoscopy is repeated to confirm positioning of the inner opening and bumper placement, as well as to confirm no bleeding from the gastrotomy site.

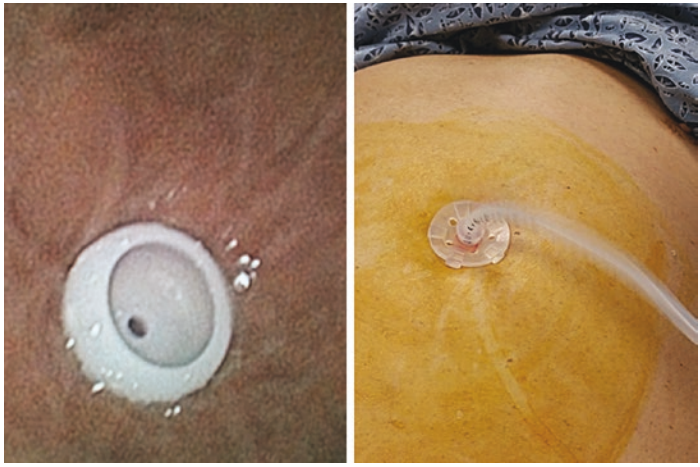

FIGURE 14.2 Endoscopic confirmation of internal bumper placement of PEG tube demonstrating absence of bleeding and opposition of both bumpers with the abdominal wall and gastric wall without ischemia

Push and Introducer Techniques

Modifications to the procedure or equipment have led to the development of other techniques for PEG. The Sack-Vine "push" method is similar to the "pull" technique, except that the tube is "pushed" through oral cavity and stomach with a more rigid introducer, until it emerges from the abdominal wall. Both "push" and "pull" technique have comparable success and complication rates [18, 19].

The Russell "introducer" method uses principles from insertion of central venous catheters and pacemaker wires. Using an introducer an after skin incision, the balloon-tube is inserted directly from the abdomen into the gastric lumen. With the catheter remaining, the introducer is removed and the balloon is inflated to affix against the stomach wall [16]. Proper placement of the catheter is confirmed endoscopically.

Safe Tract Technique

The safety of the site can be tested by performing the safe tract technique as described by Foutch et al. Using an aspirating, lidocaine-filled syringe, the needle is inserted into the stomach. If air bubble is simultaneously aspirated into the needle, then access to the stomach is successful and that a safe tract is achieved. If air or viscous fluid appears prior to entry to the stomach, then the small bowel or colon was punctured, in which case the tube insertion site should be reselected. Some experts suggest that this step may be more favorable than transillumination. The effectiveness of transillumination has been challenged. Conversely, according to Foutch, no procedural failure occurred when a successful safety tract was achieved [20].

Percutaneous Endoscopic Gastrjejunostomy

In a PEG-J procedure, a jejunal extension tube is placed through a PEG tube. Like PEG, PEG-J uses a gastrostomy site Fig. 14.3. In the past, jejunal tubes were inserted through the gastrostomy site but this often resulted in tube migration when the endoscope was withdrawn. Recent techniques and kits use an over-the-wire guide to insert a thinner jejunostomy. The procedure begins similarly to PEG with placement of a PEG tube. From the PEG insertion site, a guidewire is inserted through the PEG tube and advanced into the small bowel with endoscopic assistance. Tube placement distal to the ligament of Treitz is recommended for jejunal feeding to prevent retrograde migration. The tube is also secured by endoscopically-placed clips. Then the endoscope is then withdrawn. With the guidewire remaining, the jejunal tube is then positioned over the guidewire through the PEG tube and into the jejunum.

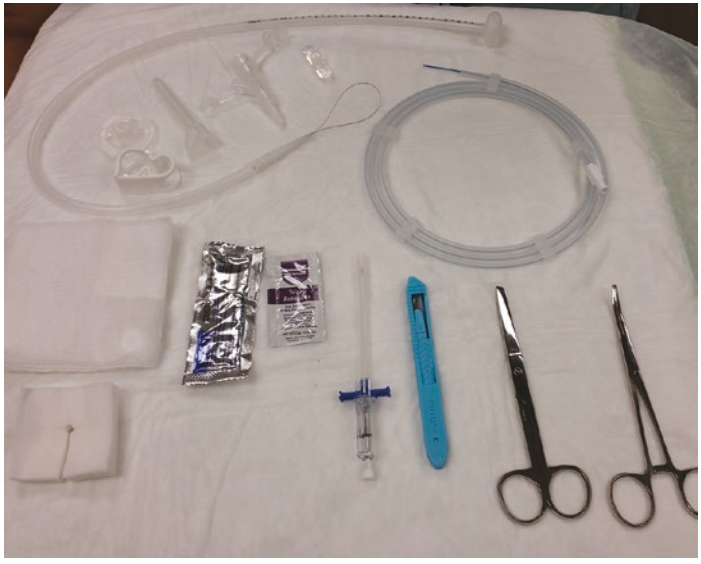

FIGURE 14.3 Standard PEG kit

Percutaneous Endoscopic Jejunostomy

Jejunal feeding tubes can also be placed directly into the jejunum via direct PEJ. The PEJ procedure evolved as a modification of the PEG procedure. Patients are prepared similarly, with conscious sedation and prophylactic antibiotics. Beginning with upper endoscopy, a longer endoscope is passed into the intestine, distal to the ligament of Treitz. In the jejunum, an insertion site is identified with maximal transillumination and intrajejunal finger indentation.

Following standard skin preparation, the insertion needle is inserted percutaneously into the jejunum. The puncture should be performed quickly as peristalsis may interfere with transillumination and cause the intestine to slide. The needle is grasped with endoscope forceps to stabilize the jejunal segment and facilitate subsequent insertion of trocar and thread. The remainder of the procedure proceeds similar to the pull-PEG technique. The thread is snared endoscopically and

withdrawn from the mouth. The jejunal tube is attached to the guidewire from the oral end and pulled into the jejunum from the insertion site. PEJ tube is secured with a bumper and proper position is confirmed by repeat endoscopy.

Laparoscopic Jejunostomy

There are two methods described to place jejunostomy tubes laparoscopically using a suturing technique or a T-fastener facilitated technique. After induction of general anesthesia and routine prophylactic antibiotics, pneumoperitoneum is obtained. In the laparoscopic technique, additional working ports are typically placed in the right lower quadrant and epigastrium. The jejunostomy tube insertion site is selected 10–30 cm distal to the ligament of Treitz and three nonabsorbable seromuscular sutures are used to adhere the antimesenteric side of the jejunum to the abdominal wall using the surgeon's preferred laparoscopic knot tying technique. Under laparoscopic visualization, the lumen is accessed by the 12Fr venous introducer kit. Using an adaptation of the Russell percutaneous technique, the 10Fr jejunostomy tube is inserted to the bowel and placement is confirmed with direct visualization or a fluoroscopic contrast injection study.

The T-fasteners technique is similar to that described for gastrostomy tube placement. With this technique, working ports are placed in the right lower and right upper quadrants after pneumoperitoneum is achieved. The jejunum is insufflated with air through the nasogastric tube. Laparoscopic graspers position the bowel to the abdominal wall and four T-fasteners are inserted to the antimesenteric border of the jejunum in a diamond pattern. The jejunostomy tube is inserted and placement is confirmed in the same manner described above. At the level of the skin, the fasteners are tightened, which secures the jejunum to the abdominal wall. After 2 weeks, the sutures may be cut and the T-pieces pass in the stool [21].

Complications

The evolution of procedural techniques and equipment have improved outcomes of PEG, with an overall success rate of 95–100% [22–24]. Failure is often attributed to improper placement of the tube due to insufficient transillumination. Procedural and 30-day mortality associated with PEG placement are low (0–2% and 1.5–2.1%, respectively) [25–27]. Up to 40% of patients develop minor complications, and 3–4% experience major complications that require hospitalization and/or surgical intervention. However, much of the complications that develop are usually attributed to underlying comorbidities and improper patient selection, rather than the procedure itself [18, 28–30]. PEG tubes can last as long as 1–2 years before requiring replacement due to tube degradation [18].

The success rate of PEG-J is approximately 93%. PEG-J tubes have a mean functional duration of 55 days in adults and 39 days in children. Re-intervention is common due to tube malfunction, such as clogging and migration. Conversely, PEJ uses a larger tube that is anchored directly to the intestine. The functional duration of PEJ tubes is longer, 113 days. PEJ is technically more difficult but success rates remain acceptable at 72–88% [31].

To ensure successful outcomes, three safety tenets have been postulated. Although intended for PEG, these may also apply to PEG-J and PEJ. These steps include: (1) endoscopic gastric distention via insufflation, (2) endoscopically visible finger-pressure indentation, and (3) transillumination. Adherence to these steps enables successful tube placement and decreases procedural complications. These techniques promote close apposition of the stomach to the abdominal wall, with no other organs interposed, and puncture of the intended organ. Performing the safe tract technique has also been shown to facilitate success of procedure.

Injury to Internal Organs

Injury to internal organs can occur from improper placement of enteral tube. Over distention of the stomach and small bowel can cause displacement of transverse colon and increase risk of injury. Injury to the small bowel is less likely due to protection by the greater omentum. However, patients who have had prior abdominal surgery may cause adhesion of the small bowel into the upper abdomen. Injury to the liver is also unusual but has been reported in a few patients. Most cases are rare but depending on the organ or severity of injury, conservative management with careful observation may be sufficient. Hemodynamically stable patients without signs of sepsis can be managed non-operatively. Conversely, colonic injury with peritonitis or liver laceration with intraperitoneal bleeding may require surgery. To avoid injury to internal organs, the safety tenets described previously should be employed for successful insertion of enteral tube. The safe tract technique and adjunctive abdominal imaging, such as ultrasound or CT, may also facilitate insertion and ensure proper placement of tube [15].

Fistula

Fistulas may occur as a result of penetration or misplacement of PEG tube into the colon, small bowel or percutaneously to the atmosphere. Fistulas are rare but can be a potentially serious complication. Many patients remain asymptomatic for months, thus the diagnosis is often delayed [32, 33]. Factors that could lead to fistula include insufficient gastric insufflation and excessive adhesions, often from the previous laparotomy. Up to 45% of colocutaneous fistulae after attempted PEG are observed in patients with prior abdominal history [32]. If there is no leakage, fistulas can be managed conservatively with removal of the PEG tube to allow spontaneous closure. In the presence of peritonitis, abscess, or leakage, operative intervention, including exploration and colonic repair or resection, may be required [34].

Tube misplacement can be minimized with adequate insufflation and choosing the proper PEG tube insertion site carefully. Transillumination, identification of digital pressure, and the safe tract technique endoscopically ensure close apposition of stomach to abdominal wall without interposition of colon or small bowel.

Additionally, chronic gastrocutaneous fistulas following removal of PEGs present with an incidence of 5.7% as noted by Currais et al. [35]. Medical treatment options include PPI, prokinetics, and antibiotics for local wound infections. Currais et al. noted clinical success in 63.2% of patients who underwent medical treatment. Morrell et al. described a success rate of 60% closure in upper gastrointestinal tract fistula's utilizing over the scope clip application [36]. Surgical intervention for closure of a chronic fistula is indicated when both medical and endoscopic modalities have failed [35, 36].

Volvulus

Gastric and small bowel volvulus are rare complications of PEG and PEJ. Gastric volvulus is more commonly observed in children as the ligamentous and omental attachments of the stomach may be more mobile. A case report has described a scenario of incorrect insertion of a PEG into the the posterior gastric wall [37]. Small bowel volvulus after PEJ has also been reported and attributed to internal hernias, adhesions, or bowel motility disorders. Additionally, the single site of attachment of the tube to the abdominal wall may predispose direct PEJ to torsion, in contrast to surgically placed jejunostomy tubes which are typically anchored at multiple sites to prevent rotation. Detorsion of volvulus is performed surgically. Volvulus can be prevented by careful placement of the enterestomy tube on the anterior gastric wall and addressing predisposing factors [38, 39].

Metastasis at PEG Site

Abdominal wall metastasis, typically from head and neck carcinoma, is a devastating complication occurring in <1% of patients. Cases of tumor have been reported with the "pull" method and overall have a poor prognosis. In patients with oropharyngeal or esophageal malignancies, the "introducer" technique, which does not involve contact of catheter or guidewire with the mouth or esophagus, may be a safer technique of choice [40]. Alternatively, a surgical gastrostomy or jejunostomy may be placed, or PEG may be withheld until surgical removal of cancer.

Aspiration and Pneumonia

Aspiration is a common concern associated with enteral feeding. Its incidence ranges from 0.3% to 18% after PEG or PEJ and is likely correlated to the patient's underlying medical conditions [21, 41–43]. Aspiration can range from minor to severe and may result in pneumonia and sepsis, if unresolved. Aspiration typically presents weeks after the procedure, but few reports showed occurrence during the procedure. Aspiration is common in patients with neurologic impairments, such as stroke or brain injury, or gastrointestinal motility disorder, such as gastroparesis. Jejunal feeding via PEJ or jejunostomy is recommended for patients at high risk for aspiration. Patients should be assessed preoperatively in order to perform the correct method for enteral nutrition. Patients with PEG recurrent aspiration can be converted to PEG-J.

Necrotizing Fasciitis

Necrotizing fasciitis is a rare but potentially fatal complication of PEG [44]. Necrotizing fasciitis can occurr in patients who have tube displacement and/or leakage [45]. Excessive

traction and pressure on PEG tubes leading to ulceration or infection can also increase the likelihood for progression to necrotizing fasciitis. Other risk factors include diabetes, wound infections, malnutrition, and impaired immunity. Allowing 3 cm space between PEG bolster and abdomen may decrease risk for wound infection, peristomal drainage, and necrotizing fasciitis, as observed in one study [15, 46].

Buried Bumper Syndrome

Buried bumper syndrome is a rare complication, in which the bumper migrates and lodges in the gastric wall or gastric lumen. Its incidence is 1.9% and presents after at least 4 months of PEG procedure. BBS is mainly caused by excessive traction between the internal and external bumper, but can also occur due to malnutrition, poor wound healing, or a stiff internal bumper. BBS is diagnosed by inability to infuse feed through tube, leakage, and abdominal pain, and is confirmed with endoscopy. Once diagnosed, the buried bumper must be removed in order to prevent further complications and death.

To prevent BBS, additional space (approximately 1.5 cm) should be allowed between external bumper and skin. Mobilizing and loosening PEG tube daily could reduce mucosal overgrowth of the inner bumper. Patients with balloon-assisted PEG introducer devices have been found to have a lower incidence of BBS compared to those with traditional bumpered- PEG devices.

Peristomal Infection

Peristomal wound infections are the most common complication after PEG, with an incidence ranging from 4–30%, depending on definitions [47]. Wound infections are often minor and most resolve with conservative treatment, including local wound care and administration of antibiotics. Preprocedural, prophylactic antibiotics should be given,

unless the patient is already taking broad-spectrum antibiotics prior to the procedure. In a pooled analysis of 13 randomized trials, preoperative administration of systemic antibiotics reduced the incidence of peristomal infection (OR = 0.36) [48]. Cephalosporin or penicillin-based antibiotics were similarly effective, but one study demonstrated that co-amoxiclav was associated with less MRSA infections [49]. Nonetheless, the emergence of Methicillin-resistant Staphylococcus aureus (MRSA) infections indicates decontamination of oral and nasally-delivered preparations and equipment. Postoperatively, regular skin and stomal care are also important in preventing local infections.

Gastrointestinal Bleeding and Ulceration

The incidence of acute bleeding after PEG tube placement is 1–2.5%. Acute bleeding usually results from direct injury to gastroepiploic arteries. Tightening internal and external bolsters may stop bleeding, however compression should be released within 48 h to prevent necrosis or ulceration. Alternatively, delayed bleeding can occur due to esophagitis, gastric pressure ulcer, or the buried bumper syndrome. Esophagitis is the most common cause of gastrointestinal bleeding, occurring in up to 39% of patients undergoing PEG placement. Studies demonstrate that PPIs may prevent and treat bleeding associated with esophagitis. Additionally, warfarin or clopidrogrel use should be temporarily discontinued when appropriate [50].

Pressure necrosis of the gastric mucosa by the internal bolster can cause ulceration of the anterior gastric wall. Pressure ulcers can be prevented by avoidance of excessive traction or tension by the internal bolster. Ulceration in the posterior gastric wall is more commonly attributed to mechanical injury from long protruding gastrostomy tubes or tall internal bumpers [51]. Ulceration from PEG tubes is treated by replacement of PEG tube at a different location or using a small internal bumper. H2 receptors may not provide protection from development of ulcers.

Leakage

Peristomal leakage is common but multifactorial. Its occurrence has been reported from excessive cleansing with hydrogen peroxide, lack of tube stabilization, infection, and gastric hypersecretion. Patients with comorbidities associated with poor wound healing are also at increased risk for peristomal leakage. Peristomal leakage is prevented and treated by management of contributing factors and examining securement of the tube and bolsters. Application of zinc-containing barrier creams may be beneficial to limit skin excoriation. If leakage persists, tube be removed and replaced after 4–6 days. Larger PEG tubes should not be inserted to avoid further injury and subsequent dilation of the tract.

Dislodgement and Inadvertent Removal

Incidental PEG dislodgement is a significant clinical and financial burden on health care systems [52] with an incidence of 1.6–4.4% [21, 53], and can be serious if a mature tract has not formed with resultant peritonitis. The maturation period of a PEG tract is 7–10 days but may be delayed to 3–4 weeks in patients with compromised healing. Immediate detection of removal allows for replacement of PEG tube at or near the original site. However, if detection is delayed in an immature site, the PEG procedure may need to be repeated with the administration of broad-spectrum antibiotics. After the maturation of the stoma, the tube can be replaced at the bedside without endoscopy. Once a PEG tube is removed, spontaneous closure of the PEG tract typically occurs rapidly. Temporary placement of PEG tract dilators or Foley tubes may prevent tract closure.

Circumstances leading to inadvertent removal should be corrected to prevent a recurrence. In general, internal bumpers anchor the tube and prevent dislodgement. The optimal placement of bumpers should secure the tube while allowing enough distance to prevent necrosis or ulceration. Steri-strips

or abdominal binders may also be beneficial. Use of a shorter tube (<18 cm) may prevent the tube from getting caught on other objects and decrease pulling by patients, especially in the setting of neurologic disorders.

Gastrointestinal Obstruction

In rare cases, dislocation of internal bolster or migration of the PEG tube into the pylorus or duodenum can cause obstruction. This complication has been observed in both children and adults and has a higher occurrence with Foley-type peg tubes. Patients with gastric outlet obstruction experience abdominal cramping and vomiting and confirmed by an upper gastrointestinal study. Treatment involves withdrawal of dislocated tube or retrieval of bumpers. Gastric outlet obstruction can be avoided by securement of PEG tubes with an external bolster, placed 1–2 cm space from the skin. In PEJ, internal bumpers <2 cm should be utilized to prevent luminal obstruction.

Clogged PEG Tube

Clogging of enteral tubes is a common minor complication of PEG due to thick feed or undissolved medications. Clogging of PEG-J tubes may also be mechanical due to kinking. To prevent this tube malfunction, the use of bulking agents should be minimized, and medications should be dissolved. Clogged tubes can be prevented and cleared by frequent water irrigation. Some studies suggest the beneficial effects of pancreatic enzymes.

Pneumoperitoneum

Pneumoperitoneum is reported in up to 18–50% of cases [54, 55]. Pneumoperitoneum related to gas insufflation or needle puncture is usually benign and self-resolving. Intervention is

not warranted unless when there is a clinical concern of worsening of intra-abdominal air, or presence of peritonitis, portal and/or mesenteric venous gas, systemic inflammatory response, and/or sepsis [56]. Symptoms persisting for >72 h may suggest the presence of a more serious complication, such as bowel injury.

Removal and Replacement of PEG

PEG tubes should be removed when it is no longer needed. The resultant gastrocutaneous fistula typically closes spontaneously within 24–72 h. Occasionally, surgical or endoscopic closure of gastrocutaneous fistula is needed, especially in children. After 2–3 weeks, the fistula tract is well epithelialized. If there is inadvertent tube removal prior to this, efforts should be made to maintain the tract to spare the patient an additional procedure. If the endoscopy unit cannot be easily accessed or replacement tubes are not readily available, a Foley catheter with an inflated balloon is a temporizing measure to maintain the tract [57].

Conclusion

The percutaneous endoscopic approach has become a widely accepted modality for enteral access. PEG, PEG-J, and PEJ have numerous applications and have been demonstrated to improve the nutritional and disease status of select chronically ill patients. Success rates for all three procedures are high, and overall procedural morbidity and mortality are low. The evolution of techniques and equipment has continued to improve patient outcomes since the first introduction of PEG.

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Chapter 15
Barrett's Esophagus Surveillance: WATS, Real-Time Endoscopic Microscopy

Joshua S. Winder and Eric M. Pauli

Introduction

Gastroesophageal reflux disease (GERD) is an increasingly common diagnosis worldwide, displaying commonality in populations with increased rates of obesity. Within the United States (US), approximately 20% of the population suffers from GERD [1]. GERD is a significant risk factor for the development of Barrett's esophagus (BE). BE is characterized by the metaplastic change of esophageal mucosa from stratified squamous epithelium to columnar epithelium (columnar-lined esophagus or goblet-cell metaplasia). The incidence of BE in the US is between 5–6% and is a known risk factor for the development of esophageal adenocarcinoma [2]. Advanced esophageal adenocarcinoma has a poor prognosis, making the early detection, proper surveillance of disease

J. S. Winder (✉) · E. M. Pauli
Division of Minimally Invasive and Bariatric Surgery, Penn State Milton S. Hershey Medical Center, Hershey, PA, USA
e-mail: jwinder@pennstatehealth.psu.edu; epauli@pennstatehealth.psu.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_15

progression, and (if indicated) eradication of BE essential components of the endoscopic management of metaplasia.

The most commonly used endoscopic detection strategy, the "Seattle Protocol, " requires the endoscopist to perform four quadrant forceps biopsies (FB) every 1–2 cm along the length of the columnar-lined portions of the esophagus, with separate biopsies of any other suspicious areas such as masses, nodules, or areas of ulceration [3]. This random sampling is performed in an attempt to identify any areas of dysplasia in an early and curable stage. A prospective study demonstrated that after the institution of a rigorous surveillance and sampling protocol for BE, there was an increase in the number of identified cases of dysplasia and invasive cancer [4]. Unfortunately, several studies have shown that as the length of the segment of BE increases, adherence to the protocol guidelines and the subsequent rate of dysplasia detection both decrease [5, 6].

Endoscopic methods of BE screening and surveillance with higher rates of detection are becoming more widely available. Wide-area transepithelial sampling of the esophagus with computer-assisted three-dimensional analysis (WATS^{3D}, CDx Diagnostics, Suffern, NY) provides more effective tissue sampling. Endoscopic microscopy (EM) utilizing confocal laser endomicroscopy (CLE) or optical coherence tomography (OCT) allow direct visual identification of dysplasia without the need for direct tissue sampling. These methods hold promise to permit the detection of dysplasia within BE sooner than could be detected by random biopsy samples, thereby altering the subsequent management strategy to one of BE eradication or resection.

Wide-Area Transepithelial Sampling

WATS^{3D} has emerged as an adjunctive therapy to current methods, assisting in the early detection and surveillance of BE. WATS^{3D} has recently been endorsed by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy [7]. The Society of American

Gastrointestinal and Endoscopic Surgeons Technology and Value Assessment Committee concluded that WATS^{3D} is "a safe and effective adjunct to forceps biopsies (FB) in the evaluation of Barrett's Esophagus, Low-Grade Dysplasia (LGD), and High-Grade Dysplasia (HGD)." [7, 8].

Technology Overview

WATS^{3D} is used as an adjunctive method to the Seattle protocol in the identification and surveillance of patients with BE. The system is comprised of an abrasive brush that is passed through the working channel of the endoscope (Fig. 15.1). This brush is passed along the esophageal mucosa

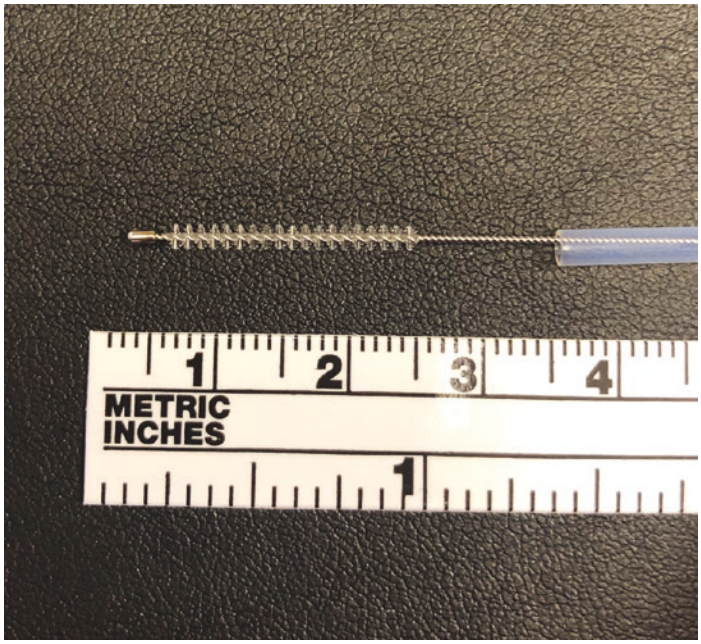

Figure 15.1 Proprietary through the scope brush used for Wide-area transepithelial sampling of the esophagus with computer-assisted three-dimensional analysis (WATS^{3D}, CDx Diagnostics, Suffern, NY)

and rotated circumferentially, obtaining transepithelial specimens over a broad area of the esophagus in contact with the device (Fig. 15.2). The brush is capable of obtaining deep samples down to the lamina propria. The WATS^{3D} sampling adds an average of 4.5 min to the total procedure time [9].

The brush is removed, and the samples are plated, stained, and examined at the CDx Diagnostics Laboratory. A computational analysis consisting of a neural network and a high-speed scanning system is capable of identifying abnormal cells. The proprietary system allows three-dimensional viewing of the tissue fragments (Fig. 15.2). Suspicious cells are flagged by the system to then be reviewed by pathologists using the 3D system, as well as conventional microscopy, using published and commonly accepted pathologic criteria used to evaluate specimens for BE (Fig. 15.3). Indications for WATS^{3D} include patients who are undergoing endoscopy for

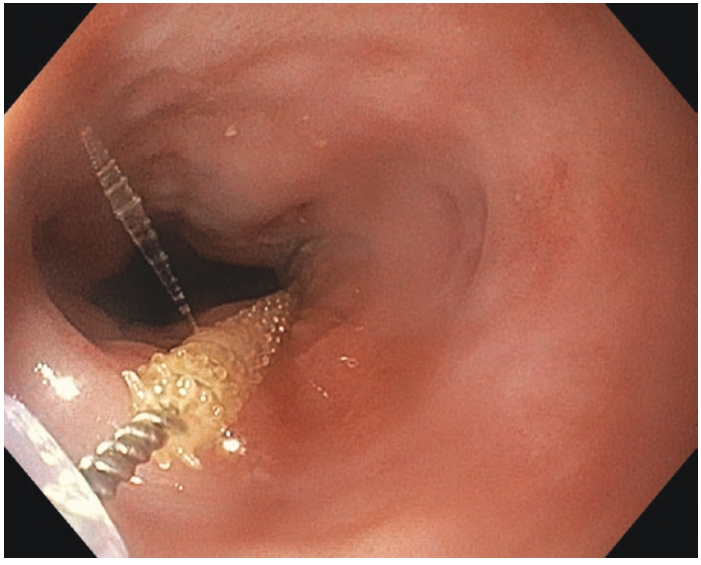

Figure 15.2 Endoscopic view of WATS^{3D} brush (CDx Diagnostics, Suffern, NY) in the distal esophagus prior to obtaining a tissue sample

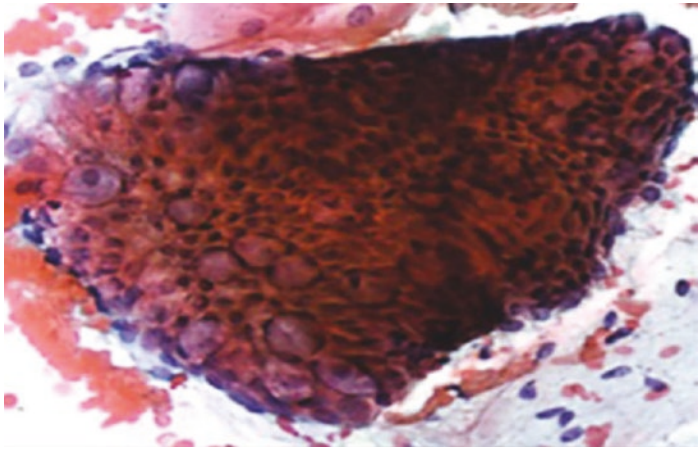

FIGURE 15.3 Computer-synthesized three-dimensional image of a gland obtained using WATS^{3D} (CDx Diagnostics, Suffern, NY)

evaluation of reflux, peptic ulcer disease, and screening or surveillance for BE. WATS^{3D} is not recommended as a substitute for the Seattle protocol but should be performed as an adjunctive measure for diagnosis and detection.

Clinical Evidence

Multiple published studies have examined the clinical validity of WATS^{3D} as an adjunct to the Seattle protocol. Johanson et al. reported their results of a multicenter prospective trial of patients who were undergoing screening for BE and esophageal dysplasia [10]. Of the 1266 patients who were enrolled, 363 were diagnosed with BE after FB, with an additional 146 cases identified after adding WATS^{3D}. This increase in BE diagnosis of 11.5% of all patients tested resulted in a number needed to test for each additional BE diagnosis of 8.7. Within the subset of patients with a history of GERD without a previous diagnosis of BE, adding WATS^{3D} to FB identified an additional 105 patients with BE increasing the detection rate by 70.5%. Finally, with FB alone, dys-

plasia was diagnosed in 16 cases, with 14 additional cases identified by adding WATS^{3D}, increasing the detection rate by 87.5%.

Anandasabapathy et al. reported their results of a multi-institution trial examining the detection of dysplasia during surveillance of patients with BE using computer-assisted brush biopsy analysis [11]. After enrolling 151 patients from 4 institutions, they identified 117 patients (77.5%) with specimens adequate for interpretation. The overall yield of FB for detection of dysplasia was 25.2% (n = 38). Brush biopsy added an additional 16 cases, increasing the yield of detection by 42%. This resulted in a number needed to test to detect one additional case of dysplasia of 9.4 (95% CI: 6.4–17.7).

Gross et al. reported the results of their multicenter prospective trial of patients with known BE undergoing surveillance and patients screened for suspected BE at 25 community-based practices utilizing WATS^{3D} adjunctively with FB [12]. Among the 4203 patients enrolled, FB diagnosed 594 with BE, with an additional 493 patients identified by adding WATS^{3D}, an increase of overall detection of BE of 83%. Low-grade dysplasia was identified in 26 patients using FB alone, with 23 additional cases identified with the addition of WATS^{3D}, increasing the identification of low-grade dysplasia by 88.5%.

Vennalaganti et al. reported their results of a multi-institutional randomized trial of 160 BE patients undergoing surveillance [9]. The primary endpoint was the detection of high-grade dysplasia or esophageal adenocarcinoma (HGD/EA) using WATS^{3D} followed by FB compared to FB followed by WATS^{3D}. Forceps biopsy sampling alone yielded seven cases (4.4%) of HGD/EA, while the addition of WATS^{3D} yielded an additional 23 cases (an absolute increase of 14.4%).

Smith et al. reported the results of their multicenter prospective trial examining WATS^{3D} as an adjunct to both targeted and random FB in patients undergoing BE screening or surveillance. Twelve thousand eight hundred ninety-nine patients were enrolled, and FB identified 88 cases of esopha-

geal dysplasia (0.68%). WATS^{3D} identified an additional 213 cases missed by FB, representing an absolute increase of 1.65% and a remarkable 242% overall increase in detection. Forceps biopsy identified 1684 cases of BE, while WATS^{3D} identified an additional 2570 cases, increasing the overall detection of BE by 153%. The number needed to test with WATS^{3D} in order to identify an additional case of BE was 5. The order in which FB and WATS^{3D} were performed did not affect the results.

Given the sampling error inherent to FB-based surveillance protocols, the need for adjunctive sampling and screening methods seems evident. Only 4% of the examined esophagus is biopsied using the Seattle protocol, leaving potential areas of dysplasia unsampled [13]. As we pointed out earlier, patients with longer segments of BE tend to undergo inadequate sampling. Alarmingly, these are the very patients who are at the highest risk of having dysplasia within their BE.

Despite these apparent advantages, there are questions that remain. It is unclear which patients would benefit most from screening or surveillance with WATS^{3D} or if all patients with suspected BE should undergo testing. Some authors worry that the addition of WATS^{3D} may result in false positives and overdiagnosis [14]. Whether this is true or not is speculation and warrants further study.

Importantly, the reported morbidity is acceptably low, with no significant morbidity or mortality reported in the literature [8]. Issues of insurance coverage for WATS^{3D} also remain; while FB is a universally afforded benefit, WATS^{3D} analysis may not be reimbursed.

Endoscopic Microscopy

Endoscopic microscopy is the name given to a variety of tools and techniques that permit the assessment of tissue architecture at a level of resolution similar to standard histopathological analysis. Compared to standard white light endoscopy

(WLE), EM permits a more in-depth analysis of the esophageal mucosa by providing a real-time in vivo histologic assessment of the whole epithelial thickness without the need for physical tissue removal via biopsy.

Confocal Laser Endomicroscopy

Confocal Laser Endomicroscopy (CLE) is an advanced imaging technique used to evaluate BE. It can magnify esophageal mucosa up to 1000 times and acquire images 250 micrometers below the tissue surface. The technology is based on the technique of illuminating the tissue with a low-power laser and detecting fluorescent light that is reflected from the target tissue. Intravenous or topically-applied agents are required to assist with the fluorescence. CLE can either be performed with a specialized scope, where the microscope is placed on the tip of the scope or probe-based, where the microscope is passed through the working channel of a standard endoscope (Figs. 15.4 and 15.5).

The probe-based system (Cellvizio, Mauna Kea Technologies, Paris, France) is the only system currently available for use in the US. It consists of a microprobe that is advanced through the working channel of most commercially available endoscopes. This probe is reusable if properly sterilized between uses. The probe has a fixed focal length and is available for different settings, including upper endoscopy, lower endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), and a probe that can be passed through a 19 g needle used during endoscopic ultrasound (EUS) used for the evaluation of pancreatic lesions [15].

In a meta-analysis examining the use of CLE for the detection of cancer in patients with BE, Wu et al. reported pooled data from 709 patients [16]. They found the per-patient sensitivity for CLE in the detection of neoplasia was 89% with a specificity of 75%. Canto et al. reported their results of a prospective, randomized control trial of 192 patients undergoing BE surveillance with either high definition WLE with

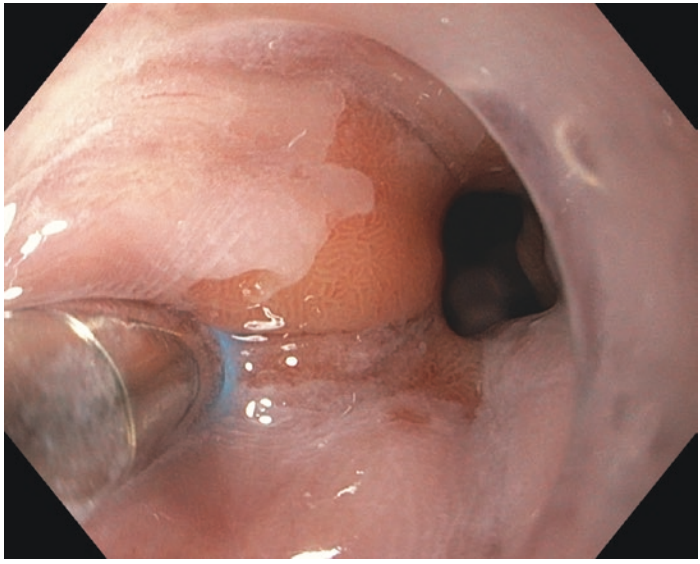

Figure 15.4 Endoscopic view of Celvizio (Mauna Kea Technologies, Paris, France) probe during the evaluation of the distal esophagus

random biopsies or high definition WLE with CLE with targeted biopsies [17]. They found that including CLE led to a lower number of biopsies with a higher diagnostic yield for cancer detection (34% vs. 7%; $P < 0.001$). However, other randomized trials had conflicting results showing no clinical benefit to using CLE compared to high definition WLE [18].

Optical Coherence Tomography

Optical coherence tomography (OCT) is a technology capable of obtaining cross-sectional images of tissue with resolution equivalent to a low-powered microscope. The methodology of OCT can be thought of as an 'optical ultrasound'; reflections of light that penetrate the tissue surface are used to create images. With standard WLE imaging, the light that hits the tissue and diffusely scatters is used to create

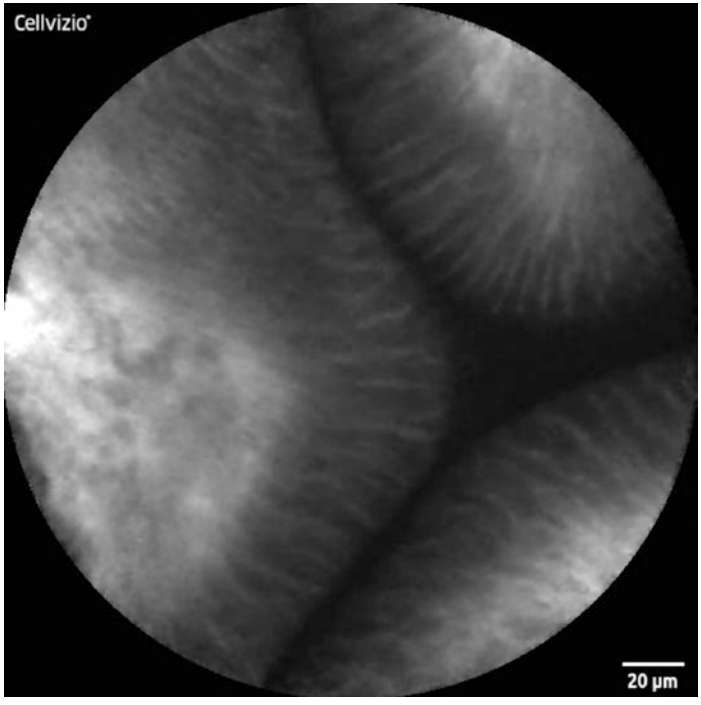

Figure 15.5 Example of images taken of esophageal mucosa evaluated using Celvizio (Mauna Kea Technologies, Paris, France)

the image. OCT is based on interferometry, a process by which light from a source is divided into two beams and directed toward the tissue and toward a moveable reference mirror. This permits the optical path length of the light beams to be measured. Photons of light that are reflected from the tissue are used to generate an image, while photons of light that have scattered before detection are rejected. As the signal is processed, OCT can build cross-sectional two-dimensional and three-dimensional images by rejecting background noise (scattered light) and accepting only light signals reflected from the sub-surface tissue layers.

In the first prospective study with the technology, using ultra-high definition OCT, 121 patients were examined for the following criteria when screening for BE: lack of normal

esophageal morphology, inhomogeneous tissue contrast, and presence of submucosal glands [19]. The authors found that when two of the three diagnostic criteria were met, the sensitivity for detecting BE was 97%, and the specificity was 92% when compared to histology. One of the drawbacks of OTC is the high interobserver variability due to the subjective nature of the interpretation of the data. Furthermore, obtaining and interpreting the data from OTC can be time-consuming and may not be ideal for screening or surveillance purposes due to the time needed to perform the test. One prospective study comparing WLE and OTC reported that using OCT imaging added an average of 12 min (range 3–20 min) to the study [20].

Conclusions

BE is a known risk factor for the development of esophageal adenocarcinoma, which holds a poor prognosis in its advanced stages. The current endoscopic diagnosis and protocolled surveillance of BE are limited by the small amount of tissue sampled and may leave behind undiagnosed dysplasia. The addition of WATS^{3D} as an adjunct to the Seattle protocol increases the diagnosis of BE, low and high-grade dysplasia, and esophageal adenocarcinoma without significant increases in time spent during the procedure or morbidity. Emerging EM and other real-time imaging modalities that obviate the need for tissue sampling are evolving and may represent a more efficient and directed form of assessment and diagnosis.

Acknowledgments Dr. Caitlin Houghton at the University of Southern California for providing images of WATS^{3D} for this manuscript.

Disclosures JSW recieves consulting fees from Boston Scientific. EMP receives honoraria from Becton Dickinson, Medtronic, Ovesco, Cook Biotech, Boston Scientific, Actuated Biomedical, Baxter, Wells Fargo, CMR Surgical, and royalties from Up-To-Date and Springer.

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Chapter 16
Barrett's Esophagus Treatment: Radiofrequency and Other Ablation Modalities

Michael T. Fastiggi and Leena Khaitan

Introduction

Barrett's esophagus occurs as a sequela of gastroesophageal reflux disease (GERD), where continued irritation of the normally stratified squamous epithelial lining of the distal esophagus undergoes metaplasia to become intestinal-type columnar epithelium. Approximately 10–20% of patients with GERD have Barrett's esophagus [1, 2]. As such, treatment of GERD can halt the progression Barrett's esophagus, but does not necessarily eliminate it. A feared complication Barrett's esophagus is progression to esophageal adenocarcinoma. The risk of progression in patients with non-dyspBarrett's esophagus is 0.2–0.5% per year, approximately 0.7% per year in patient low-grade dysplasia, and about 7%

M. T. Fastiggi · L. Khaitan (✉)
University Hospitals, Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH, USA
e-mail: leena.khaitan@uhhospitals.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_16

in patients high-grade grade dysplasia [2]. Guidelines have been established by the American College of Gastroenterology regarding surveillance and management of Barrett'srett's esophagus, and are summarized in Table 16.1 [2, 3].

Initially, a diagnosis of dysplasia, part high-grade dysplasia, carried with it a recommendation for esophagectomy. However, new evidence has become available and since endoscopic techniquest have improved, endoscopic eradication therapies have become the standard of care [4]. Successful endoscopic ablative low-grade high-grade dysplasia, as well as in cases of intramucosal carcinoma that have first been treated with endoscopic mucosal resection, aims to remove the entirety of the metaplastic tissue in the mucosa but preserve the submucosa in order to prevent complications such as stricture [2]. These include radiofrequency ablation, chemical photodynamic therapy, and cryotherapy. This chapter will discuss the techniques, complications, and outcomes of ablative therapies, as well as comparisons between them. Endoscopic mucosal resection is discussed elsewhere.

Table 16.1 ACG guidelines for surveillance and management of Barrett's esophagus according to histology

Surveillance and ManagemenBarrett'sett's Esophagus					
Pathologic Finding	Barrett's without dysplasia	Indefinite for dysplasia	Low grade dysplasia	High grade dysplasia or T1a esophageal adenocarcinoma	Esophageal adenocarcinoma T1b or greater
Recommendation	Four quadrant biopsies every 2cm, every 3 to 5 years	Confirm the with second pathologist, repeat endoscfour-quadrant quadrant biopsies every 1cm in 2 to 6 months	Endoscopic eradication; endoscopic surveillance is an acceptable alternative	Endoscopic eradication	Referral to oncology

Radiofrequency Ablation

Introduction

Radiofrequency ablation (RFA) has become the most frequently performed method of endoscopic eradication of Barrett's esophagus [5]. While very effective, it is imperative that any nodular abnormalities or raised lesions in the presence of dysplasia be resected via endoscopic mucosal resection (EMR). EMR ensures that a flat concentric surface is present for maximal effectiveness of the RFA procedure so that it can adequately penetrate through to the submucosa, and in turn, RFA augments the effectiveness of the EMR, which alone would only remove a focal segment, and overcomes the risk of leaving behind a small focus of residual dysplasia [6].

RFA is usually accomplished initially with a circumferential balloon-based bipolar electrode catheter, followed by focal ablation of residual Barrett's esophagus endoscope mounted articulating bipolar device [7, 8]. In the past, circumferential ablation consisted of a two-step procedure, which first involved placing a sizing balloon, placement of an appropriately-sized ablation catheter, followed by the deli preset amount of radiofrequency energy density set at 300 W to the electrode of the ablation catheter [7]. This device uses an adjustable pneumatic stable balloon that can fir the diameter of the esophagus, usechan adjustable pneumatic stable balloon that can fit the diameter of the esophagus. This balloon contains catheter electrodes around the circumference, thereby eliminating the need for a sizing step and reducing procedure time for two-step procedure. The catheter consists of a 4 cm segment of circumferential copper sheet of bipolar electrodes. The balloon has a variable diameter from 1 to 31 mm, and automatically inflates to 3 PSI when activated via foot pedal with pneumatic dilation. The catheter is then actiavated and delivers radiofrequency energy at a preset setting of 10 J/cm^2, with the generator adjusting energy delivery by measuring tissue impedance [9].

Indications

Generally, the ideal candidate for an RFA is a patient with a high-grade dysplasia. As mentioned previously, patients with nodular Barrett's esophagus or with visible lesions require EMR prior Long-term data is not yet available for RFA alone in the treatment of flat intramucosal carcinoma, so care must be taken to rule out intramucosal carcinoma in the set high-grade dysplasia. It is generally recommend high-grade dysplasia be confirmed with two separate endoscopic four-quadrant biopsies eery 1 cm, within 2 months of RFA [8, 10]. In the case that intramucosal carcinoma is identified, RFA can proceed after EMR. In the preset low-grade dysplasia, RFA can be offered. A randomized controlled trial comparing RFA to observation in patients with Barrettlow-gradew grade dysplasia showed a significantly decreased rate of progress high-grade dysplasia or adenocarcinoma compared to control, and while rates of complication (mainly stricture) were higher in the intervention group, the study was terminated early due to the superiority of ablation [11]. However, observation is still considered a viable alternative, and is considered an acceptable option by the American College of Gastroenterology [2]. For intestinal metaplasia, ongoing surveillance is still recommended, as outlined above.

Technique

Circumferential RFA is usually performed on an outpatient basis, generally under monitored anesthesia care. The patient is placed into the left lateral decubitus position, and the endoscope is inserted. The esophagus is prepped with 1% acetylcysteine and flushed with water to clear away excess mucus in order to help the balloon catheter maximize contact with the mucosa. The length of the segment of Barrett's esophagus is measured, from the proximal extent to the proximal gastric mucosa (Fig. 16.1a, b). A guidewire is then passed, and the scope retracted proximally above the segment of Barrett's

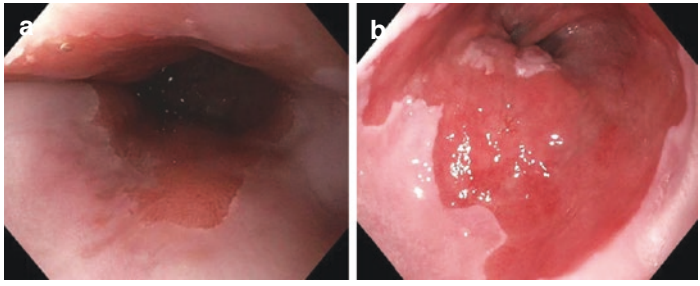

FIGURE 16.1 (**a**) Barrett's esophagus. (**b**) Barrett's esophagus with high-grade dysplasia on biopsy

esophagus. The balloon of the radiofrequency ablation catheter is then inserted under vision, with approximately 1 cm overlap onto normal esophageal squamous mucosa [6]. The catheter is then inflated, and when mucosal contact is confirmed under vision, the electrode is activated and the ablation commences. If the segment of Barrett's esophagus exceeds the catheter electrode length of 4 cm, the balloon is deflated and advanced to the distal end of the previously ablated segment with 5 mm of overlap from the previous segment [6]. The endoscope is then, removed and the balloon is cleaned. A cap is applied to the endoscope, and it is reinserted. The cap at the end of the endoscope is then used to gently clean away the coagulated mucosa from the first application of radiofrequency energy, and this area is rinsed with water. When the entire segment has been cleaned, the guidewire is reintroduced, and the balloon catheter is again inserted over the guidewire and placed into position under endoscopic guidance, and a second round of RFA is performed. A completion endoscopy is then performed to inspect the area of ablation, and the procedure is complete (Fig. 16.2a–c). Repeat endoscopy at 12 weeks is recommended, and if there is either residual circumferential Barrett's esophagus or multiple foci, repeat circumferential ablation is performed. If small or scattered foci are present, then focal RFA is performed.

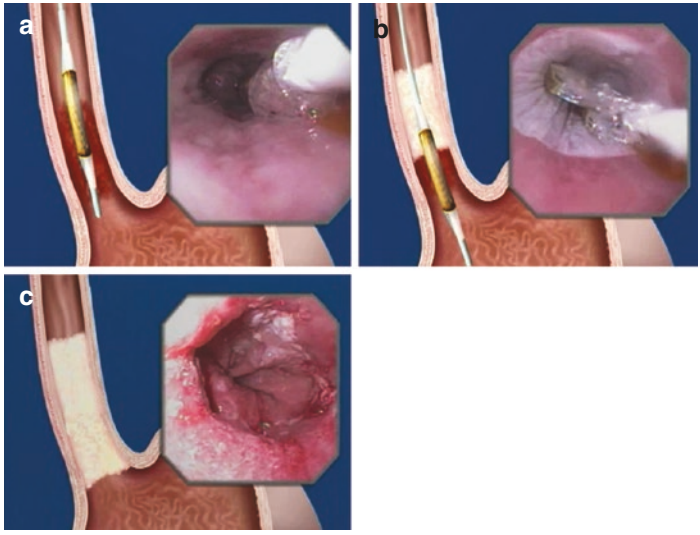

FIGURE 16.2 (**a**) Placement of RFA balloon. (**b**) Balloon deployment. (**c**) Completion endoscopy

Focal RFA is accomplished via a mounted catheter attached to the end of the endoscope, with the electrode at the 12 o'clock position. The endoscope and catheter are then inserted, and the targeted area of Barrett's esophagus is oriented at the 12 o'clock position on the video monitor. The electrode is then placed directly onto the tissue and RF energy is applied at 15 J/cm^2. This is repeated for each focal segment present. Historically, the catheter was then cleaned, the coagulum lifted, and another double set of ablation was performed. However, recently a simplified triple ablation without cleaning or removal of the coagulated tissue has shown noninferiority compared to the standard regimen [12]. The Z line is also recommended to be ablated circumferentially to ensure complete eradication of any residual Barrett's esophagus [6]. The procedure is then completed, and the endoscope is withdrawn.

Post procedurally, it is important to maintain patients on acid suppression, as persistent GERD is an independent risk factor for poor response to RFA [13]. Generally, patients are placed on a 2–4 week regimen of twice daily PPI, nightly ranitidine, and sucralfate four times daily, with continuation of the proton pump inhibitor. Patients should be on a liquid diet for the first day after the procedure, and then gradually advance as tolerated to a soft and then regular diet. As an adjunctive antireflux intervention, antireflux surgery should be considered if indicated to further prevent reflux following an ablative procedure.

Complications

Common symptoms post RFA are sore throat, chest pain, dysphagia, and nausea/vomiting. For pain and discomfort, patients are advised to take liquid acetaminophen or ibuprofen as needed, and if severe, may require codeine with lidocaine. On meta-analysis, complications after RFA included stricture (5%), pain (3%), and bleeding (1%) [14]. Perforation is theoretically possible but rare, and imaging should be obtained if clinical suspicion is high.

Rates of stricture, the most common adverse event after RFA, range from about 5–8%. This rate is higher in phototherapy but similar or lower in cryotherapy (Table 16.2). Factors that predict stricture after RFA include long segment length (>9 cm), longer longitudinal length of involved segment, and higher treatment area [15]. Treatment usually includes balloon dilation.

Table 16.2 Summary of endoscopic eradication methods

Therapeutic technique	Barrx	Photodynamic therapy	Cryotherapy
Stricture rate	5–8%	36%	3–9%
Eradication of dysplasia	78–95%	54–78%	81–97%
Reversion to squamous epithelium	93%	75–80%	57–84%
Incidence of buried Barrett's	0.9%	14.2%	3%
Recurrent metaplasia or dysplasia	4–13%	24%	18–19%
Surveillance	High-resolution endoscopy at 3, 6, and 12 months, then annually	High-resolution endoscopy at 3, 6, and 12 months	High-resolution endoscopy every 3 months for the first year, every 6 months for years two to three, then annually

Outcomes

There has been a good amount of evidence from several studies, both prospective and in meta-analysis, as well as long-term follow-up data, that have shown RFA is safe and effective for treatment of Barrett's esophagus with dysplasia. The consistent depth of penetration yields reliable results, which has been verified in the literature.

The AIM dysplasia trial was a prospective trial of 119 patients with low or high-grade dysplasia randomized 2:1 to ablation versus sham endoscopic therapy, with outcomes looking at complete eradication of dysplasia and metaplasia, durability of response, disease progression, and complications [14]. RFA was performed a maximum of four times in the first year, with an option for an additional focal ablation at 15 months if residual metaplasia or dysplasia remained. Of the initial cohort, 106 subjects reached the 2-year follow-up mark, including crossover of 35 out of 39 patients from the sham arm to RFA at 1 year per the eligibility of the study. Of these 106 patients, 95% had complete eradication of dysplasia and 93% had complete eradication of intestinal metaplasia at 2 years. Of the patients with low-grade dysplasia, 51 of 52 (98%) had complete eradication of dysplasia and metaplasia.

Of patients with high-grade dysplasia, all dysplasia was eradicated in 50 of 54 (93%) and intestinal metaplasia was eradicated in 48 of 54 (89%). Fifty-six patients continued to participate through 3 year follow-up, showing complete eradication of dysplasia in 55 of 56 patients (98%), and complete eradication of intestinal metaplasia in 51 of 56 patients (91%) [14]. Five of 119 patients (4.2%) experienced disease progression—three progressed from low to high-grade dysplasia, one patient with low-grade dysplasia developed esophageal adenocarcinoma, and one patient with high-grade dysplasia developed esophageal adenocarcinoma. Four adverse events of the 119 patients receiving RFA occurred: one patient on dual antiplatelet therapy developed bleeding requiring endoscopic management, and three patients required admission for management of chest pain that resolved with supportive care. Nine of 119 patients (7.6%) developed stricture, and there were no perforations or procedure-related mortalities [14].

Similarly, a meta-analysis consisting of 18 studies with 3802 patients reporting efficacy and 6 studies with 540 patients

reporting durability, complete eradication of intestinal metaplasia was seen in 78% of patients (95% CI, 70–86%), complete eradication of dysplasia was seen in 91% of patients (95% CI, 87–95%), recurrence of intestinal metaplasia was 13% (95% CI, 9–18%), and 0.7% of patients progressed to esophageal adenocarcinoma after achieving complete eradication of intestinal metaplasia [13]. The most common adverse events were stricture (5%), followed by pain (3%), and bleeding (1%).

Surveillance endoscopy regimens depend on the degree of dysplasia. For patients that had complete eradication of high-grade dysplasia or intramucosal carcinoma, surveillance with high-resolution endoscopy and narrow band imaging is recommended at 3 months, 6 months, and 12 months, with annual endoscopies every year for 5 years, whereas patients with low-grade dysplasia are recommended to have surveillance endoscopy at 3 months and 12 months [3].

Special Considerations

A concern after RFA is that underneath the neo epithelium that arises after the metaplastic and dysplastic tissues are eradicated, residual glands containing Barrett's esophagus may progress to esophageal adenocarcinoma underneath, known colloquially as "buried Barrett's" [6]. A systematic review of patients undergoing photodynamic therapy versus RFA found that baseline prevalence of buried Barrett's before endoscopic eradication ranged from 0 to 28%, and that buried Barrett's was seen in 14.2% of patients after photodynamic therapy compared to 0.9% of patients after RFA [16]. Despite the limitations of the study, such as non-uniformity of biopsy depth, there is a clear and significant difference in the incidence of buried Barrett's after RFA compared to photodynamic therapy.

Conclusion

RFA with Barrx FLEX (Medtronic, Minneapolis, MN) is the most commonly performed endoscopic eradication method for Barrett's esophagus with low or high-grade dysplasia. It consists initially of circumferential radiofrequency ablation followed by targeted focal ablation. It has been proven to be safe and effective with a good initial response as well as durability of response at 3–5 year follow-up, and it is considered the gold standard treatment for Barrett's with dysplasia.

Chemical Photodynamic Therapy

Chemical photodynamic therapy (PDT) combines a chemical, sodium porfimer (Photofrin), with argon laser phototherapy to activate and induce mucosal damage. Indications for treatment include Barrett's esophagus with low- or high-grade dysplasia, as well as intramucosal esophageal adenocarcinoma (T1, N0, M0).

Sodium porfimer, the chemical cytotoxic agent, is given intravenously 48–72 h prior to planned endoscopy. Endoscopy is then performed at the appropriate time period, usually under conscious sedation or monitored anesthesia care. After confirming the position on endoscopy, a windowed esophageal centering balloon is placed over a guidewire and inflated at the desired position, and a cylindrical diffuser is passed through the center channel of the balloon. 630 nm light from an argon-pumped laser dye is then applied to the targeted area of esophageal mucosa via the cylindrical diffuser [17]. The light energy activates the chemical agent, inducing mucosal damage via free radical formation [4, 18]. Endoscopies are usually repeated at 48 h to determine if further light treatment is required, and again at 1 week. Endoscopies to check for healing and for biopsies to confirm eradication are then performed at 3, 6, and 12 months [17].

Follow-up data has shown complete eradication of dysplasia to range from 54 to 78%, and complete eradication of

intestinal metaplasia with conversion to squamous epithelium to range from 75 to 80% [17, 19]. Rates of stricture are 28 to 34%, with the increased stricture rate thought to be secondary to the multiple exposures of the argon laser from the overlapping of treatment margins [9, 16]. Perforation is rare but has been described [16]. Other adverse reactions included photosensitivity, vomiting, and odynophagia. Anecdotally, this is often a major concern for patients, as they are advised to avoid sun exposure for at least 30 but up to 90 days [17]. Thus, although photodynamic therapy is a minimally invasive treatment option for Barrett's esophagus with dysplasia, its side effect profile limits its widespread use, and its efficacy is less than that of RFA.

Cryotherapy

Cryotherapy, also known colloquially as spray cryotherapy, works by spraying liquid nitrogen onto Barrett's tissue, causing the disruption of cell membranes, leading to apoptosis and thrombosis in the mucosa [3, 18]. The procedure is performed under conscious sedation or monitored anesthesia care. Endoscopy is performed, and the target area of Barrett's esophagus tissue is identified. A catheter is then placed through the endoscope, and a pressurized system sprays −196 °C liquid nitrogen onto the target tissue, with duration controlled by pressing a foot pedal [20]. The targeted site is treated with 40s total duration, either in two treatments of 20s or four treatments of 10s, with time between to allow for reperfusion of the tissue [20]. Depending on the total length of Barrett's tissue present, treatment of three to five target areas may be required (Fig. 16.3) [21]. The procedure is then repeated every 2–3 months until the Barrett's esophagus is eradicated, confirmed both on endoscopy and histology [20]. Surveillance is done with high-resolution endoscopy every 3 months for the first year, followed by every 6 months for years 2–3, then annually [22].

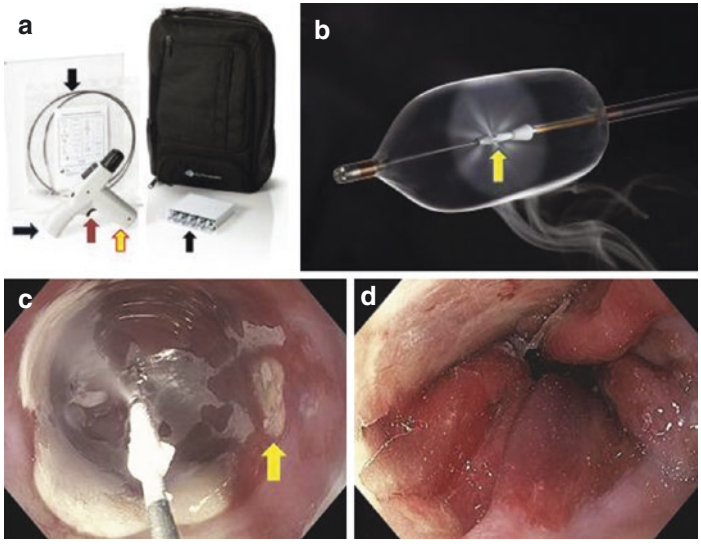

Figure 16.3 (**a**) Controller (left image) with handle that holds the nitrogen cartridge (yellow arrow), trigger (red arrow), and attachment site (black right arrow) for the balloon catheter (black down arrow). The catheter is attached to a reusable light weight portable handle, which controls the delivery of liquid nitrous oxide stored in a small cartridge. (**b**) External view of focal cryoballoon ablation catheter (30 mm) with diffuser (arrow) and nitrous oxide spray. (**c**) Endoscopic view of focal cryoballoon ablation through the balloon using a high-definition endoscope showing the cryogen released from the diffuser within the balloon and resulting ice patch. The active ablation is the fourth one applied in a clockwise circumferential fashion, with the first ice patch melting (arrow). (**d**) Endoscopic view of the distal esophageal and gastric cardia mucosa with red color change and edema immediately after cryoablation. (Figure and text description taken from the following reference, permission pending: Canto MI. Cryotherapy for Barrett's esophagus. Gastrointestinal Endoscopy Clinics. 2017 July 1;27(3):503–13)

In a series of 60 patients with Barrett's esophagus and high-grade dysplasia, 58 (97%) had complete eradication of high-grade dysplasia, 52 (87%) had complete eradication of

dysplasia overall, and 34 (57%) had complete eradication of intestinal metaplasia, with mean follow-up of 10.5 months [20]. Three percent of patients were found to have buried Barrett's. Three patients (3%) developed strictures, and no perforations occurred. Another retrospective series of 32 patients aiming to look at long-term data for cryotherapy in Barrett's esophagus with high-grade dysplasia found that at 2-year follow-up, all 32 patients (100%) had complete eradication of high-grade dysplasia, and 27 patients (84.4%) had complete eradication of intestinal metaplasia [22]. Six patients (19%) developed recurrent high-grade dysplasia and received either RFA (four patients) or argon plasma coagulation (one patient, with eradication in all treated patients. One of the six progressed to esophageal adenocarcinoma. At long-term follow-up (mean 37.8 months), complete eradication of high-grade dysplasia (counting the patients that had repeat treatment for high-grade dysplasia with subsequent eradication after treatment) was seen in 31 patients (97%), but if considering only cryotherapy, the durability of response was 81% [22]. Three patients (9%) had strictures, and no serious adverse events occurred.

Cryotherapy is a quick and overall safe minimally invasive method for endoscopic eradication of Barrett's esophagus with dysplasia, considering its ease of use and side effect profile. Most data is not long term, however, and so the overall durability remains to be seen and should be further studied.

Conclusion

Barrett's esophagus is an unfortunately common condition that carries with it a risk of malignant transformation, especially in the setting of dysplasia. Endoscopic treatments offer a minimally invasive treatment for a disease process that historically mandated esophagectomy, a procedure with significant morbidity. While technologies associated with endoscopic therapies are constantly evolving, the current most

common method of endoscopic eradication of Barrett's esophagus, radiofrequency ablation with Barrx FLEX (Medtronic, Minneapolis, MN) technology, remains the most studied therapy with durable long-term results showing eradication of dysplasia and metaplasia, along with a relatively safe side effect profile. The depth of penetration of the treatments is directly related to stricture rates. Despite the effectiveness of these procedures, ongoing surveillance is required. Antacid therapy should be continued in the form of medications, or one can consider antireflux procedures 3–6 months after the ablative therapies to prevent ongoing gastroesophageal reflux.

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Chapter 17
Endoluminal Gastroesophageal Reflux Disease Therapies

Lubomyr Boris and Sofiane El Djouzi

Introduction

Gastroesophageal reflux disease (GERD) is a potential precursor to esophageal adenocarcinoma, one of the fastest rising incidences of cancer in developed countries [1]. Other major complications of GERD include stricture and Barrett's esophagus, which lead to altered quality of life. Approximately 25% of patients living in North America are affected by GERD, leading to increased spending and substantial healthcare costs estimated around $18.1 billion annually [2]. Current first-line treatment efficacy, such as acid-suppressive medication and weight loss, has been ineffective in up to 40% of patients [3, 4]. Those patients who either fail medical therapy or lifestyle changes may wish to pursue more definitive treat-

L. Boris
Bariatric and Metabolic Surgery, Allegheny Health Medical Center, Pittsburgh, PA, USA

S. El Djouzi (✉)
Advanced Gastrointestinal and Bariatric Surgery at BariJuve Surgical, Advent Health Bolingbrook Medical Center, Bolingbrook, IL, USA
e-mail: Sofiane.eldjouzi@barijuve.com

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_17

ment such as laparoscopic or endolumenal therapies. Patients undergoing surgical intervention have consistently demonstrated symptomatic relief and durability, as noted by long-term follow-up studies. Endoluminal therapies, which will be discussed in this section, offer a wide variety of benefits, including but not exclusively minimal IV sedation, decreased pain and recovery, limited incisions, as well as offering lower perioperative patient risks.

Diagnosis and Management

The extent of the work-up is directly associated with patient symptom characteristics, age, risk factors, and alarm features. Those who have typical GERD symptoms of regurgitation and heartburn should be given a trial of proton pump inhibitors along with lifestyle modifications [5]. Lifestyle modification and medication trials are usually the first-line treatment of gastroesophageal reflux disease. Surgical management may be offered to those who fail medical therapy, have persistent or progressive symptoms, noncompliance with medication, or are unwilling to commit to long-term medication therapy [6]. In contrast, any patient over the age of 50 with atypical symptoms such as anemia, vomiting, dysphagia, weight loss, or with alarm symptoms should be evaluated with esophagogastroduodenoscopy (EGD) (Fig. 17.1). The role of EGD is to rule out any neoplastic process, strictures, Barrett's esophagus, ulcerations, infections, or GEJ defects that may be contributing to GERD. Patients who undergo EGD frequently have normal studies and adjunct studies such as barium swallow, high-resolution manometry, pH impedance, and BRAVO studies are available to further delineate any abnormalities in patients' anatomy, the functionality of the LES, and acid exposure [5].

Surgical management can be divided into either laparoscopic, open repair, or natural orifice endoluminal surgery. The principal objective of surgical intervention is to restore the anatomy in order to achieve normal lower esophageal sphincter pressure and overall shorter sphincter length [7]. Laparoscopic Nissen fundoplication is proven, effective, and

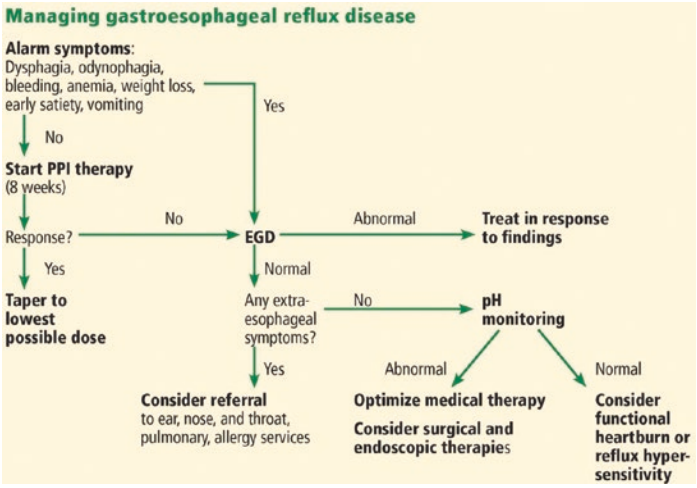

FIGURE 17.1 Practical algorithmic approach to managing patients with gastroesophageal reflux disease based on their initial symptoms, response to medical therapy, and EGD findings (Courtesy of: Young A, Kumar MA, Thota PN. GERD: A practical approach. Cleve Clin J Med. 2020 Apr;87(4):223–230)

durable. However side effects exist, including gas bloat, inability to belch, dysphagia, and inability to vomit. Natural orifice endoluminal techniques offer minimally invasive procedures for patients who are poor surgical candidates or prefer to avoid standard surgical procedures. It is associated with fewer adverse effects. However, its evaluation of efficacy and durability is still yet to be determined as research studies are currently evaluating its outcomes.

Specific Endoluminal Therapies

Several FDA-approved therapies will be discussed in this section. As of today, multiple FDA-approved GERD treatment devices are available in the USA, including EsophyX and Stretta®, both of which will be discussed at length below.

Esophyx and Transoral Incisionless Fundoplication

The EsophyX device was initially designed in 2006 to create an internal esophagogastric fundoplication by restoring the angle of His [8]. Since its inception, EsophyX (Fig. 17.2) has evolved to the EsophyX 2 and most recently EsophyX Z (Fig. 17.3). As the models improved over the years, the device became more user friendly with more consistent and reproducible results amongst different users. Figure 17.5 compares all three models. The device is introduced over a flexible

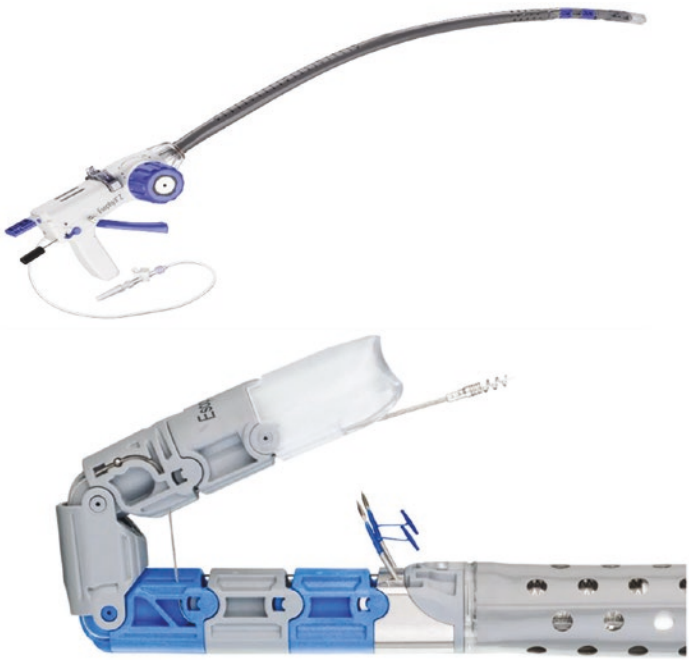

FIGURE 17.2 The EsophyX device illustrates the handle and shaft (*top*) and the distal end with tissue mold, helical retractor, tissue invaginator, and stylet with fastener (*bottom*) (courtesy of EndoGastric Solutions)

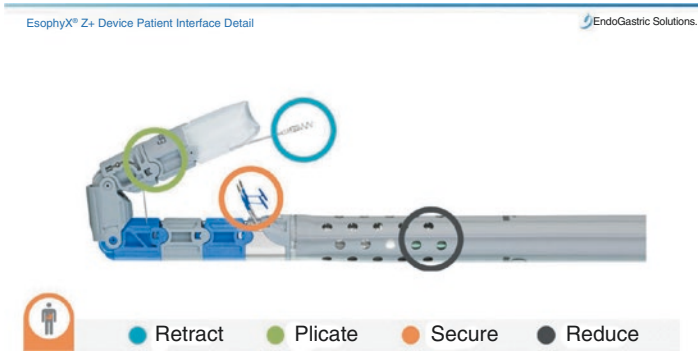

Figure 17.3 EsophyX Z+ device demonstrating the area of plication used to rotate tissue *(green)*, Helical retractor used to grasp tissue in order to create valve length *(blue)*, H-shaped polypropylene fasteners used to fire through tissue *(orange)*, and invaginator suction area of the shaft used to reduce small hiatal hernia's *(black)* (courtesy of EndoGastric Solutions)

endoscope with an over-tube with the patient under general endotracheal anesthesia. A helical screw on a cable is used to hold one tissue plane while the device's tip is folded on itself, creating tissue apposition and compression. A small "H"-shaped polypropylene suture fastener is then delivered across the apposed tissue to fix the plication. These full-thickness fasteners create a serosal fusion of the apposed tissues, and between the two legs has a length of 6.5 mm and is equivalent in strength to a 3-0 prolene suture [8] (Fig. 17.4). Providers demonstrated concern of excessive compression on the tissue which led to fastener pull-through. Thus the "H" fastener was widened to 7.5 mm, which is the current standard size used today with the EsophyX2 model. Not only did widening the fastener solve the pull-through issue, but it also improved the ease of deployment and overall delivery. The EsophyX Z device upgrades incorporated a change to the folding, which tubularized the tissue mold, streamlining the end of the device with the endoscope. This was a significant safety concern that was addressed to avoid injuring the esophagus. In addition, a separate channel for the second leg of the fastener

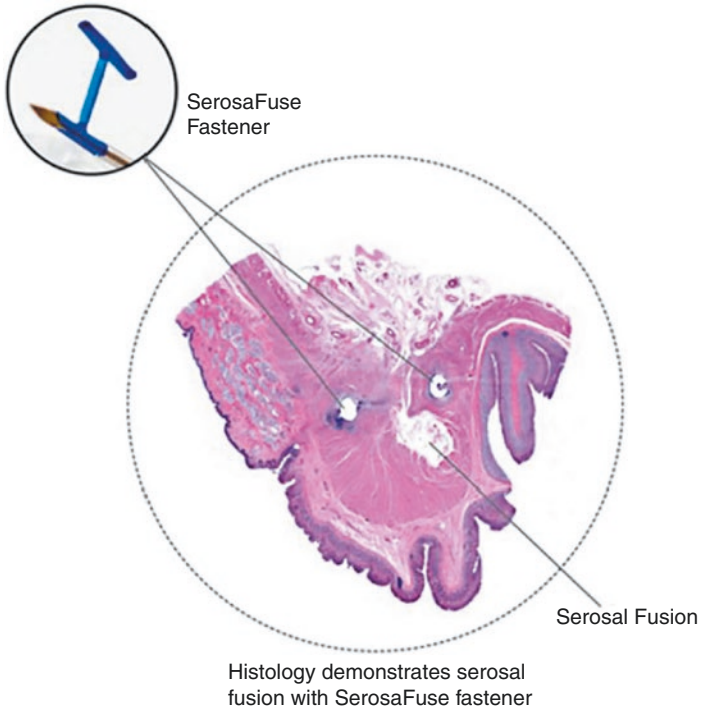

FIGURE 17.4 Porcine photomicrograph illustrating fusion of apposed serosa by the EsophyX fastener (courtesy of EndoGastric Solutions)

was created to allow for simultaneous advancement and deployment, making this automated delivery standardized and reproducible [8] (Fig. 17.5).

The EsophyX device is composed of:

1. A handle wherein the various controls are located.
2. A chassis of 18 mm diameter through which the endoscope is inserted and control channels run.
3. Side holes on the distal end of the chassis to which external suction can be applied (the tissue invaginator).
4. A tissue mold, which, when brought into retroflection, pushes tissue against the shaft of the device.

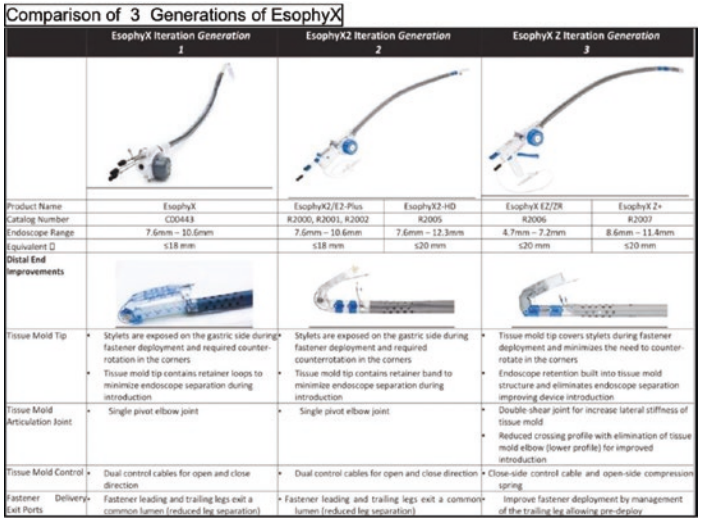

Figure 17.5 Comparison of 3 generations of EsophyX. EsophyX Generation 1 *(far left)* demonstrating the endoscope range, tissue mold tip and articulation joint as well as its control and delivery. EsophyX2 *(middle)* demonstrating wider endoscope range compared to the first generation, with similar mold tip, articulation joint as well as mold control and delivery as the first generation. EsophyX Z *(far right)* demonstrating its endoscope range as low as 4.7 mm, as well as double shear joint for increased lateral stiffness and improved scope introduction due to lower profile, and improved fastener deployment (courtesy of Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol. 2020 May 21;13:1756284820924206)

5. A helical screw is advanced into the tissue to pull tissue caudally between the tissue mold and the shaft.
6. Two stylets, which advance from the shaft of the device through the plicated tissue and then through eyelets in the tissue mold.
7. A cartridge containing polypropylene H-shaped fasteners (or plicators), which are deployed over the stylets so that the trailing leg engages within the esophageal lumen and the leading leg engages within the gastric lumen.

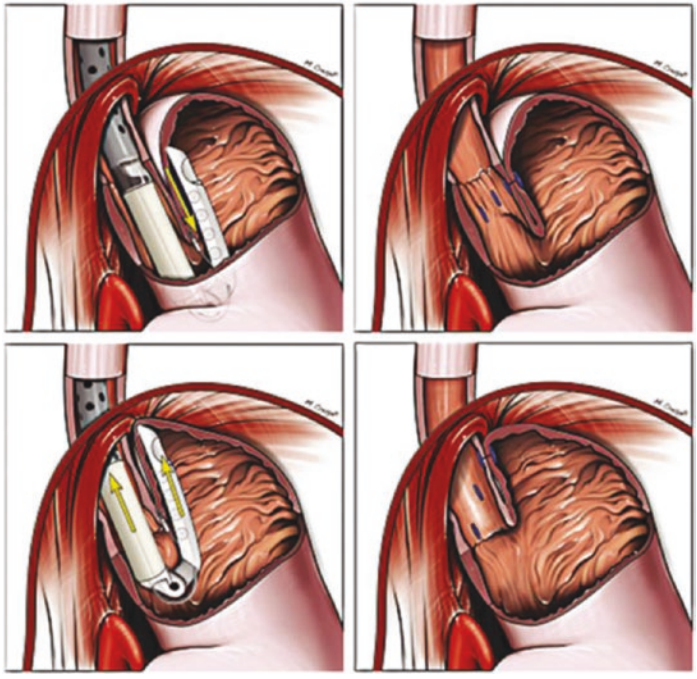

Figure 17.6 Illustration of use of EsophyX device create gastrogastric plication (*top*) or esophagogastric plication (*bottom*) (artist: Massimilano Crespi, info@max-medicalillustrator.com)

Multiple fasteners can be deployed in a circumferential fashion to create either a gastrogastric (original technique) or an esophagogastric (current technique) plication (Fig. 17.6). A rotational element was also developed to fold tissue around the esophagus. The techniques have been described in detail by Jobe [9] and Bell [10]. The TIF 2 is the procedure most commonly performed today using the EsophyX device. The final construct has an endoscopic appearance similar to a surgical fundoplication (Fig. 17.7).

Canine studies of a gastrogastric plication created with the EsophyX device demonstrated an increase in lower esophageal sphincter length and pressure, primarily due to pressure

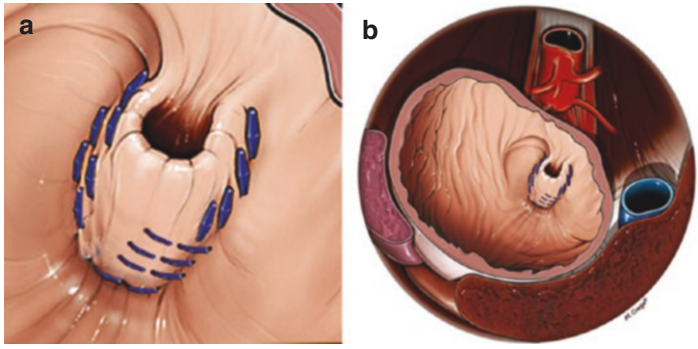

FIGURE 17.7 Completed TIF esophagogastric fundoplication with external structures in both panel **a** (zoomed in) and panel **b** (artist: Massimilano Crespi, info@max-medicalillustrator.com)

augmentation at the lower end of the LES. The TIF 2 esophagogastric plication resulted in a valve with sphincter vector–volume characteristics similar to a Nissen procedure [9]. Human studies using endoluminal functional imaging and impedance have demonstrated a decrease in EG junction distensibility immediately after the procedure and decreased liquid and mixed TLESR-related reflux events at six months post-TIF (16.8 ± 1.5 vs. 9.2 ± 1.3; $p < 0.01$). TIF also led to a decrease in the number and proximal extent of reflux episodes and improved acid exposure in the upright position [11]. The mechanism by which the TIF procedure keeps a hiatal hernia reduced has not been thoroughly investigated. Canine studies found that the TIF 2 procedure "captured" a loose phrenoesophageal membrane within the plication. In some cases, bulking the GE valve, or capturing the PE membrane at the edge of the hiatus during fastener delivery, may have a role in keeping the hiatal hernia reduced.

Similar criteria to other endoluminal therapies have been used for the TIF procedure. Patients with symptomatic GERD who have Hill grades I-II, hiatal hernia <2 cm, and those refusing medical therapy or surgery, are candidates for TIF as a safe and effective therapeutic option [12]. Contraindications have been severe esophagitis, Barrett's, gastroparesis, a hiatal her-

nia of >2 cm, and BMI >35. Additionally, a transverse hiatal dimension of >3 cm may be a limiting factor as the patient likely will require a crural closure [10]. Patients undergoing the TIF procedure should undergo the same preoperative objective documentation of GERD as a patient undergoing a laparoscopic fundoplication.

The TIF procedure is performed under general endotracheal anesthesia. Medication to decrease postoperative nausea, a proton pump inhibitor, and antibiotics are administered preoperatively. Proton pump inhibitors are continued postoperatively for two weeks to aid in healing the gastric portion of the plication. Before device introduction, endoscopic evaluation of the hiatus for hernia dimensions and measurement of the distance to the diaphragm is performed. The endoscope is placed through the EsophyX device and introduced into the esophagus, and then both are advanced carefully, especially as the elbow of the device passes through the cricopharyngeus. The device is visualized entering the stomach, and then the endoscope is pulled back and reintroduced so that it is outside the tissue mold. The tissue mold is retroflexed under direct visualization as the spleen lies outside the stomach on the greater curve.

With both the tissue mold and the endoscope in a retroflexed position, the helical retractor is engaged at the gastroesophageal junction (generally the Z-line) at the posterior corner of the anticipated fundoplication position. The tissue mold is partially opened and rotated out of this corner. The device is then pulled back (cranially) a predetermined amount, generally 1–3 cm. The tissue mold is then rotated back into the corner while tension is applied to the helical retractor and the stomach is desufflated. With the fundus so rotated, the tissue mold is closed and locked in place, the helix is locked, and the tissue invaginator is placed on suction. This set of maneuvers accomplishes the following: withdrawing the device moves the set point for the emergence of the stylets cranial to the GE junction so that an esophagogastric plication is created; rotation of the tissue mold with the device at this set distance then rotates the fundus around the

esophagus; tension on the helical retractor pulls the GE junction slightly caudally and stabilizes the tissue; desufflation of the stomach enables rotation of the gastric fundus.

With the tissue in position, the position of the plication in relation to the diaphragm is assessed so that the stylets and fasteners will not traverse the diaphragm. Understanding anatomic relations, palpating the diaphragm with the tissue mold before tissue positioning, and ensuring that the device is introduced beyond the depth of the diaphragm (as previously measured to the incisors) are essential. Advancing the device caudally with the tissue invaginator on suction enables caudal advancement of gastroesophageal junction below the diaphragm without displacing the device in relation to the esophagogastric junction. Concurrent laparoscopic visualization in humans has confirmed that 2–3 cm of additional separation between the esophagus and diaphragm can be obtained with this maneuver.

The stylet furthest away from the corner is advanced until visible beyond the tissue mold (e.g., the anterior stylet when in the rear corner). At times, counterrotation of the device is needed to reduce tension on the tissue mold aligning it with the stylet course. With stylet in view, the fastener is advanced gradually, allowing the trailing leg of the fastener to deploy within the esophageal lumen and the leading leg to deploy within the gastric lumen, creating a full-thickness "H" fixation. The fastener closest to the corner is then deployed, leaving two fasteners at the same depth, a "plication set." The device is reloaded, the tissue mold and helix unlocked, the tissue invaginator taken off suction, and the procedure repeated at a different location.

The precise positions of the plication sets are a matter of surgical judgment. The initial TIF 2 technique involved creating two plication sets 1 cm deep at the anterior and posterior corners (towards the lesser curve). Two plications were set 3 cm deep along the greater curve, with a helical deployment at each location with mild degrees of rotation. The evolution of the technique has included increasing the number of plication sets from 6 to 10 or more, decreasing the number of heli-

cal deployments, and increasing the rotational component compared with the longitudinal movement.

Once the fundoplication has been created, the tissue mold is straightened under direct vision, and the device is withdrawn. Positioning the endoscope at the very end of the chassis during final withdrawal enables careful inspection of the esophageal lumen during the retreat. A final endoscopy without the device is performed to evaluate for bleeding and to assess the final result. In a retrospective review in 2011, data suggested that TIF 2.0 may be improved if hiatal hernia repair was performed just prior to the fundoplication. In patients who had undergone TIF 2.0, at 6 months follow-up, endoscopy demonstrated a significantly dilated hiatus, thus bringing up the concern for symptom recurrence. Table 17.1 shows superiority in patient symptom score in the post-TIF with crural repair vs. TIF alone [8].

Table 17.1 Demonstrates comparison between patients who underwent TIF and those who underwent TIF with crural closure. Their respective follow-up GERD quality of life scores, reflux symptoms scores, reflux symptom index scores, regurgitation and satisfaction were compared (courtesy of Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol)

Table 17.1 TIF 2.0 *versus* TIF 2.0 w/CC$_{\text{(median scores)}}$

Post TIF		**Post TIF w/CC**	
• GERD-HRQL	5	• GERD-HRQL	3
• RSI	5	• RSI	4
• GERSS	6	• GERSS	1
• Regurgitation	5	• Regurgitation	0
• Satisfaction	50%	• Satisfaction	83%

$p < 0.001$ for all changes

CC, crural closure; GERD, gastroesophageal reflux disease; GERSS, gastrocsophageal reflux symptom score; HRQL, health-related quality of life; RSI, reflux symptom index; TIF, transoral incisionless fundoplication

Most patients stay overnight to help with pain and nausea management and are discharged from the hospital the following day. A soft diet is prescribed as postoperative edema narrows the esophageal lumen. Regular diet will resume over the next couple of weeks. Direct procedure-related complications have been bleeding and infection. Bleeding during the advancement of a stylet will generally stop with fastener deployment. Pneumoperitoneum may be seen after TIF and in and of itself does not indicate a clinically significant complication. Full-thickness injury to the esophageal or gastric wall has been reported after the TIF procedure, generally developing a few days afterward. This is likely due to fasteners pulling through the wall of the viscera from excess tension, retching, or vomiting. Abdominal or mediastinal infection can result. Laparoscopy with mediastinal drainage and removal of offending fasteners has been performed successfully. Procedural technique predicated upon understanding external anatomic relations decreases the potential for these complications.

Major procedure-related complications were seen in 2.4% of 635 patients in the reported series, including perforation (0.7%) or bleeding requiring transfusion (1%). Technique modification to ensure that stylet and fastener deployment occurs below the diaphragm has reduced the perforation rate, and recent series have reported no perforations in 160 patients [13–15]. As of July 2019, a review of the safety data reveals a markedly lower SAE rate of 0.41% when compared to laparoscopic fundoplication out of a total of 22,000 procedures. Figure 17.8 demonstrates the events by type.

Multiple single-arm clinical studies have been published with 6–36-month follow-ups. A meta-analysis of 15 studies published through 2012 found that GERD-HRQL scores (21.9 vs. 5.9) and Reflux Symptom Index (RSI) scores (24.5 vs. 5.4) were significantly reduced after TIF ($p \leq 0.0001$). PPI discontinuation was 67% across all studies, with a mean follow-up of 8.3 months [16]. Recent long-term data on patients who were followed for ten years after TIF demonstrated a high rate of cessation or decrease in antisecretory medical

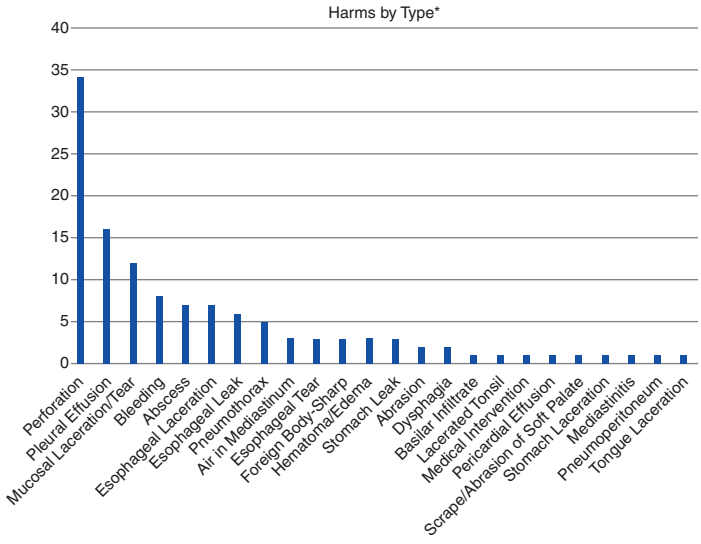

Figure 17.8 Figure demonstrating predominance of complication events from TIF. Perforation on the far left is the most predominant complication followed by pleural effusion, mucosal laceration or tear, bleeding, abscess, leak, and pneumothorax as most common (courtesy of Ihde GM. The evolution of TIF: transoral incisionless fundoplication. Therap Adv Gastroenterol)

therapy at 2 (86.7%), 3 (84.4%), 5 (73.5%), 7 (83.3%), and 10 (91.7%) years after the procedure [12].

Regurgitation symptoms respond very well to TIF. In a recent study of 63 patients at 6-month follow-up, troublesome regurgitation was eliminated in 97% of TIF patients vs. 50% of PPI patients, relative risk (RR) = 1.9, 95% confidence interval (CI) = 1.2–3.11 (p = 0.006) [17]. Patients with a history of esophagitis grade A and B, proven GERD on pH monitoring, and with typical symptoms of GERD underwent TIF using Esophyx demonstrating promising results. The specific symptoms of heartburn, regurgitation, and chest pain were eliminated in 57.1%, 88.2%, and 83.3%, respectively, at a median follow-up of 59 months [18].

A single sham-controlled study of the TIF 2 technique has been reported. Patients were assigned to groups that underwent TIF and then received 6 months of placebo ($n = 87$) or sham surgery (endoscopy and dilation for 45 min under general anesthesia) and six months of once or twice-daily omeprazole (controls, $n = 42$). Patients were blinded to therapy and reassessed at 2, 12, and 26 weeks. At six months, patients underwent 48-h esophageal pH monitoring and esophagogastroduodenoscopy. By intention-to-treat analysis, TF eliminated troublesome regurgitation in a larger proportion of patients (67%) than PPIs (45%) ($p = 0.023$). Control of esophageal pH improved following TF (mean 9.3% before and 6.3% after, $p < 0.001$), but not after sham surgery (mean 8.6% before and 8.9% after). Subjects from both groups who completed the protocol had similar reductions in GERD symptom scores. Severe complications were rare (3 subjects receiving TF and 1 receiving the sham surgery) [19].

Several studies of esophageal pH alterations after the TIF 2 technique have demonstrated statistically significant improvement in esophageal acid exposure measured by DeMeester score, % time pH less than 4, and a number of reflux episodes [20, 21], though some have not [9]. A recent open-label RCT comparing PPI treatment with TF demonstrated benefit for TF over PPI in control of troublesome GERD symptoms, with 54% of patients achieving normalization of intra-esophageal pH off PPI following TF [17]. A study of 15 patients before and six months after having TIF demonstrated a reduced number of postprandial TLESRs (16.8 ± 1.5 vs. 9.2 ± 1.3; $p < 0.01$) and the number of postprandial TLESRs associated with reflux (11.1 ± 1.6 vs. 5.6 ± 0.6; $p < 0.01$), but the proportion of TLESRs associated with reflux was unaltered (67.6 ± 6.9 vs. $69.9 \pm 6.3\%$). TIF also led to a decrease in the number and proximal extent of reflux episodes and improved acid exposure in the upright position. TIF did not affect gas reflux, which may be why TIF has not been associated with increased gas-related symptoms [11].

In a retrospective review by Ihde et al., where the investigators reviewed pH scores in hiatal hernia repair combined

with TIF demonstrated improvement in the mean pH score from 35.3 (SD, 2.27) to 10.9 (SD, 11.5), $p < .001$ with short-term follow-up data [22]. However, when comparing only TIF to PPI in a randomized controlled trial over 12 months, despite the improved quality of life in the TIF group, there was no improvement in esophageal acid exposure compared to baseline ($p = 0.171$) [23]. Normal pH levels were only accomplished in 29% of the population in the TIF group, with 61% having to restart the PPI's. More long-term studies and objective data are needed to evaluate TIF without any adjuncts further.

Only a few studies have reported longer-term follow-up. Two-year results of a US Multicenter study found that GERD health-related quality of life and regurgitation scores improved by ≥50% in 63 of 96 (66%) and 62 of 88 (70%) of patients who had elevated preoperative scores. The RSI score normalized in 53 of 82 (65%) patients. Daily PPI use decreased from 91 to 30% [24]. Muls reported a 3-year follow-up on 66 of 79 initial patients. GERD- HRQL improved to 4 (0–32) from 25 (13–38) off PPI, 9 (0–22) on PPI before TIF. By modified intention to treat, 61% of patients remained off daily PPIs (unpublished report, in review, by Testoni, 50 patients, 84% off or halved PPI therapy at 3 and 6 years post-TIF).

The TEMPO trial demonstrated TIF 2.0 durability, safety, and clinical outcomes evaluated at five years. Patients with chronic GERD and refractory to PPI with small or absent hiatal hernia and abnormal acid exposure were randomized to TIF or PPI groups. Resolution and elimination of regurgitation at 1, 3, and 5 years were 88%, 90%, and 86%, respectively, without any significant adverse events, concluding the safety and sustainability of providing long-term symptomatic relief in this cohort of patients [25].

Some patients seem to derive no benefit after a TIF procedure. Edema in the distal esophagus persists for some weeks after the TIF procedure, and some patients have a recurrence of their symptoms after this edema resolves. These are probably initial technical failures. The TIF procedure is technically

more demanding than other endoluminal GERD procedures; technique may play a role in these early failures.

Postoperative retching or coughing has been associated with disruption of the TIF fundoplication. Unrecognized or developing hiatal hernia may be the leading reason for technical failure of the TIF procedure, and studies have shown that any hernia is associated with a lower success rate than no hernia [13].

Two European studies have reported on 26 patients having laparoscopic fundoplication for recurrent reflux after TIF [26, 27] with complications of infection (2 patients). Although objective parameters improved, quality of life did not, and dysphagia was noted to be a problem. Two US studies [24, 28] reported on 33 patients having a laparoscopic revision of prior TIF. There were no perforations, and short-term follow-up indicated the improved quality of life and no issue with dysphagia. Long-term outcome has not been reported.

Ten to twenty percent of laparoscopic fundoplication failures are due to loosening of the fundoplication alone, without any evidence of hiatal failure. Results of utilizing the TIF procedure in 11 patients with failed laparoscopic fundoplication demonstrated resolution of primary symptom in 8 of 10 patients at a median 14-month follow-up, and reduction in esophageal acid exposure from 8.1% (21–4.8%) to 0.6% (13.4–0.01%) ($p = 0.008$) [29].

Compared to laparoscopic Nissen Fundoplication, a direct comparison of TIF was performed in a systematic review and meta-analysis of randomized control trials by Richter et al. in patients with GERD. Seven studies with compiled 1128 patients were analyzed for quality of life and physiologic parameters. Although TIF demonstrated the highest probability of increasing patients' health-related quality of life (0.96), compared to LNF (0.66), sham procedures (0.35), and PPIs (0.042), however, in terms of physiologic parameters, laparoscopic Nissen Fundoplication had the highest probability of decreasing percent time at pH <4 (0.99) and increased LES pressure (0.78) when compared to TIF (0.32) and (0.72) respectively [30].

In Summary, transoral incisionless fundoplication creates a valve that resembles a laparoscopic fundoplication endoscopically without restricting the ability to belch and vomit. Gas bloat has been a rare event. Clinical success at normalizing GERD quality of life and decreasing dependence on daily PPIs has been seen in 65–80% of patients, and this effect persists up to 3 years and beyond. Most esophageal pH studies have demonstrated improvement in esophageal acid exposure after TIF, with normalization of pH in about 50% of patients.

TIF has been demonstrated to be an effective option in patients with Hill grades I-II, small hiatal hernia <2 cm, or in those who do not wish to be on lifelong medical therapy and do not wish to undergo surgery [12]. Patients were able to significantly decrease or discontinue their medical treatment up to 10 years after the procedure.

Although TIF has produced the most significant increase in health-related quality of life in a systematic review meta-analysis in a study by Richter et al., it has yet to replace Laparoscopic Nissen Fundoplication as a long-term alternative treatment of GERD. Further studies need to be performed to evaluate the device further [30].

Stretta® Radiofrequency Treatment of the Gastroesophageal Junction

Introduction

Non-ablative radiofrequency (RF) treatment of the GE junction can be performed with an endoluminal catheter with an inflatable and flexible balloon- basket with four needle electrode sheaths [31] (Fig. 17.9). The electrodes are introduced into the esophageal wall in the LES region, and RF energy at 465 kHz is delivered to the electrodes. Cellular heating results in tissue remodeling. A thermocouple on the electrode enables control of the power delivered to reach but not exceed 50 °C. Irrigation of the overlying mucosa minimizes heat injury to the esophageal lining (Fig. 17.10) [32].

FIGURE 17.9 The Stretta® device illustrating the handle, catheter with balloon, and extruded radiofrequency needle (courtesy of Mederi Therapeutics)

Figure 17.10 The Stretta® device, illustrates the balloon in place, subsequent areas of ablation (*circles*), and proposed thickening of lower esophageal sphincter tissues (courtesy of Mederi Therapeutics)

Mechanism of Action

Radiofrequency energy produced by the Stretta® device induces collagen contraction in animal and human tissue. Animal models show that Stretta results in thickening of the LES decreased transient LES relaxations (TLESRs) and subsequent decrease in reflux events. Human studies have shown decreased gastric distention-induced TLESRs (3.5/h pretreatment vs. 1/h posttreatment) [33]. A double-blind, sham-controlled study showed that sildenafil, a smooth muscle relaxant, normalized GE junction compliance to pre-Stretta levels; the authors believe that this argues against fibrosis being a mechanism of action of Stretta® [13]. Esophageal motility studies after Stretta have not shown a consistent change in resting LES pressure, nor LES relaxation, compared to pretreatment parameters. Animal studies of RF energy applied to the intestine demonstrate an increase in smooth muscle fiber size, with more muscle fibers per muscle bundle that result in the lengthening and thickening of the sphincter [34].

Patient Selection

Clinical studies have excluded patients with a hiatal hernia of >2 cm, severe esophagitis (Grade C or D) despite medical therapy, and Barrett's esophagus. Patients with medically

responsive but refractory GERD have comprised the bulk of study subjects. Patients undergoing the Stretta® procedure should undergo the same preoperative objective evaluation as patients undergoing a laparoscopic fundoplication.

Stretta® Technique

Under deep sedation, endoscopy confirms eligibility criteria and measures the position of the squamocolumnar junction. A guidewire is introduced, the endoscope is withdrawn, and the RF delivery catheter is introduced orally over a guidewire. The balloon is inflated to 2.5 psi starting 2 cm proximal to the squamocolumnar junction, and the electrode needles (22 gauge, 5.5 mm length) are deployed into the esophageal wall. RF energy is delivered from a device-specific energy source from 60 to 90 s to reach a target temperature of 50 °C. The needles are pulled back, the balloon is deflated, the catheter is rotated 45°, and the procedure is repeated. This sequence is repeated serially every 0.5 cm to cover an area 2 cm above and 1.5 cm below the squamocolumnar junction. An average of 22 sets of needle deployments with RF energy delivery is performed. Additional sets are deployed below the cardia. During the procedure, the mucosa is cooled with water irrigation to prevent injury to the mucosa. The procedure takes 30–40 min to perform. Following the procedure, chest pain is relatively common, and patients are treated with analgesics as needed. Stretta is typically performed as a same-day procedure.

Complications and Safety

Temporary gastroparesis and erosive esophagitis have been the most commonly reported SAEs [35]. Double-dose Stretta® was associated with gastroparesis in 2 of 12 patients [36]. Stretta is performed under intravenous sedation, obviating the need for general anesthesia. Published reports of the

Stretta procedure indicate only mild complications, including minor GI bleeding, aspiration pneumonia, fever, leukocytosis, sedation-associated hypotension, or superficial mucosal injury. Immediate complications have been few and occurred primarily early in the overall learning curve for the device. There have been no reports of death, esophageal perforation, or other serious adverse events in these trials except for several patients who developed transient gastroparesis or esophagitis. Modifications to the Stretta® device employed in the current Mederi device, including more sensitive temperature regulation and prong redesign, have further increased the safety profile [37].

Clinical Results

Numerous studies show that patients treated with Stretta® have a significant improvement in quality of life. In the meta-analysis by Perry, 18 studies containing 1441 patients evaluated the effect of treatment on patient quality of life (QOL). The Velanovich GERD- HRQL scale was measured in 433 patients (9 studies) with an average follow-up interval of 19.8 months. The QOL scores improved from 26.11 ± 27.2 at baseline to 9.25 ± 23.7 after treatment ($p = 0.0001$). QOLRAD scores were collected from four studies comprising 250 patients and improved from 3.3 ± 5.9 to 4.97 ± 4.9 at a mean follow-up interval of 25.2 months ($p = 0.001$). SF-36 was utilized to assess the global QOL of the patient population in six studies. The SF-36 physical form evaluated in 299 patients with a mean follow-up period of 9.5 months demonstrated an improvement from 36.45 ± 51.6 at baseline to 46.12 ± 61.9 after the procedure ($p = 0.0001$). The SF-36 mental form was included in 5 of the six studies and 264 patients, with an improvement from 46.79 ± 20.5 to 55.16 ± 17.6 at 10-month follow-up ($p = 0.0015$) [35].

Stretta® has been compared to proton pump inhibitors in patients with non-erosive reflux disease with a six-month follow-up. Both groups demonstrated improved symptoms

and quality of life through the RDQ and SF-36 score, respectively; however, the Stretta® group revealed a statistically significant improvement in the RDQ score at six months follow-up compared to the PPI group alone [38]. At this time, the recommendation is that the Stretta® procedure is effective for patients with non-erosive reflux disease (NERD) [39].

Three sham-controlled studies of Stretta® have been published [36, 40, 41]. Objective data was variable. There was a statistically significant improvement in medication use, GERD-HRQL, and satisfaction scores in treatment groups but not sham procedure groups. At crossover, similar improvements occurred in the sham patients. No sham group patient was able to discontinue medical therapy, while 50–56% of treated patients had discontinued PPI therapy at one year in two of the three studies.

Stretta® has been compared to Laparoscopic repair with Toupet Fundoplication in a specific cohort of GERD patients with extra-esophageal symptoms, including pneumonia, bronchitis, asthma, and extra-esophageal symptoms globus, and chronic cough with three years of follow-up data. There was no significant difference regarding discontinuation of PPI as both groups achieved significant PPI independence (61.7% vs. 64.7%, $p = 0.835$). Despite the promising results demonstrating safety with Stretta®, effective GERD control of extra-esophageal symptoms, and reducing PPI use following a 3-year prospective study, patients in the laparoscopic repair group achieved better improvement in symptoms with higher patient satisfaction [42].

A recent report by Dughera et al. reported on 26 patients who had completed 4- and 8-year follow-up after Stretta® [43]. GERD-HRQL scores were significantly improved than baseline at both 4 and 8 years, as were QOL scores. At four years, 21 (80.7%) of patients and at eight years, 20 patients (76.9%) were entirely off PPIs. Interestingly, mean esophageal acid exposure was improved at four years but returned to baseline values at eight years. A second report by Noar et al. of 99 patients completing a 10-year follow-up (217

patients in the initial cohort) found that peak improvement in GERD-HRQL, patient satisfaction, and medication use occurred two years after Stretta. That significant improvement compared to baseline continued out to 10 years [44]. All patients were on double-dose PPI therapy before Stretta®; at ten years, 64% sustained at least a 50% reduction in PPI use, and 41% of patients remained off PPIs altogether. These results are echoed in the Stretta vs. PPI study by Suyu, Fei, et al., which demonstrated a statistically significant number of patients who were successfully weaned off PPI (60%) in a short time period six month follow-up [38].

Although few studies evaluating esophageal function by manometry have demonstrated no significant change in LES resting and nadir pressure and no change in esophageal body peristalsis in the past [33]. In the recent study by Suyu, Fei, et al., as mentioned earlier, the Stretta® group was able to demonstrate statistically significant higher LES resting pressure on six months follow-up when compared to the proton pump inhibitor group (14.2 ± 4.4 mm Hg vs. 10.1 ± 4.1 mm Hg, p = .002) [38].

The Stretta® procedure appears to decrease distal esophageal acid exposure. In the abovementioned meta-analysis by Perry and colleagues [35], seven studies with 267 patients reported DeMeester scores before Stretta® and at a mean of 13.1-month follow-up. The DeMeester score improved from 44.37 ± 93 before the procedure to 28.53 ± 33.4 post-procedure (p = 0.0074). Eleven studies comprising 364 patients demonstrated improvement in percent time esophageal acid exposure from 10.3 ± 17.8% to 6.5 ± 12.5% at a mean of 11.9-month follow-up (p = 0.0003). The improvement in pH at 1-year follow-up appeared to be better than the improvement reported at six months in other studies. The significance of improvement in pH control with time is not clear.

Some patients have undergone repeat Stretta® procedure after an initial failure or after a recurrence of symptoms, with some marginal benefit. Rates of conversion to laparoscopic

fundoplication lack in most published reports, but technically the conversion has been straightforward.

Safety and efficacy of Stretta® device have been studied in patients who previously underwent sleeve-gastrectomy with 6 months of follow-up data by Khidir et al. The data demonstrated that only 20% of patients were able to discontinue the PPI and that 66.7% of patients were not satisfied based on the HR-QoL questionnaire [45].

Although the mechanism by which RFA to the lower esophagus and cardia improves GERD symptoms is still not clear, studies indicate that postulated mechanisms such as fibrosis or sensory denervation probably are not the major mechanism. Reduction in TLESRs appears to have the most support [37]. Heartburn, daily PPI use, and standardized quality of life questionnaires have seen improvement following Stretta® in most studies, and 8–10 years' data indicate durable success at symptom control in the range of 40%. Objective data (esophageal acid exposure and lower esophageal sphincter measurements) have been conflicting. However, meta-analysis indicates that esophageal acid exposure does decrease in many patients after the procedure, and LES resting pressures are significantly elevated in the short-term follow-up [38]. The safety profile of Stretta® in its current configuration and use is excellent.

The Future of Endolumenal GERD Therapies

GERD is a chronic and progressive disease manifested primarily by symptoms that affect the quality of life. Strategies for treating chronic disease often involve management over cure. In this context, managing a GERD patient's quality of life may include multimodality therapy, including altering a medical treatment or repeating interventions. The need for reintervention with cardiac stents, or repeat arthroscopies, is not so much a failure of technique as it is the nature of a chronic illness. In this light, the ability of the endolumenal

procedures to normalize GERD-HRQL in patients with PPI-refractory symptoms, do so with minimal side effects, and achieve >65% elimination of PPI therapy in the process, is a significant success.

An increasing body of evidence exists that endoluminal therapies effectively manage GERD-related symptoms in patients who have incomplete control with medical treatment. Efficacy is in the 65–75% range and appears durable up to 3 years and beyond. The option of endoluminal therapy should be provided to patients with symptomatic medically refractory GERD or those wishing to reduce or eliminate dependence on intrusive lifestyle modification or medication. In light of increasing recognition that PPI therapy is effective at symptom control in only 60–80% of patients, endoluminal therapies have demonstrated similar efficacy and should be considered a maintenance option for patients wishing to decrease or eliminate dependence on PPIs.

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Chapter 18
Endomucosal Resection of the Upper GI Tract

Steven D. Scoville, Sara Mansfield, and Sabrena F. Noria

Abbreviations

BE	Barrett esophagus
EGC	Early gastric cancers
EMR	Endoscopic mucosal resection
EUS	Endoscopic ultrasound
FAP	Familial adenomatous polyposis
GERD	Gastroesophageal reflux disease

S. D. Scoville
The Ohio State University, Wexner Medical Center, Department of Surgery, Columbus, OH, USA
e-mail: Steven.scoville@osumc.edu

S. Mansfield
The Ohio State University, Wexner Medical Center, Department of Surgery, Division of Pediatric Surgery, Columbus, OH, USA
e-mail: sara.mansfield@nationwidechildrens.org

S. F. Noria (✉)
The Ohio State University, Wexner Medical Center, Department of Surgery, Division of General & Gastrointestinal Surgery, Columbus, OH, USA
e-mail: Sabrena.noria@osumc.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_18

HGD	High-grade dysplasia
IMC	Intramucosal carcinoma
LGD	Low-grade dysplasia
SDA	Sporadic duodenal adenomas

Esophagus

Over the last 20 years, the incidence of adenocarcinoma of the esophagus has substantially increased [1]. This can be attributed to the increased rates of gastroesophageal reflux disease (GERD), which leads to an inflammatory condition of the distal esophagus [2]. Cigarette smoking, obesity, GERD, and low fruit and vegetable consumption all increase the risk of esophageal adenocarcinoma, with a combined population attributable risk of 78.7% [3].

The underlying mechanism of action of the preceding risk factors is longstanding exposure of the esophagus to gastric acid. This acidic environment can lead to metaplastic changes of the normal squamous epithelium to columnar-lined epithelium containing goblet cells (intestinal metaplasia), otherwise known as Barrett's esophagus (BE,) and is estimated at 1.6% prevalence in the general population [4, 5]. BE is the only known pre-malignant condition that can sequentially progress to low-grade dysplasia (LGD), high-grade dysplasia (HGD), intramucosal carcinoma (IMC), and advanced esophageal adenocarcinoma (EAC). Progression of BE to EAC has been estimated at 0.6% to 2.7% per patient year [6–8]. Therefore, in an effort to catch the early-stage disease and reduce disease progression, patients with BE are recommended to undergo surveillance endoscopy with multiple biopsies of the diseased tissue every 2–3 years.

Classically, EAC has been treated with esophagectomy, chemotherapy, or a combination of these two, depending on staging. Despite advances from open to minimally invasive techniques, and even in chemotherapy regimens, 5-year survival remains <20% [9]. Furthermore, surgical resection car-

ries a 6–10% perioperative mortality and up to 20–50% morbidity rate. Although surgery can be curative in the setting of early -stage EAC, functional outcomes related to upper gut function, remain less than ideal due to esophageal dysmotility. As such, esophageal-sparing procedures have become attractive options for those with HGD or intramucosal (T1) esophageal malignancies. These techniques aim to eliminate dysplastic areas before the malignant transformation. One such technique is endoscopic mucosal resection (EMR) through which focal areas of concern can be resected while preserving esophageal function and structure. With this, EMR may provide a potential cure for early esophageal cancer through endoscopic resection of suspicious lesions otherwise managed through esophagectomy.

Stomach

The incidence of gastric cancer has decreased substantially over the last 50 years, likely due to changes in food preparation and storage. However, it remains the most common cancer diagnosed in most Asian countries [10]. Diet remains the main risk factor for gastric cancer. A high intake of salted, smoked, cured, or pickled foods increases the risk , while high consumption of fruits and vegetables lowers the risk [11]. Smoking, genetic factors, and blood type A are also implicated [12].

Population-based screenings in Japan have led to earlier detection, with nearly 50% of gastric cancers being diagnosed as early -stage diseases [13]. Gastrectomy with lymph node dissection had been the gold standard treatment for all patients with operable gastric cancer, including early T1 lesions. This policy of radical surgery carries significant risks of morbidity and mortality and can be associated with a long-term reduction in patients' quality of life [14]. EMR has become the cornerstone of treatment in early gastric cancers in Asian countries, with most outcome trials coming from

Japanese medical centers [15]. Unfortunately, given the lack of formalized screening, late presentation still predominates in western countries [16].

Duodenum

Duodenal polyps or tumors are found in reportedly less than 1–5% of all upper endoscopies [17] and are comprised of lipomas, gastrointestinal stromal tumors (GIST), carcinoids, and adenomas or hamartomas. Duodenal adenomas account for approximately 25% of benign neoplasms of the small bowel and can occur as part of a familial polyposis syndrome such as familial adenomatous polyposis (FAP) or as sporadic duodenal adenomas (SDAs) [18]. Given the rarity of FAP, the majority of duodenal adenomas found at endoscopy are of the sporadic type. Duodenal adenomas have the potential for malignant transformation, with estimated progression rates ranging from approximately 4% with small, low-grade dysplasia to 54% with high-grade dysplasia [19]. Traditionally SDAs have been treated with radical surgical excision, most commonly the Whipple procedure. However, the mortality (<5%) and morbidity (37–41%) rates remain high for surgical resection [20]. Endoscopic resection of duodenal lesions is technically challenging given the small space, sharp curve, and thin wall of the duodenum [21]. Combined with the fact that duodenal adenomas are a rare entity, there is little data in the literature regarding safety and efficacy [22].

Other lesions, such as carcinoid tumors, may also arise in the duodenum, albeit at lower rates than gastric and rectal carcinoids. In general, carcinoid tumors of the GI tract that are limited to the submucosal layer and small in size (<10 mm) demonstrate a low frequency of lymph node metastasis and are good candidates for endoscopic resection. Although there are no formal recommendations, endoscopic resection appears to be safe and effective for these lesions in early studies [23].

Patient Selection and Pre-operative Considerations

As with all invasive procedures, a pre-procedure history, and physical exam is required to elucidate cardiac and respiratory risk factors. Conscious sedation or monitored anesthesia care is necessary for complex endoscopic resections. Patients at risk for aspiration should be considered for general endotracheal anesthesia [24].

Workup for the preceding pathologies requires a systematic approach to defining the depth of invasion and ruling out metastatic disease (Tables 18.1 and 18.2). Lesions amenable to EMR are typically limited to superficial pre-malignant and malignant lesions, such as in the case of high-grade dysplasia in BE and T1N0 intramucosal carcinoma for esophageal lesions (Fig. 18.1). Therefore, having accurate pre-procedural workup is essential to differentiating lesions amenable to

Table 18.1 Esophageal cancer work-up

H&P
Upper GI endoscopy and biopsy
CT of chest/abdomen
PET-CT if no evidence of M1 disease
EUS if no evidence of M1 disease
EMR considered if:
Lesion <2 cm
Well or moderate differentiation
No invasion beyond muscularis mucosa
No lymphovascular invasion
Clear lateral and deep margins

Summary of NCCN guidelines for esophageal cancer workup [71]

Table 18.2 Gastric cancer work-up

H&P
Upper GI endoscopy and biopsy
CT of chest/abdomen/pelvis
PET-CT if no evidence of M1
EUS if no evidence of M1
EMR considered if:
≤2 cm in diameter
Well or moderately differentiated
Limited to superficial submucosa
No lymphovascular invasion
Clear lateral and deep margins
Summary of NCCN guidelines for gastric cancer workup [72]

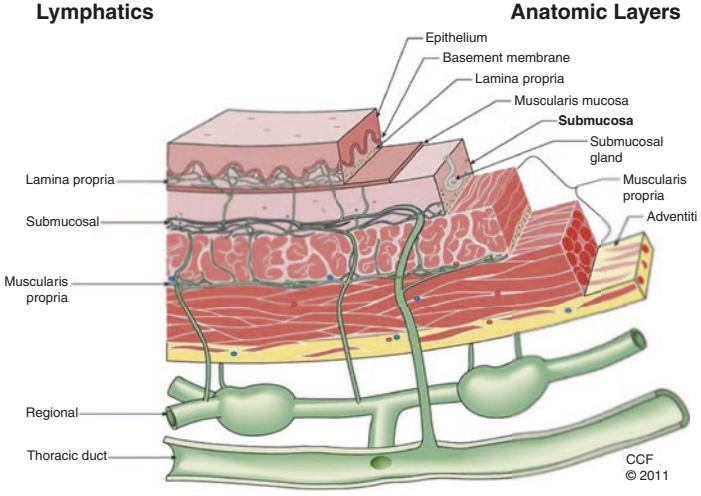

Figure 18.1 Diagram of esophageal walls with depth of lesions amenable to endoscopic resection (adapted from [69])

EMR versus those that require more invasive surgical intervention. Endoscopic ultrasound (EUS) has shown to be a useful adjunct in the pre-procedural diagnostic workup . However, even in instances of uncertain or inaccurate preoperative testing, EMR resected specimens themselves provide more accurate tumor depth to assess invasion, which may be used for both diagnostic as well as therapeutic purposes [25, 26]. Therefore results from EMR can upgrade or downgrade the pre-procedure diagnoses and thus change patient m anagement. Specifically, infiltration of lymph or blood vessels, poor differentiation, submucosal infiltration, and residual tumor at the base of the resection margin have all been indicated as criteria for surgical resection after EMR [27]. Furthermore, it is also important to note that the risk of unexpected lymph node metastases for patients with T1 lesions of the esophagus is in the range of 1–2% [28].

Similar to early esophageal cancers, early gastric cancers (EGC) have demonstrated a low risk of metastatic disease if certain features are present. Criteria for candidates for EMR for gastric cancer include T1a, well-differentiated lesions <2 cm, no evidence of neoplastic ulcer, or lymphovascular involvement [29]. These characteristics have been shown to similarly carry a low risk of lymph node involvement, and therefore these patients are ideal for EMR [30, 31]. EMR is similarly accepted for superficial mucosal duodenal lesions >10 mm and even in the case of ampullary lesions, although both can be more technically challenging given the anatomic challenges posed by the duodenum [32].

Technique

The following EMR techniques are designed to completely remove pathologic mucosa by dissection through the submucosa (Fig. 18.1). Before starting, it may be helpful to superficially mark the margins of the target lesion with electrosurgical coagulation. The following techniques are ideally used on lesions 2 cm or smaller due to the size of the cap, ligation

devices, and snare. Piecemeal resection of larger lesions is not recommended because it prevents accurate pathologic evaluation. These larger lesions can be considered for endoscopic submucosal dissection (ESR) described elsewhere.

Injection-Assisted EMR

This technique starts by elevating the mucosa to produce an easier target to snare. This may be accomplished using several mediums, including saline, a fibrinogen mixture, sodium hyaluronate, hydroxypropyl methylcellulose, glycerol, or hydroxyethyl starch. This step provides a "safety cushion" by minimizing mechanical or electrosurgical damage to the deep layers of the GI tract wall. Autologous blood may provide a longer-lasting cushion without inflammation [33]. To aid in identifying deep margins of the lesion, staining dyes may be added to the fluid [34]. To decrease the theoretical risk of bleeding, epinephrine may be added in diluted amounts [35]. Resection of the target lesion is then performed with a standard snare technique. Importantly, if a cushion does not develop when performing the submucosal lift (i.e., the lesion does not "rise"), EMR should not be attempted (Fig. 18.2), as this can be a predictor of deeper invasion, and perhaps a

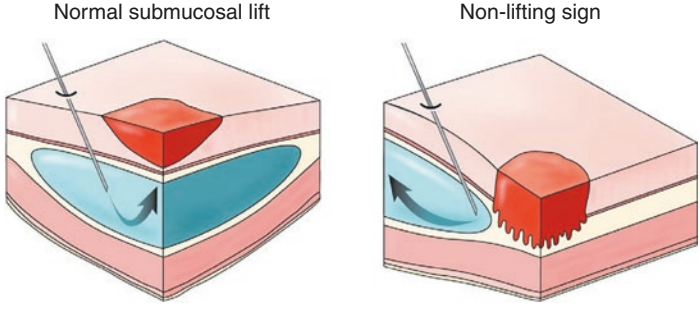

Figure 18.2 Development of normal cushion during submucosal injection of saline (left). Non-lifting of lesion can predict deeper invasion of lesion (right) (from [70])

lesion that is not amenable to endoscopic removal. The method may be modified by using a dual-channel endoscope, wherein a grasping forceps is inserted into one channel to lift the lesion, and a snare is inserted into the second channel to loop around the base of the lesion. For large gastric lesions, counter-traction can be provided via forceps inserted through a separate percutaneous endoscopic gastrostomy tract [36].

Cap-Assisted EMR

This technique utilizes an endoscope fitted with a cap that applies suction to the lesion of interest, facilitating resection via a standard snare excision technique (Fig. 18.3). The avail-

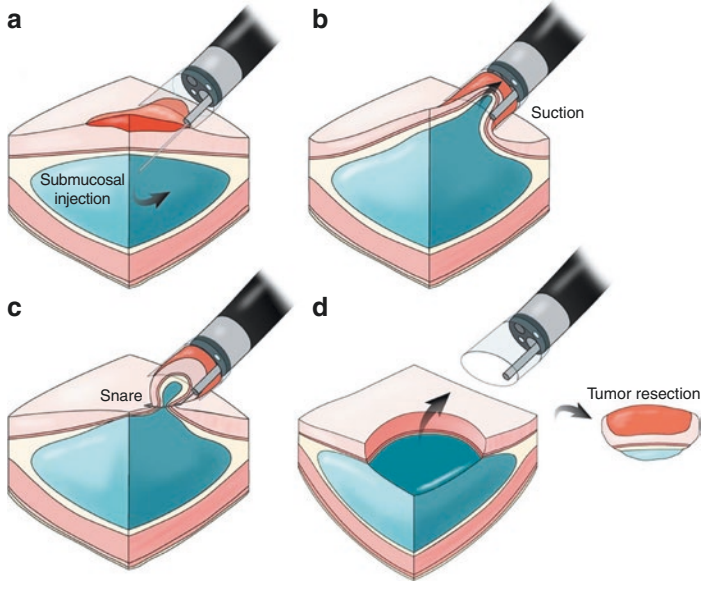

Figure 18.3 Cap-assisted EMR. Injection of saline to raise target lesion (**a**). Suction used to raise lesion into cap (**b**). Snare is inserted into working channel and deployed deployed around lesion (**c**). Specimen with rim of normal tissue removed (**d**) (from [70])

able cap-assisted mucosectomy devices differ primarily in the characteristics of the cap. Caps are composed of clear plastic that may be soft or hard. The caps are cylindric and available with flat circular (straight) or oblique-shaped tips, both with outer diameters ranging from 12.9 to 18 mm. The oblique caps are usually used for resection of esophageal lesions to compensate for the parallel position of the endoscope relative to the esophageal wall, whereas the straight caps are most commonly used for gastric EMR [36].

Ligation-Assisted EMR

In ligation-assisted EMR, a variceal band ligation device is positioned over the target lesion with or without prior submucosal injection. Suction is applied to retract the lesion into the banding device, and a band is deployed to capture the lesion (Fig. 18.4). The band has enough contractile force to squeeze the mucosal and submucosal layers, but it is not strong enough to capture the muscularis propria layer. The banding device is then removed, and a standard electrosurgical snare is used to resect the lesion above or below the band [36].

Underwater EMR

Underwater EMR involves the removal of luminal air and the introduction of water to fill the gastrointestinal lumen [37]. This replaces the traction force of cap or ligation-assisted devices with a 'floatation' force. Underwater approaches offer an alternative approach in locations that are difficult for submucosal injection. Theoretically, this approach avoids further displacement of neoplastic cells, as can be seen with submucosal injections.

For all techniques, appropriate and adequate depth of resection is a key factor in determining effectiveness, durability, and side effects. The optimal depth of resection should extend down to include the muscularis mucosa (Fig. 18.1),

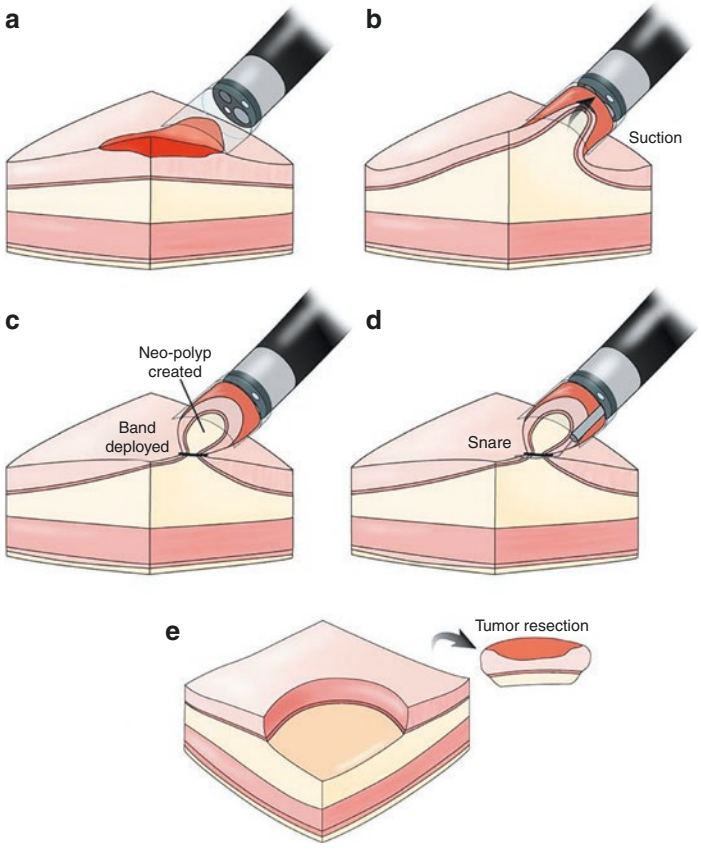

Figure 18.4 Ligation-assisted EMR. Cap is positioned overlesion (**a**), and suction is used to raise lesion into cap (**b**). Band is deployed around the lesion (**c**). The neo-polyp is then resected using electrosurgical snare (**d**). Specimen with rim of normal tissue removed (**e**) (from [70])

allowing for complete resection of metaplastic cells. Resection deeper into the submucosa results in high rates of stricture and perforation. Handling the resected specimen with care is essential and must be carefully examined for accurate staging [38].

Avoiding Complications

Bleeding

Bleeding is the most common post-EMR complication and can occur during or within 24 h of the procedure, or later up to 30 days after the completion of the procedure. Estimated rates of early and late bleeding are less than 5% for esophageal and gastric resections [39–41]. Duodenal resections are associated with a higher rate of bleeding with ranges of 7–18% of early and 3–22% late bleeding [42]. A larger resection size increases the risk for both immediate and delayed bleeding in all anatomic locations. Early bleeding is usually identified as oozing or a visible bleeding vessel at the end of the procedure. Endoscopic clips, epinephrine injections, endoloops, and electrosurgical coagulation can all be used to control bleeding in these instances. Using clips or injections when a visible vessel is seen is effective in preventing early bleeding [43]. Lepilliez et al. found that clipping and/or APC of the resection bed in duodenal EMR can significantly reduce the rates of delayed bleeding [21].

Aside from tumor size and location use of antiplatelet agents has also been associated with an increased risk of post-procedure b leeding [44, 45]. Importantly prompt resumption of medications after EMR has not been associated with an increased risk of b leeding [46]. However, prolonged cessation does increase the risk of cardiac ischemic events [43]. Current guidelines from the American Society of Gastrointestinal Endoscopy guidelines recommend stopping anticoagulation 5–7 days prior to the procedure, with resumption on post-procedure day one [47].

Stricture

EMR-induced strictures are encountered most commonly in relation to esophageal resections. The rates of stricture are related to the extent of resection, with both large mucosal resections and resection of multiple lesions at the initial pro-

cedure implicated as risk factors [48]. Several techniques to prevent strictures are being investigated. These include injection of anti-scarring agents into the BE resection bed (e.g., steroids, mitomycin) [49], systemic anti-inflammatory agents (e.g., steroids) [50], prophylactic biodegradable stent placement [51], and application of autologous cells [52]. Prophylactic pneumatic dilation, seven days after circumferential BE resection, has also been tried, but little data is available regarding its e fficacy and risks [53]. The current approach to esophageal stenosis post-EMR is treatment with endoscopic dilation. The major risk factor of endoscopic dilation is perforation, with reported rates of approximately 1% [54, 55].

Perforation

Perforations are extremely rare in the EMR of the esophagus and stomach [56]. If perforation occurs, it usually manifests as mediastinal emphysema. In an otherwise stable patient, conservative m anagement can be trialed. Rarely is surgery necessary for perforation following esophageal EMR [57, 58]. Duodenal EMR carries a higher risk of perforation (up to 2%), likely due to the thinner wall of the duodenum and limited space to maneuver the endoscope [59]. Risk factors for perforation include larger tumor size (>2 cm) and longer procedure times (>2 h). In many cases, endoscopic suturing or clipping can be utilized to repair defects and avoid further surgical intervention [60]. Delayed perforations, thought to be secondary to thermal damage of the muscular layer, do exist and require urgent surgical intervention [61].

Complete Barrett's Eradication Versus Targeted Resection

Although targeted EMR of visible lesions is effective, synchronous lesions and a high rate of recurrence have prompted some endoscopists to employ circumferential EMR, with the

goal of completing Barrett's eradication (CBE). This can be performed using any of the above techniques. The most common approach is to resect ≤50% of the esophageal circumference in one session, followed by a repeat session at 6–8 weeks until the visible Barrett's is completely eradicated. Chennat et al. demonstrated that stricture rates were higher when complete BE eradication was attempted in one session as compared to a multistep approach (i.e., every 2–6 months until complete eradication of all BE) (51% vs. 26%, $p < 0.01$, respectively) [62]. The authors speculate that the presence of larger areas of directly adjacent ulceration might predispose to stricture formation [62]. Generally, most patients are instructed to consume liquids for the first 24 h, followed by soft foods, and then a regular diet by post-procedure day three [25].

Circumferential EMR results in a complete response in 62–100% of patients (Table 18.3), whereas residual diseases (synchronous lesions) are detected in 11–45% of patients undergoing targeted EMR, thereby necessitating frequent

Table 18.3 Complete Barrett's eradication-EMR

	Patients, n	Follow-up (months)	Outcome	Stricture formation
Seewald, Akaraviputh, et al. 2003	12	9[a]	100% complete removal	16%
Giovannini, Bories, et al. 2004	21	18[b]	62% complete removal	0%
Peters, Kara, et al. 2006	37	11[a]	81% complete removal	27%
Larghi, Lightdale, et al. 2007	24	28[a]	87.5% complete removal	12.5%

[a] Median
[b] Mean

surveillance [39, 40, 63–68]. Further studies are needed before formal recommendations can be made on "relaxing" surveillance after CBE.

Conclusions

EMR has evolved into an effective alternative to surgery for early-stage cancers of the upper GI tract. However, as with any technology, there are associated risks/complications. Therefore, when employing EMR, a thorough understanding of potential risks and techniques for avoiding or dealing with these complications is mandatory (Table 18.4). EMR can be curative for lesions restricted to the mucosa and may be considered in selected patients with the submucosal disease and no lymphovascular invasion. The risk of metastatic cancer is acceptably low in this setting. Therefore, success is dependent upon accurate patient selection. Endoscopic surveillance should continue post-procedure to monitor for metachronous lesions.

Table 18.4 Summary of effectiveness and complications of EMR

Organ	References	Initial effectiveness	Metachronous/ recurrence	Bleeding	Perforation	Stricture
Esophagus	[39, 40, 57, 73–75]	64–99%	11–30%	1.2–11%	0–0.4%	0–7.1%
Stomach	[76]	43–59%	5%	7.09%	1.03%	–
Duodenum	([21], [77–79] sessile, sporadic nonampullary, [80])	70–100%	22–28%	4–13.9%	0–2.3%	–

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Chapter 19
Endoscopic Mucosal Resection: Colon and Rectum

Ammar O. Kheir

Key Points

- Endoscopic mucosal resection of large non-pedunculated colorectal polyps is the safest, most effective, and most efficient method for treating most lesions.
- Lesion assessment is reliable in detecting areas of submucosal invasive cancer (especially in flat lesions) and guiding the best management strategy.
- Thermal ablation of the endoscopic mucosal resection margin reduces the risk of recurrence substantially.
- Clipping is now recommended for proximal lesions to prevent delayed bleeding after endoscopic mucosal resection.
- Recurrence can be reliably detected by optical diagnosis and effectively treated on surveillance.
- Previously attempted non-lifting lesions can still be salvaged and successfully treated using CAST or hot avulsion techniques.
- Cold endoscopic mucosal resection is now the preferred resection method for large sessile serrated lesions.

A. O. Kheir (✉)
Digestive Disease Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE
e-mail: kheira@clevelandclinicabudhabi.ae

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_19

Introduction

Most colorectal cancers arise from precancerous adenomatous and sessile serrated lesions of the colon [1, 2]. This process occurs through predicted, gradual, and well-described molecular pathways, the conventional adenoma-carcinoma pathway, and the more recently discovered serrated pathway [1–3]. This gradual process allows for effective endoscopic intervention and removal of these lesions prior to developing invasive cancer [4, 5]. Approximately 5% of these lesions are large (size >10 mm) and non-pedunculated, named laterally spreading lesions (LSLs). The risk of submucosal invasive cancer (SMIC) in such lesions is approximately 8% and can be managed effectively by endoscopists who undergo dedicated training in endoscopic imaging and endoscopic resection techniques [6–9]. Given the majority of LSLs are benign, recent society guidelines recommend management of such lesions by endoscopic resection, primarily endoscopic mucosal resection (EMR), and not surgery [10, 11]. The majority of the cases can be discharged on the same day.

EMR complications are often predicted and inevitable in centers with significant EMR volume that receive referrals for more complex lesions. Most of these complications can be precisely and effectively managed endoscopically if recognized swiftly. EMR complications can be categorized as:

- Intraprocedural (immediate) EMR complications
- Post-procedural (delayed) EMR complications

Bleeding (immediate or delayed) is the most common risk [6–17]. Immediate bleeding is rarely significant and is easily managed endoscopically. Clinically significant delayed bleeding requiring blood transfusion or intervention is also rare and almost never fatal.

Why Should These Lesions Be Managed Primarily by Endoscopic Mucosal Resection and Not Surgical Colectomy?

All extensively benign colorectal polyps should be primarily managed endoscopically and not surgery [10, 11]. In a large Australian multicenter prospective study of 1050 patients undergoing EMR for colonic LSLs (≥20 mm in size), the actual endoscopic mortality was 0% (0 patients). In comparison by modeling the predicted surgical mortality using validated surgical scoring systems (ACPGBI & CR-POSSUM) showed predicted surgical mortality of 3.3% (35 patients) [18]. The NNT to prevent 1 death was 30, indicating endoscopic management of these lesions can save lives. In a larger nationwide US study of 262,843 surgical colectomies for nonmalignant colorectal polyps, mortality was approximately 1%, and postoperative adverse events were 25% [19].

Another advantage of endoscopic resection over surgical colectomy is significant cost savings. In a large multicenter study of 1353 patients with 1489 colonic LSLs managed by EMR, the predicted mean cost savings per patient managed by EMR compared with best surgical outcome was $7602 (95% CI $8458–$9220; $P < 0.001$) and reducing inpatient hospital stay per patient by 2.81 nights (95% CI 2.69–2.94; $P < 0.001$) [20]. When factoring in surgical complications, the cost and inpatient hospital stay is much greater.

Recent society guidelines endorsed the primary management of large colorectal LSLs by endoscopic removal and not surgery [10, 11].

Preparation for Endoscopic Mucosal Resection

What Are the Main Aims of Endoscopic Mucosal Resection of Benign Colorectal Neoplasia?

1. Safely, effectively, and completely resecting these lesions.
2. Minimize invasiveness and avoid harm to the patient.
3. Avoid lesion recurrence post-EMR.
4. Avoid unnecessary surgical-related morbidity and mortality.
5. Improving the efficiency of healthcare resources through avoiding unnecessary healthcare expenses and time expenditure.

What to Do When These Lesions Are Discovered During Routine Colonoscopy?

Large colonic lesions requiring EMR are different from standard polypectomy. Detailed informed consent for EMR is needed as it involves higher risks than standard polypectomy and mostly includes alternative options, including surgery [7, 8, 21]. In addition, referral to an internal or external EMR expert endoscopist in a tertiary setting, longer allocated procedure time, with the preparation of required ancillary EMR equipment is preferable.

Endoscopic Prerequisites for Performing Endoscopic Mucosal Resection

Carbon Dioxide Insufflation

Carbon dioxide (CO_2) insufflation has been shown to reduce pain scores after colonoscopy and polypectomy compared to air insufflation [22–27] due to the rapid absorption of CO_2

from the colonic lumen, causing less post-procedural luminal distension and reduced colonic wall tension. The use of CO_2 for insufflation during colonoscopy has also been confirmed to be safer and superior to air insufflation, causing less tension on large mucosal defects during wide-field colonoscopic resection of advanced colorectal neoplasia [28–30]. Bassan et al. prospectively studied 575 large colonic lesions (size ≥20 mm) resected with air or CO_2 [30]. EMR with CO_2 resulted in a 62% reduction (3.4% vs. 8.9%, $P = 0.01$) in post-EMR admission compared with air. Furthermore, there was an 82% reduction (1% vs. 5.7%, $P = 0.006$) in post-EMR admission due to pain when using CO_2 compared with air.

Microprocessor-Controlled Electrosurgical Generators

The use of modern microprocessor-controlled electrosurgical generators minimizes the risk for deep mural injury during tissue resection. For snare-based endoscopic resection (such as EMR), most experts recommend the use of *ENDO CUT Q mode, effect 3, cutting duration 1, cutting interval 6*, shown in Fig. 19.1 (ERBE VIO 300D, Tübingen Germany) [7, 8].

Submucosal Injectate

The constituents of the submucosal injectate include a submucosal lifting solution and a chromic dye with or without epinephrine. For the submucosal injectate, a colloidal solution (e.g., succinylated gelatin) is preferred over a crystalloid solution, as it provides a longer-lasting submucosal lifting cushion [31]. An inert chromic dye (e.g., indigo carmine 80 mg in 500 mL solution of methylene blue 20 mg in 500 mL solution) is helpful in recognizing submucosal fibrosis and easier delineation of the unstained muscularis propria [32]. Epinephrine (1:100,000) is commonly used, which may reduce intraprocedural bleeding (IPB) [8].

FIGURE 19.1 Example of commonly used electrosurgical generator EMR settings (ERBE VIO 300D, Tübingen Germany). For resection, *ENDO CUT Q mode, effect 3, cutting duration 1, cutting interval 6* (red box), and for snare-tip-soft-coagulation for controlling intraprocedural bleeding or thermal ablation of the post-EMR margin *SOFT COAG mode 80 W, effect 4* (green box)

Snares

Several snares with different characteristics, shapes, and width are available. In general, we do not recommend using a snare diameter size larger than 20 mm, as this increases the risk of muscularis propria entrapment and the risk of deep mural injury or perforation. Stiff, braided snares facilitate better tissue acquisition and are less likely to slip during snare closure. Examples of commonly used EMR snares are shown in Fig. 19.2.

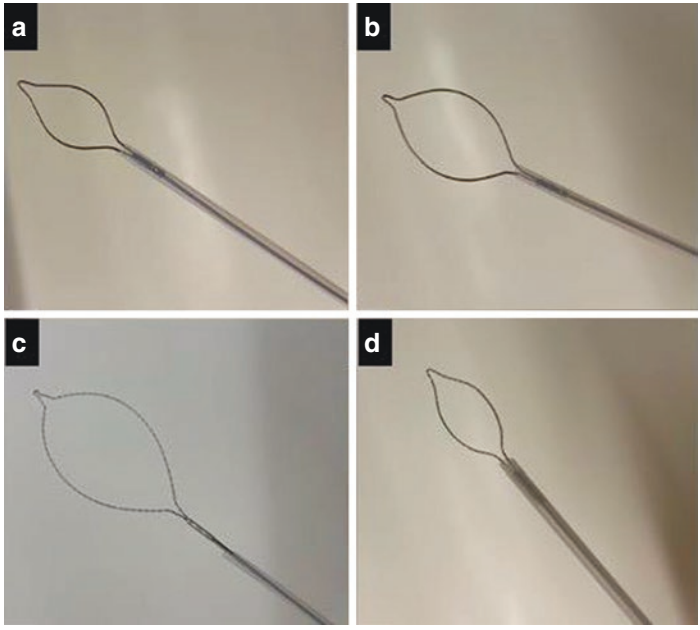

FIGURE 19.2 Examples of commonly used snares, (**a**) 10 mm Captivator II (Boston Scientific, USA); (**b**) 15 mm Captivator II (Boston Scientific, USA); (**c**) 20 mm SnareMaster (Olympus America); (**d**) 10 mm Captivator COLD (Boston Scientific, USA)

Lesion Assessment

Overview and Focal Lesion Assessment

Overview and focal lesion assessment for excluding visible areas of submucosal invasive cancer (SMIC) estimate the risk for covert SMIC, and the suitability of endoscopic resection is pivotal prior to attempting piecemeal or en bloc EMR. Also, whether the lesion is adenomatous or serrated will guide whether electrocautery use is needed. For large sessile serrated lesions, cold EMR is increasingly becoming the preferred method for endoscopic removal because of the attractive safety and efficacy profile for this technique over conventional EMR [33–36].

Focal interrogation of the lesion is performed using dye chromoendoscopy to assess for the surface pattern (Kudo classification, Table 19.1) [32, 37]. More common these days is the use of electronic chromoendoscopy (e.g., narrow-band imaging) to assess the vascular and surface patterns. The simple and validated Narrow-Band Imaging International Colorectal Endoscopic (NICE) classification (Fig. 19.3 and

TABLE 19.1 Polyp histology and corresponding imaging classifications

Histology	Surface pattern	Vascular pattern
Sessile serrated polyp	Kudo II	NICE type 1/JNET type 1
Tubular adenoma	Kudo III	NICE type 2/JNET type 2A or 2B
Villous adenoma	Kudo IV	NICE type 2/JNET type 2A or 2B
Submucosal invasive cancer	Kudo type V	NICE type 3/JNET type 3

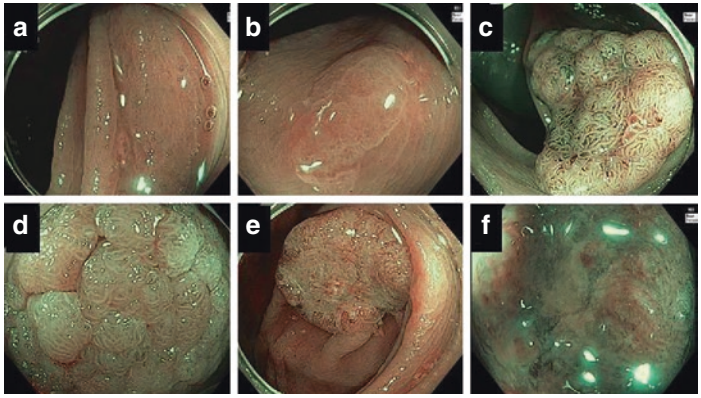

FIGURE 19.3 NICE classification, (**a**, **b**) Type 1, sessile serrated lesion; (**c**, **d**) Type 2, adenomatous lesion; (**e**, **f**) Type 3, submucosal invasive cancer

Table 19.1) or the Japan Narrow-Band Imaging Expert Team (JNET) classification is the most commonly used [32, 38–42]. Optical magnification increases the confidence in focal interrogation of the lesion and stratifies endoscopic resectability (non-cancerous lesions) or the need for surgery for lesions with SMIC (cancerous).

Risk Stratification of Covert Submucosal Invasive Cancer

An overview assessment of the lesion should be described using the Paris classification (morphology) and surface granularity (topography) to stratify the risk for SMIC [9, 43–45]. Location of the lesion is also important as the risk for SMIC is increased in distal lesions (especially in the rectum) compared to proximal lesions [44]. In general, bulky lesion (Paris Is), presence of a nodule (Paris IIa + Is), non-granularity, and distal location increase the cumulative risk for SMIC [44]. In a prospective multicenter EMR study of 1712 LSLs (≥20 mm in size), the risk of covert SMIC is summarized in Table 19.2 [44].

Endoscopic Mucosal Resection Technique

Lesion Access and Positioning

Lesion access needs to be optimized for maximizing technical success. Some techniques include:

- Reducing all colonoscopic loops for optimizing scope tip control and precision.
- The lesion is ideally positioned at the 6 o'clock position along the scope working channel.
- The use of distal transparent cap improves technical access in difficult locations (e.g., behind folds, ileocecal valve, anorectal junction).

Table 19.2 Risk of covert SMIC stratified by Paris morphology, granularity, and location [44]

Morphology granularity	Proximal SMIC risk (%)	Distal SMIC risk (%)	Overall SMIC risk (%)
Paris IIa Granular	0.7	1.2	0.8
Paris IIa + Is Granular	4.2	10.1	7.1
Paris Is Granular	2.3	5.7	3.7
Paris IIa Non-granular	3.8	6.4	4.2
Paris IIa + Is Non-granular	12.7	15.9	14.1
Paris Is Non-granular	12.3	21.4	15.3

- The use of distal attachment allows for swift temporary control of intraprocedural bleeding by tamponading the bleeding point while exchanging devices.
- The patient's position change may be necessary to shift the pooling luminal fluid and resected specimens away from the EMR working field to minimize extraluminal fluid spillage and procedural interference [9].
- Retroflection position can optimize access, especially in the proximal colon and rectum.

Submucosal Injection Technique

- We prefer using a 23 G, 3 mm long injection needle.
- Ensure that the needle catheter is fully primed with the submucosal injectate solution and no air bubbles to avoid injecting air into the submucosa.

– Position the needle tip tangentially against the lesion (we usually touch the mucosa with the needle tip).
– Ask the assistant to start the injection, then push the needle catheter to stab the mucosa, and you should instantly find the submucosal plane.
– Lift the lesion away using the scope knobs and by pulling back the needle catheter into the colonoscope working channel using the "dynamic submucosal injection" technique [46, 47].

Resection Technique

Well-planned and meticulous high-quality resection technique with continuous attention to snare tissue acquisition, snare slippage during the closure, EMR defect for deep mural injury, and residual neoplasia is critical for safe and effective EMR (Figs. 19.4, 19.5, and 19.6 and Box 19.1)

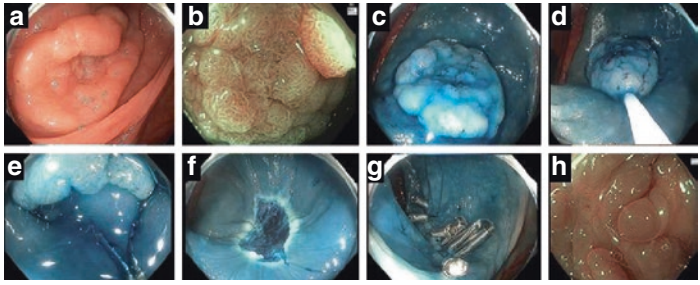

FIGURE 19.4 En bloc EMR of a 25 mm Paris IIa granular adenomatous lesion, (**a**) Lesion overview using high-definition white light; (**b**) NICE classification Type 2, adenomatous lesion; (**c**) submucosal injection using chromosaline (methylene blue with epinephrine 1:100,000); (**d**, **e**) en bloc snare placement including 2 mm of normal mucosa; (**f**) exposed submucosa following resection without evidence of DMI or residual neoplasia, thermal ablation to the margin applied; (**g**) clips applied to prevent delayed bleeding; (**h**) clip artifact within post-EMR scar with normal mucosa

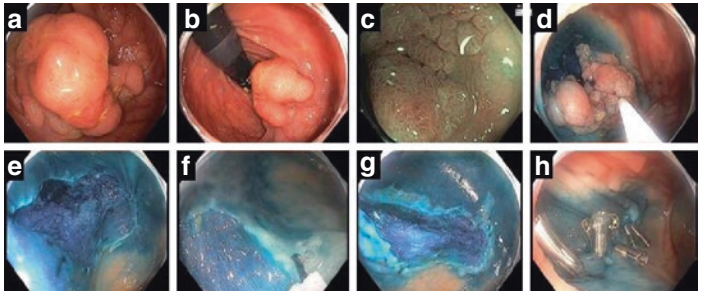

Figure 19.5 Piecemeal EMR of a 50 mm hepatic flexure Paris Is + IIa mixed-granularity adenomatous lesion. (**a**) Lesion overview on forward-view using high-definition white light; (**b**) lesion overview on retroflection view; (**c**) NICE classification Type 2, adenomatous lesion; (**d**) snare placement including 3 mm of normal mucosa; (**e**) exposed submucosa following resection without evidence of DMI or residual neoplasia; (**f**, **g**) thermal ablation to the margin applied; (**h**) clips applied to prevent delayed bleeding

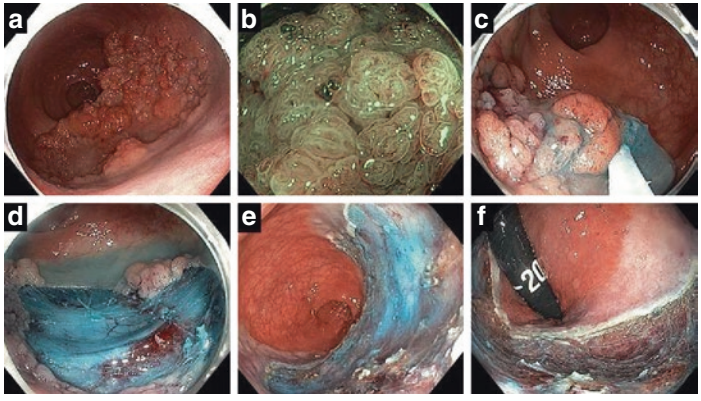

Figure 19.6 Piecemeal EMR of a 70 mm half-circumferential rectal Paris IIa granular adenomatous lesion. (**a**) Lesion overview on forward-view using high-definition white light; (**b**) NICE classification Type 2, adenomatous lesion; (**c**) dynamic submucosal injection; (**d**) EMR in progress with exposed submucosa with visible uninjured muscularis propria—DMI type I; (**e**) EMR completed without evidence of DMI; (**f**) retroflexion-view after thermal ablation to the margin

- Start resecting at the most technically difficult area first.
- Then place opened snare on the target neoplasia and included a 3 mm margin of normal mucosa.
- During snare closure, ensure that tissue margins within the snare are continuously maintained. This is better achieved by controlled-speed snare closure by the assistant, while the endoscopist is simultaneously advancing the snare catheter to guard against snare slippage and compromising tissue margins.
- The snare should be closed to maximum snare-handle resistance (usually up to 1–2 cm from complete snare handle closure).
- Check mobility: when swiftly moving the snare catheter, the entrapped tissue should move on the screen relatively independent of the colonic wall. If independent movement is lost, this could indicate entrapped muscularis propria and can risk DMI. This can be managed by partially opening the snare-handle to halfway to the point where snare-handle resistance is almost lost. Check mobility again and when independent mobility is achieved, reclose the snare handle to resistance.
- Transect the ensnared tissue rapidly using fractionated current. We use *ENDO CUT Q mode, effect 3, cutting duration 1, cutting interval 6*, shown in Fig. 19.1 (ERBE VIO 300D, Tübingen Germany). Usually, 1–3 pulses of a microprocessor-controlled electrosurgical generator are needed. If the snare stalls and does not transect after three pulses, this could be caused by entrapped muscularis propria, submucosal fibrosis, or submucosal invasive cancer.
- Examine the submucosal defect and utilize the water-foot pump to irrigate the defect and expand the submucosa for detecting residual neoplasia or DMI.
- Work systematically from one point and continue until the lesion is completely removed.

Box 19.1 Summary of Endoscopic Mucosal Resection Steps for Non-pedunculated Colorectal Laterally Spreading Lesions

- Optimize access and patient position.
- Place lesion at the 6 o'clock position.
- Careful lesion assessment in overview and focal mode to exclude areas of SMIC prior to EMR.
- Dynamic submucosal injection (preferably using colloidal solution when possible) to improve lesion access and prevent DMI.
- Use stiff, braided snares, and avoid using snare size >20 mm.
- The place opened snare on the target neoplasia and included a 3 mm margin of normal mucosa.
- Controlled-speed snares closure while observing margins of snare tissue acquisition.
- Transect the ensnared tissue rapidly using fractionated current (usually 1–3 pulses of a microprocessor-controlled electrosurgical generator).
- Examine the submucosal defect and utilize the water-foot pump to irrigate the defect and expand the submucosa for detecting residual neoplasia or DMI.
- Work systematically from one point and continue until the lesion is completely removed.
- Treat intraprocedural bleeding using STSC with or without coagulation forceps.
- Examine defect and remove any islands of residual neoplasia at defect or at margins.
- Examine defects for areas of DMI and use TSC for the unstained area.
- Apply clips to areas of DMI type II–V and consider antibiotics with overnight admission for treated DMI type IV–V.
- Apply thermal ablation to the post-EMR defect after removing all visible neoplasia.

- Consider clipping post-EMR defects in the proximal colon to prevent delayed bleeding.
- Post-EMR scar surveillance in 6 months and 18 months.
- Use image-enhanced endoscopy (e.g., NBI) to detect neoplasia recurrence.
- Re-resect all non-fibrotic residual neoplasia using cold snare polypectomy. Then remove fibrotic residual neoplasia using salvage avulsion techniques (CAST or hot avulsion).
- Examine treated areas for DMI and consider clipping if needed.

Complications and Optimizing Outcomes

Intraprocedural (immediate) or post-procedural (delayed) EMR complications are often predicted and inevitable in centers with significant EMR volume. Most of these complications can be effectively and safely managed endoscopically if they are recognized swiftly. Bleeding (immediate or delayed) is the most common risk. Immediate bleeding is rarely significant and is easily managed endoscopically.

Intraprocedural Bleeding

Intraprocedural bleeding (IPB) frequency is usually one in ten EMR cases. This can be swiftly and effectively controlled by snare-tip-soft-coagulation (STSC) in >90% cases, Fig. 19.7. If STSC fails to achieve hemostasis, Coagulation forceps using the same electrocautery settings as STSC is almost always successful. The technique for using both is described below:

- Use a fixed low-voltage output (190 V maximum) microprocessor-controlled electrosurgical generator (e.g. *SOFT COAG mode, 80 W effect 4, ERBE VIO300D, Tübingen Germany*) (Fig. 19.1).

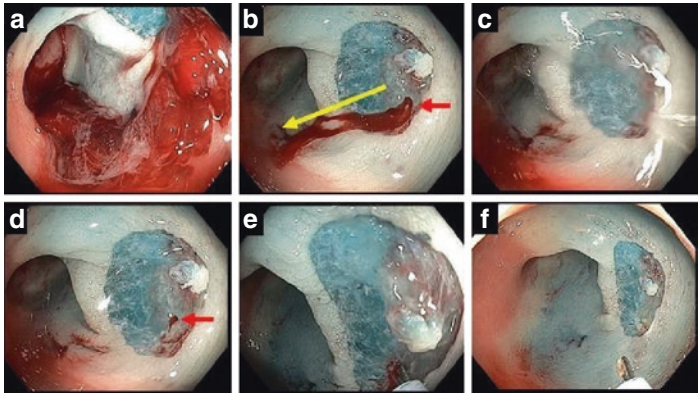

Figure 19.7 Intraprocedural bleeding controlled by STSC, (**a**) intraprocedural bleeding with fresh clot concealing bleeding point; (**b**) clots suctioned and active oozing from the bleeding point (red arrow) toward the gravitational side were luminal fluid pools (yellow arrow); (**c**) irrigating EMR defect to confirm bleeding point; (**d**) bleeding point confirmed (red arrow); (**e**) STSC applied to bleeding point; (**f**) hemostasis achieved

- Use the water-jet function and gravity direction to your advantage to detect the bleeding point.
- STSC: With the tip of the snare protruding 1–2 mm, apply pressure to the bleeding point. Often you will notice a tamponade effect with partial or complete hemostasis confirming that you are tamponading the culprit bleeding point. Apply brief 2–3 s duration of energy application to the bleeding point as needed until bleeding stops.
- Coagulation forceps: If STSC fails after three attempts, then use a coagulation forceps. Using the same setting, grasp the bleeding point, and then lift the vessel 3 mm into the lumen to limit injury to the muscularis propria, before applying brief 2–3 s duration of energy application to the bleeding point prior to releasing the vessel to confirm hemostasis.
- If thermal hemostasis fails although is rare, then clipping can be used in difficult cases.

Delayed Bleeding

Delayed bleeding post-EMR requiring hospitalization, blood transfusion, or intervention is termed *Clinically significant post-EMR bleeding (CSPEB)* [15, 17]. In a large prospective multicenter study of 1172 patients with colorectal polyps ≥20 mm in size (mean size, 35.5 mm), CSPEB occurred in 6.2% of patients [17]. More than two-thirds of patients with CSPEB presented within 48 h. Predictive risk factors for CSPEB were:

- Intraprocedural bleeding (IPB).
- Proximal colon location.
- Using a non-microprocessor-controlled electrosurgical unit.

More than half of CSPEB resolve spontaneously without intervention [15]. Predictive factors for requiring intervention for hemostasis are:

- Severe hematochezia.
- American Society of Anesthesiologists grades 2 or higher.
- Blood transfusion.

CSPEB remains a challenge with suboptimal prophylactic measures. In a randomized controlled trial of 347 receiving prophylactic thermal ablation of visible vessels within the EMR defect did not result in a significant reduction of CSPEB compared with no additional therapy [16]. A single-center retrospective case–control study of 524 EMR defects showed prophylactic clipping to reduce delayed bleeding from 9.7% to 1.8% [48]. However, there is a lack of prospective data and economical modeling studies have shown prophylactic clipping not to be cost-effective even for high-risk EMR defects [13, 49]. More recently, a novel synthetic hemostatic agent appears to mitigate against delayed bleeding but more studies are needed [50].

Deep Mural Injury and Perforation

Perforation is the most serious complication of EMR. Significant deep mural injury (DMI) and perforation occur in up to 3% of EMR cases [51–53]. Risk factors are en bloc resection for LSLs ≥25 mm in size, transverse colon location, and presence of high-grade dysplasia or covert submucosal invasive cancer.

An important endoscopic sign for the colonoscopist to be aware of during EMR is the *Target sign* [54]. This appears as a white-cautery ring within the EMR defect or the resected specimen and indicates an excision to the muscularis propria. The *target sign* is easily recognized and a reliable marker of MP injury and should be treated by mechanical closure using clips to avoid delayed perforation. White or unstained areas within the EMR defect interfere with endoscopic interpretation of the EMR defect resection depth. Unstained areas can be caused by submucosal fibrosis (SMF) or MP injury [7]. Topical submucosal chromoendoscopy (TSC) is a simple and helpful technique to identify the resection plane and recognize MP injury [55]. This is performed by injecting the EMR defect using the same injectate and the injection catheter without the needle (Fig. 19.8).

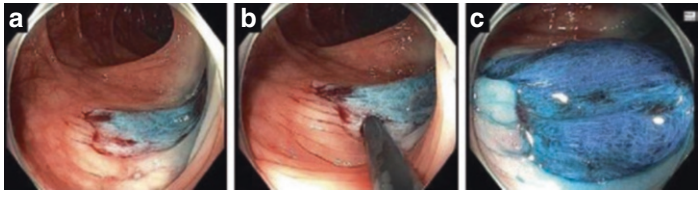

Figure 19.8 Topical submucosal chromoendoscopy, (**a**) Unstained area rendering the defect uninterpretable for excluding DMI; (**b**) topical submucosal chromoendoscopy applied to the unstained area; (**c**) blue dye submucosal uptake confirming no DMI and no need for clipping

DMI during EMR can be classified using the *Sydney Classification of DMI* Table 19.3, Fig. 19.9 [53]. Burgess et al. retrospectively studied images and histologic specimens of consecutive 911 LSLs ≥20 mm in size (mean size 37 mm) that underwent EMR. Deep mural injury occurred in 83 patients (10.3%) with significant DMI (type III–V) occurring in 24 patients (3%). All DMI cases were successfully clipped and 85.5% of patients were discharged on the same day. DMI type III–V was associated with transverse colon location, en bloc resection, presence of high-grade dysplasia, or covert submucosal invasive cancer.

Table 19.3 Sydney classification of deep mural injury [7, 53]

DMI type	Definition	Recommendation
0	Normal defect with blue submucosa and non-visible muscularis propria	No endoscopic intervention needed
I	Visible but uninjured muscularis propria	No endoscopic intervention needed
II	Focal loss of the blue submucosal plane causing uninterpretable muscularis propria to exclude injury	Clipping and may be discharged if asymptomatic
III	Injured muscularis propria with defect or specimen target sign	Clipping and may be discharged if asymptomatic
IV	Hole within a white-cautery ring, without observed contamination	Clipping, antibiotics, and admission for overnight monitoring
V	Hole within a white cautery ring, with observed contamination	Clipping, antibiotics, and admission for overnight monitoring

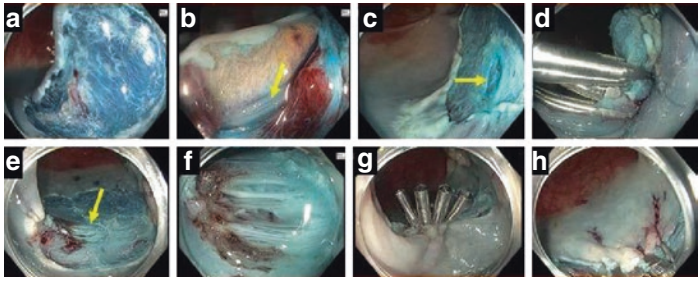

Figure 19.9 Examples of Sydney Classification of DMI, (**a**) normal post-EMR defect with homogenous blue submucosa without visible muscularis—DMI type 0; (**b**) visible uninjured muscularis propria during cold EMR—DMI type I, patient was stable and discharged same day; (**c**) defect target sign during EMR—DMI type III; (**d**) treated using clips, patient was stable and discharged on the same day; (**e**, **f**) defect target sign during EMR (DMI type III); (**g**) treated using clips; (**h**) clips deflected to ensure effective closure of the DMI, patient was stable and discharged on the same day

Adenoma Recurrence

The most frequent criticism of colonic EMR is adenoma recurrence. At the first surveillance colonoscopy, adenoma recurrence is proportionally high ranging from 15% to 30% [56–58]. However, this is often diminutive in size and can still be managed endoscopically. Thermal ablation of the post-EMR margin has been shown to significantly reduce adenoma recurrence on surveillance [59]. An Australian prospective multicenter randomized trial examined 416 large LSLs (size ≥20 mm) undergoing colorectal EMR. Post-EMR defects were randomized to thermal ablation of the post-EMR margin using STSC or receiving no additional treatment. Thermal ablation of the post-EMR margin resulted in a fourfold reduction in adenoma recurrence at first surveillance (21.9% vs. 4.7%, $p < 0.001$) [59].

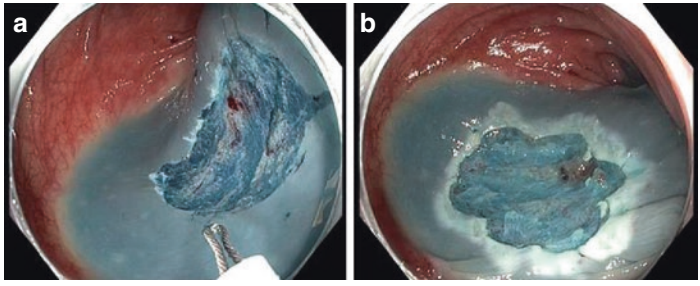

FIGURE 19.10 (**a**) Thermal ablation of post-EMR defect using STSC; (**b**) completed

Thermal Ablation of the Post-EMR Margin Technique

- All visible residual adenoma needs to be resected prior to applying thermal ablation.
- Use a fixed low-voltage output (190 V maximum) microprocessor-controlled electrosurgical generator (e.g., SOFT COAG mode, 80 W effect 4, ERBE VIO300D, Tübingen Germany) (Fig. 19.10**).**
- With the tip of the snare protruding 1–2 mm, confluent energy application to the post-EMR defect is applied, aiming for a 3 mm rim of ablated margin.

Special Locations and Salvaging Techniques

Anorectal Junction Lesions

Lesions involving the anorectal junction (ARJ) can still be effectively managed by EMR, Fig. 19.11 [7, 8, 60]. In an Australian prospective study, 24 large adenomatous LSLs (size ≥20 mm) involving the ARJ were successfully removed using EMR. Adenoma recurrence at first surveillance colonoscopy was 22% and all cases were managed endoscopically without recurrence at second surveillance [60].

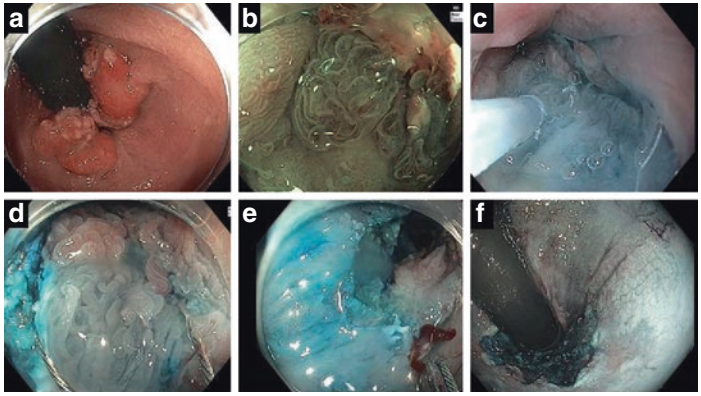

Figure 19.11 Piecemeal EMR of a 50 mm, semi-circumferential anorectal Paris IIa + Is symptomatic inflammatory polyp causing severe anemia, (**a**) lesion overview on retroflexion-view using high-definition white light; (**b**) focal lesion assessment using NBI; (**c**) dynamic submucosal injection starting at the anal side to improve access by pushing the lesion into the rectum; (**d**) snare placement including normal anal mucosa; (**e**) STSC applied to bleeding point; (**f**) EMR completed

Additional EMR steps recommended for ARJ lesions include:

- Use of long-acting anesthetic in the submucosal injectate (e.g., Ropivacaine 0.5%, up to 40 mg). This is injected at the ARJ and provided anesthesia for 4 h and analgesia for 12 h.
- Empirical single dose of broad-spectrum IV antibiotic (e.g., Cefazolin 2 g) can be given intraprocedurally to guard against bacteremia for distal rectal lesions (within 10 cm from the dentate line) and size >30 mm in diameter. This is because the inferior hemorrhoidal veins drain systematically bypassing the portal lymphovenous drainage system and may result in clinical bacteremia (fever and rigors).
- Use of distal attachment to optimize access and lesion positioning.

- Start the submucosal injection at the distal part of the involved area of the ARJ to push the lesion into the rectum.
- Use small diameter size snares (10 mm) when resecting over the ARJ.
- Retroflexion position and switching to a pediatric colonoscope or gastroscope can improve access and technical success.
- Post-EMR oral analgesia (e.g., Paracetamol 1 g every 6 h) can be used for another 24 h, then as needed over the next 72 h.
- Laxatives to maintain soft stool for 2 weeks.

Ileocecal Valve Lesions

Lesions involving the ileocecal valve (ICV) are challenging with a fourfold increased risk for recurrence, Fig. 19.12 [61, 62]. In a prospective Australian study of 44 large adenoma-

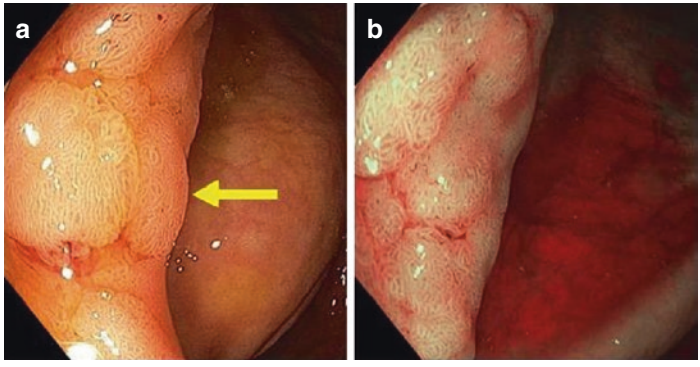

FIGURE 19.12 (**a**) Cecal adenomatous laterally spreading lesion extending into the ileocecal valve, overview using high-definition white light; (**b**) NICE classification Type 2, adenomatous lesion

tous LSLs (size ≥20 mm) involving the ICV, EMR technical success was 94%. Predictive factors for EMR technical failure were adenomatous infiltration to the ileum and involvement of both ICV lips [62].

Additional EMR steps recommended for ICV lesions include:

- Use of distal attachment to optimize access and lesion positioning.
- Start the submucosal injection at the proximal part of the involved area of the ileum and avoid over injecting.
- Retroflexion position can improve access and technical success.

Circumferential Lesions

Colorectal circumferential or semi-circumferential LSLs are very rare (approximately 1%) and can still be managed effectively by EMR, Fig. 19.13 [7, 63]. In an Australian prospective

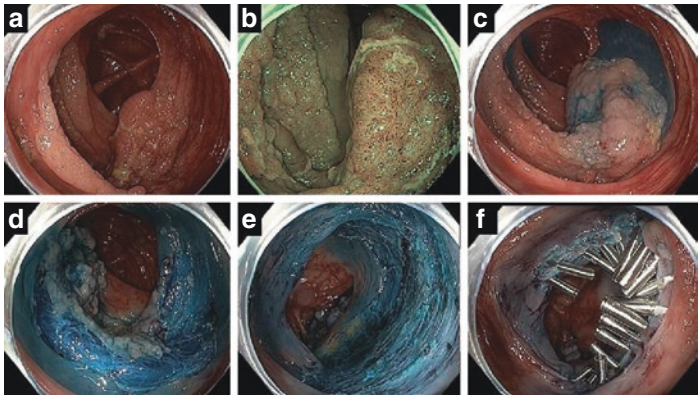

Figure 19.13 Piecemeal EMR of a 90 mm, semi-circumferential, Paris IIa, mixed-granularity, proximal ascending colon, adenomatous lesion. (**a**) Lesion overview using high-definition white light; (**b**) NICE classification Type 2, adenomatous lesion; (**c**) submucosal injection; (**d**) progressive EMR; (**e**) resection completed; (**f**) clipping after thermal ablation of margins

study of 979 patients with LSLs (≥20 mm in size), 12 patients had circumferential or semi-circumferential lesions [63]. All lesions were Paris IIa + Is, median length 95 mm (range 60–160 mm), and more than half were found in the rectum. EMR was successfully completed in all cases without major complications. Up to half of the cases can develop post-EMR luminal stricture.

Additional steps recommended for mitigating stricture formation in circumferential and semi-circumferential lesions include [7, 63]:

- Preserving a rim of normal mucosa during EMR if possible.
- Post-EMR corticosteroid enemas for rectosigmoid lesions (e.g., prednisolone sodium phosphate 20 mg twice daily for 8 weeks).
- Elective gradual colonic multidiameter balloon dilation (10–12 mm and up to 15 mm) starting at 2 weeks post-EMR and repeat dilation is guided by symptoms and ceased after maintaining 15 mm diameter.

Non-lifting Lesions

Some areas of neoplasia can be flat and resistant to snare capture despite good technique. If encountered during EMR, this is often caused by iatrogenic submucosal fibrosis (caused by previous attempts from biopsy or incomplete resection) or naïve submucosal fibrosis (associated with flat non-granular lesions) which manifest endoscopically when there is partial or complete non-lifting after submucosal injection Fig. 19.14. Such challenging lesions can still be safely and effectively salvaged endoscopically and avoid surgery. Salvage endoscopic techniques include

- Cold-forceps avulsion with adjuvant STSC (CAST) technique, Fig. 19.15 [7, 64]:
  - Isolate the fibrotic non-lifting area by snare excision of surrounding neoplastic and/or normal mucosa.

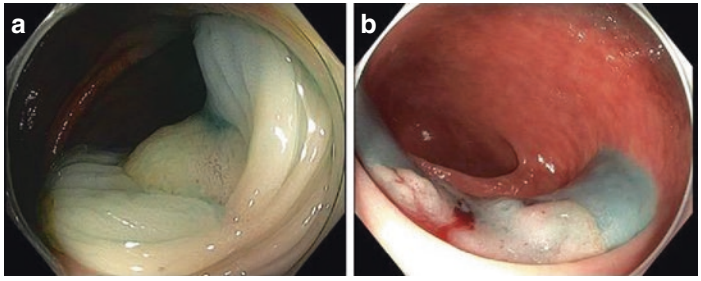

Figure 19.14 Adenomatous non-lifting lesions. (**a**) Iatrogenic central submucosal fibrosis from previous incomplete resection attempt; (**b**) iatrogenic central submucosal fibrosis from previous biopsy

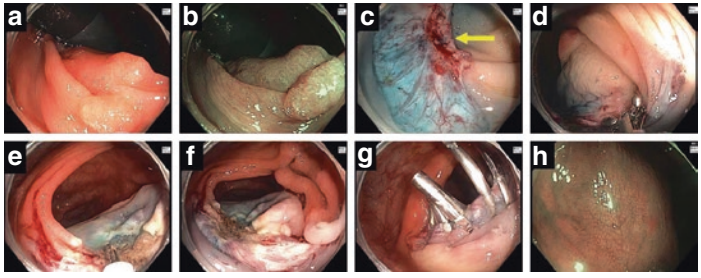

Figure 19.15 Previously attempted incompletely resected distal ascending colon lesion. (**a**) Lesion overview on retroflexion using high-definition white light; (**b**) NICE classification Type 2, adenomatous lesion; (**c**) fibrotic non-lifting area isolated; (**d**) cold-forceps avulsion of all visible fibrotic neoplasia prior to STSC; (**e**) adjunctive STSC of the avulsed fibrotic area; (**f**) EMR defect after CAST showing DMI type II; (**g**) targeted prophylactic clipping to the area of DMI type II; (**h**) EMR scar at 6-month surveillance showing normal bland EMR scar without adenoma recurrence

- Use cold biopsy forceps to grasp the fibrotic tissue.
- Repeat the steps until all visible fibrotic neoplastic tissue is removed.
- Minor ooze is usually encountered which is often transient.

  - STSC electrosurgical generator settings (*SOFT COAG mode, 80 W effect 4, ERBE VIO300D, Tübingen Germany*).
  - After removing all visible neoplasia, adjunctive STSC is applied to the avulsed fibrotic area for destroying microscopic residual and to control any persistent ooze.
  - Examine the EMR defect for features of DMI using the Sydney classification of DMI and manage accordingly.

- Hot avulsion technique, Figs. 19.16 and 19.17 [7, 65]:
  - Isolate the fibrotic non-lifting area by snare excision of surrounding neoplastic and/or normal mucosa.
  - Use hot biopsy forceps to grasp the fibrotic tissue.

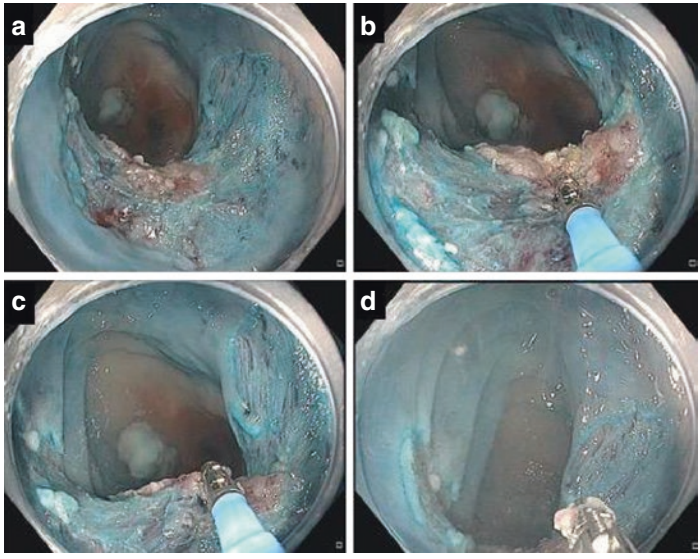

Figure 19.16 A 50 mm, distal ascending colon, half-circumferential, Paris IIa, granular adenomatous lesion with central submucosal fibrosis from previous resection attempt. Hot avulsion steps, (**a**) fibrotic non-lifting area isolated; (**b**) hot biopsy forceps used to grasp fibrotic residual; (**c**) grasped fibrotic tissue is tented and lifted away from the colonic wall to limit deep thermal injury prior to applying electrocautery; (**d**) electrocautery applied while pulling the tissue off

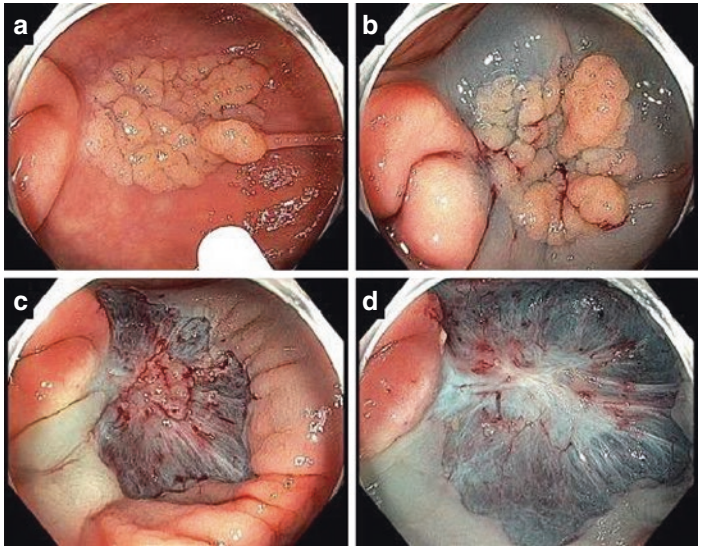

Figure 19.17 A 35 mm, cecal, Paris IIa, granular adenomatous lesion with central submucosal fibrosis from previous biopsy. (**a**) Lesion overview using high-definition white light; (**b**) non-lifting sign; (**c**) fibrotic non-lifting area isolated; (**d**) EMR defect after avulsion

- Tent and lift the fibrotic tissue away from the colonic wall to limit deep thermal injury prior to applying electrocautery.
- Electrosurgical generator settings (*ENDO CUT I mode, effect 3, cutting duration 1, cutting interval 3, or effect 1, cutting duration 4, cutting interval 1, ERBE VIO 300D, Tübingen Germany*).
- Electrocautery applied while pulling the fibrotic tissue off.
- Repeat the steps until all visible neoplastic tissue is removed.
- Examine the EMR defect for features of DMI using the Sydney classification of DMI and manage accordingly.

Surveillance and Post-EMR Scar Assessment

Typically, the first surveillance colonoscopy (SC1) is performed in 4–6 months post-EMR and the second surveillance colonoscopy (SC2) is performed after 12 months from SC1, if there was no recurrence. Recurrence at SC1 is commonly diminutive in size (1–5 mm) and easily manageable [58]. Post-EMR clipping can result in clip artifact on surveillance in 32–47% of cases [66, 67]. However, optical imaging using near-focus narrow-band imaging (NBI) can be used with high accuracy and sensitivity for detecting residual adenoma within post-EMR scars, Fig. 19.18 [68, 69].

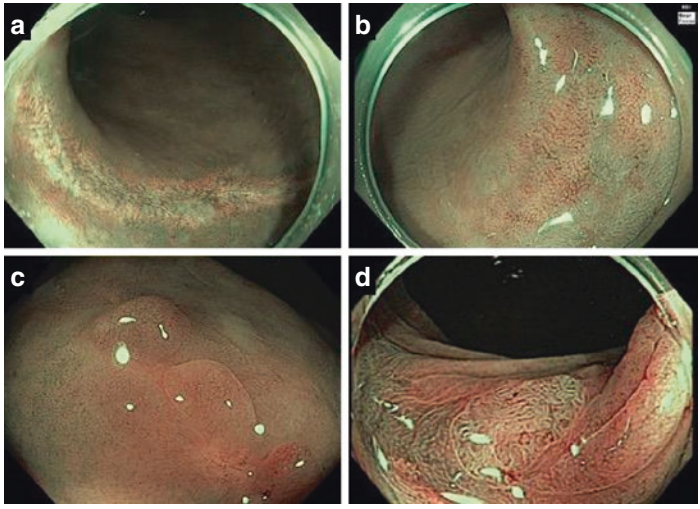

Figure 19.18 Post-EMR scar surveillance (**a**, **b**) normal flat bland post-EMR scar with normal mucosa and regenerative changes without recurrence, (**c**) clip artifact within post-EMR scar with normal mucosa, (**d**) diminutive residual adenoma within post-EMR scar

Post-procedural Care

Close post-procedural monitoring is needed to monitor for complications [7, 8]. Uncomplicated cases are closely monitored in the recovery area and discharged after 2 h.

Diet

We recommend keeping the patient NPO for 1-h post-EMR and can start a clear liquid diet after that in recovery and if no pain can be discharged home after 2 h and often resume regular diet next day.

Pain

Extramural injection of the dye can sometimes cause post-procedural pain. Often the pain can be quite severe with tender palpation and minimal guarding but the abdomen is often soft. This seems to be more common when epinephrine is used in the submucosal injectate. These situations need to be monitored in the recovery area often for a couple of hours as the pain improves significantly or resolves. The following steps are recommended:

1. Check vitals (often the blood pressure and oxygen saturation will be normal with transient mild tachycardia due to pain and distress).
2. Reassure the patient especially when the risk of deep mural injury or perforation is confidently excluded peri-procedurally (e.g., in cold EMR or if the EMR defect was closed effectively with clips in the case of conventional EMR).
3. Give simple analgesia (e.g., Paracetamol 1000 mg IV for analgesia).
4. Get a bladder scan to exclude urinary retention that can occur rarely with prolonged anesthesia.

5. If the pain does not improve after 1-h post recovery or the development of complications signs, then an urgent CT scan of the abdomen is recommended to exclude colonic perforation and free air under the diaphragm. Some patients will require admission overnight even if the CT was normal for supportive treatment and rarely for endoscopic or surgical management of complications.

Cold Endoscopic Mucosal Resection

Over the last few years, cold resection techniques including piecemeal cold endoscopic mucosal resection (CEMR) have revolutionized the management of colorectal neoplasia due to the safety and efficacy profile of this technique compared to conventional EMR and hot resection techniques [10, 11, 33]. For example, for large sessile serrated lesions, piecemeal CEMR is now becoming the standard of care [33–36]. Cold resection techniques eliminate electrocautery-related delayed complications. These include:

– Delayed bleeding
– Deep mural injury (immediate and delayed)
– Perforation (immediate and delayed)

It is still unclear how far can CEMR go in replacing conventional EMR as there are still unresolved questions (Box 19.2) [33]. The CEMR technique is described below, Fig. 19.19 [33].

Cold Endoscopic Mucosal Resection Technique

– Principles of lesion access, positioning, and submucosal injection techniques are the same as conventional EMR. Note that the volume of submucosal injection needed with CEMR is often less as the aim is to delineate the lesion's borders rather than guard against DMI Fig. 19.19.

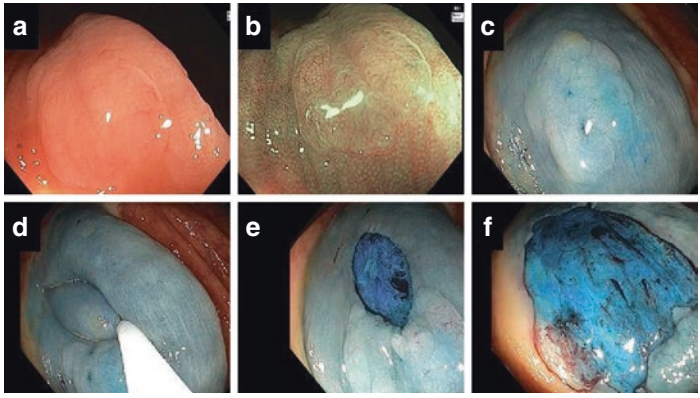

Figure 19.19 CEMR of a 20 mm Paris IIa sessile serrated lesion. (**a**) Lesion overview using high-definition white light, (**b**) NICE classification Type 1, sessile serrated lesion, (**c**) submucosal injection using chromosaline (methylene blue with epinephrine 1:100,000), (**d**) 10 mm dedicated cold snare placement including 5 mm of normal mucosa, (**e**) exposed submucosa following resection, (**f**) CEMR completed without evidence of DMI

- Use dedicated cold snares Fig. 19.2.
- Start resecting at the most technically difficult area first.
- The place opened snare on the target neoplasia and included 5 mm margin of normal mucosa.
- Limit the diameter of snare tissue acquisition to 10 mm or less to prevent snare stalling.
- During snare closure, ensure that tissue margins within the snare are continuously maintained. This is better achieved by controlled-speed snare closure by the assistant, while you simultaneously advance the snare catheter to guard against snare slippage and compromising tissue margins.
- Snare-handle should be closed to the end until transection occurs.
- Suctioning resected fragments as you go is possible and efficient, especially when using a scope with a working channel size of 3.7 mm or more.

- If snare stalls, do not use electrocautery as this risks DMI or perforation. Instead, partially open the snare-handle to a third or halfway and lift the entrapped tissue away from the colonic wall to facilitate slippage of the muscularis propria, and then slowly reclose the snare to transect the tissue.
- Examine the submucosal defect and utilize the water-foot pump to irrigate the defect and expand the submucosa for detecting residual neoplasia or DMI.
- Work systematically from one point and continue until lesion is completely removed.
- Persistent IPB is very rare, especially when using epinephrine, and prophylactic clipping to prevent delayed bleeding is not required unless the patient is on antithrombotics [70].

Box 19.2 Unanswered Research Questions for COLD Endoscopic Mucosal Resection

- What lesions are suitable for CEMR?
- Is thermal ablation of the margin needed for CEMR.
- Is epinephrine needed, especially in CEMR, to improve intraprocedural visualization by reducing intraprocedural bleeding and results in reducing residual neoplasia on surveillance?
- Can CEMR be safely and effectively performed without cessation of antithrombotic agents?

Summary

The last decade has seen a plethora of high-quality evidence of endoscopic techniques and tools revolutionizing the management of noninvasive colorectal neoplasia. In expert centers, the majority of these complex lesions are cured by EMR and avoid surgery in long-term follow-up. A unique advan-

tage of endoscopic resection over surgery is the ability for treatment revision. However, significant surgical colectomies for noninvasive colorectal neoplasia are still performed despite societies' endorsement of primary endoscopic management. Scheduled surveillance after EMR is important. Thermal ablation of the EMR margin has further enhanced the efficacy of EMR and substantially reduced recurrence . Widespread adoption of EMR is still required to enhance outcomes further.

Disclosure Statement Nothing to disclose.

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Chapter 20
Endoscopic Submucosal Dissection: Upper Gastrointestinal Tract

Abel Joseph and Amit Bhatt

Introduction

Endoscopic submucosal dissection (ESD) is an advanced endoscopic resection technique gaining popularity in the West as a minimally invasive treatment for early cancerous lesions of the gastrointestinal (GI) tract [1–3]. ESD was first developed in Japan about 20 years ago as a method to treat early gastric cancer and more recently has evolved to include esophageal and colonic lesions. ESD allows for en bloc removal of superficial tumors despite their size or associated fibrosis, resulting in higher curative resection rates, lower recurrences, and accurate histopathological staging. Despite initial concerns for increased risk of bleeding, perforation, and lack of local experts, ESD is now increasingly practiced

A. Joseph
Department of Medicine, Cleveland Clinic, Cleveland, OH, USA
e-mail: josepha10@ccf.org

A. Bhatt (✉)
Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH, USA
e-mail: bhatta3@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_20

in the West due to its wider applicability and advantages over conventional approaches such as endoscopic mucosal resections (EMR) and surgery [4].

Comparison to Traditional Endoscopic Mucosal Resection

Traditional EMR is a safe, efficient, and well-established technique for the removal of mucosal lesions in the upper GI tract. Its main limitations are the need for piecemeal resection of tumors >2 cm in size and the lack of precise control of lateral margin dissection. Piecemeal resection is unfavorable as it yields fragmented histopathological specimens that are associated with higher local recurrence rates and limit precise histopathologic analysis. A large meta-analysis including over 20 studies of esophageal cancer resection showed ESD had significantly higher en bloc and curative resection rates for lesions >10 mm [5] (Table 20.1). ESD is also a highly effective treatment for superficial gastric cancers with a high en bloc

Table 20.1 Meta-analysis comparing ESD versus EMR in resection of upper gastrointestinal tract lesions [5, 7, 8]

	Favors	Odds ratio (References)
En bloc resection		
Esophagus—BE/EAC	ESD	36.32 (95% CI: 20.64–63.91; $P < 0.0001$) [5]
≤10 mm	EMR	3.02 (95% CI 0.45–20.31; $P = 0.256$) [5]
11–20 mm	ESD	19.29 (95% CI 7.37–50.50; $P < 0.0001$) [5]
>20 mm	ESD	54.84 (95% CI 13.86–217.05; $P < 0.0001$) [5]
Esophagus—SCC	ESD	43.93 (95% CI 17.16–122.44; $P < 0.0001$) [5]
Stomach	ESD	9.00 (95% CI 6.66–12.17; $P < 0.001$) [7, 8]

Table 20.1 (continued)

	Favors	Odds ratio (References)
Curative resection		
Esophagus—BE/EAC	ESD	6.16 (95% CI 2.50–15.19; $P < 0.0001$) [5]
≤10 mm	EMR	1.90 (95% CI 0.24–14.99; $P = 0.543$) [5]
11–20 mm	ESD	17.47 (95% CI 4.62–66.00; $P < 0.0001$) [5]
>20 mm	ESD	52.35 (95% CI 2.75–997.99; $P = 0.008$) [5]
Esophagus—SCC	ESD	14.54 (95% CI 5.09–41.54; $P < 0.0001$) [5]
Stomach	ESD	2.92 (95% CI 1.85–4.61; $P < 0.001$) [7, 8]
Local recurrence		
Esophagus—BE/EAC	ESD	0.19 (95% CI 0.05–0.81; $P = 0.025$) [5]
≤10 mm	EMR	0.54 (95% CI 0.10–2.87; $P = 0.465$) [5]
11–20 mm	ESD/EMR	0.28 (95% CI 0.06–1.38; $P = 0.118$) [5]
>20 mm	ESD	0.06 (95% CI 0.02–0.19; $P < 0.0001$) [5]
Esophagus—SCC	ESD	0.09 (95% CI 0.04–0.19; $P < 0.0001$) [5]
Stomach	ESD	0.18 (95% CI 0.09–0.34; $P < 0.001$) [7, 8]

BE Barrett's esophagus, *EAC* early adenocarcinoma, *SCC* squamous cell carcinoma

and R0 resection rate (92% and 82%) and low local recurrence rate (3.9%) [6]. However, ESD has a few disadvantages, including longer procedure time and increased complexity.

ESD Indications

The key difference between surgery and endoscopic resections is the absence of lymph node dissection with endoscopy. Thus, ESD should only be considered in lesions with a negligible risk of lymph node metastasis, or risk less than the mortality of its surgical counterpart. The indications, and pre-ESD assessment, are largely focused on estimating the risk of LMN metastasis. While some factors will be known before ESD, others are not. The size of the lesion, presence of an ulcer, endoscopic, endosonographic appearance, and tumor differentiation are generally known prior to resection and help make up the indications for ESD. On the other hand, the presence of lymphovascular invasion (LI) and precise depth of invasion are generally identified on post-resection pathology and help determine if the ESD is curative or further treatment is required. The indications for ESD differ, by location, as factors related to LMN metastasis differ in each organ.

Gastric ESD Indications

Gastric ESD is a well-established technique for early gastric cancer (EGC), and large series have shown its effectiveness in the minimally invasive treatment of early gastric cancer in Asia. A recent North American series has also shown the potential for ESD to be an effective treatment of early and precancerous GI neoplasia in a Western population [6]. The risk of lymph node metastasis from EGC is derived from large Japanese surgical gastrectomy series that identified risk factors for LMN, and identified groups that had a negligible risk of lymph node metastasis. These make up the absolute and expanded indications for gastric ESD as per the Japanese Gastroenterological Endoscopy Society (JGES), which are used throughout the world [9] (Table 20.2).

Table 20.2 Indications for gastric ESD

	Mucosal adenocarcinoma/HGD					
	Without ulceration (−)		With ulceration (+)		Submucosal adenocarcinoma	
Pathology	≤2 cm	>2 cm	≤3 cm	>3 cm	<500 μm submucosal invasion	Any size
Well-differentiated/ intestinal type	ESD (absolute indication)	ESD	ESD	Surgery	ESD	Surgery
Poorly differentiated/ diffuse type	ESD	Surgery	Surgery	Surgery	Surgery	Surgery
References: [10–12]						

Esophageal ESD Indications

There are three main considerations in selecting a treatment modality for early esophageal cancer (EEC): risk of LMN metastasis, risk of morbidity and mortality from surgery, and risk of developing esophageal stricture after ESD resection. First, in contrast to the stomach, there is a greater risk of LNM with EEC. This is due to the unique anatomy of the esophagus, wherein the lymphatics penetrate through the muscularis mucosa and reach the lamina propria beneath the basement membrane [13]. This gives even T1a esophageal cancer a theoretical risk of LMN [14]. In esophageal cancer, this risk of LMN needs to be weighed against the risk of mortality and morbidity associated with esophagectomy. The Society of Thoracic Surgeons (STS) noted the operative mortality of esophagectomy to be 3.1% and morbidity associated with esophagectomy for esophageal cancer was 33.1% in a large study involving over 4321 patients [15]. Besides, many of the elderly patients that develop esophageal cancer have co-morbidities that preclude them from being candidates for surgery. Performing endoscopic resection of >3/4 the circumference of the esophageal lumen is a risk factor for esophageal stricture formation [16].

Despite stricture prevention methods, many at-risk post-ESD patients will develop strictures, and these strictures can be refractory, requiring long-term dilation that can result in significant morbidity for the patient [17]. This risk and the potential for repeated dilation post-resection need to be discussed with patients prior to ESD resection of larger lesions. The indications for esophageal ESD (Table 20.3) differ between SCC and EAC. For SCC, superficial lesions >10 mm in size involving m1 and m2 are absolute indications for ESD. Well-differentiated m3/sm1 (<200 μM submucosal involvement) lesions can be considered for ESD. However, the risk of LNM must be weighed against the surgical risk of esophagectomy [3, 18, 19]. However, some patients develop stenosis despite preventive strategies, which can be managed endoscopically. In EAC, endoscopic mucosal resection has

Table 20.3 Indications for esophageal ESD

Esophageal SCC		**Barrett's esophagus/ EAC**
HGD to well (G1) to moderately (G2) differentiated Paris 0–II lesions >10 mm in size		HGD to moderately (G1 or G2) differentiated T1a (m1–m3) ≥15 mm or not amenable to en bloc resection by EMR
Absolute indications	Expanded indications	Visible lesion ≥15 mm
m1–m2 involvement with <2/3 of the esophageal circumference	m3 or sm <200 μm involvement without lymphovascular invasion	
	m1 or m2 cT1a involvement with complete circumferential involvement and length <50 mm	Slightly depressed lesions (Paris IIc)
		Poorly lifting lesions
		Suspicion of submucosal invasion
		Salvage for EMR histology specimen with positive lateral margins
References: [3, 11, 18, 19, 23–26]		[3, 18, 26–30]

been a mainstay in the treatment of early esophageal cancer and caused a paradigm shift from surgical to endoscopic resection of tumors [20]. But lesions >1.5 cm generally require piecemeal resection that may be associated with increased local recurrence and lower curative resection rates. In a study

by Codipilly et al., comparing EMR to ESD outcomes in dysplastic Barrett's, ESD patients reached complete remission of intestinal metaplasia at higher rates than those treated with EMR, but rates of complete remission of intestinal metaplasia were similar at 2 years [21]. In a study by Meija-Perez et al., comparing ESD vs. EMR in treatment of early Barrett's neoplasia, ESD resulted in more definitive treatment, with en bloc resections in 98% of patients versus only 57% of patients following EMR. Recurrent disease was observed in 5% of patients in the ESD group versus 39% of all patients undergoing EMR for BE. The 48-month recurrence-free survival was found to be significantly higher in the ESD group (93% in the ESD group vs. 55% in the EMR group). Also, patients undergoing ESD had less need for repeat endoscopic resection procedures, whereas patients in the EMR group required up to seven additional resection procedures [22]. According to ESGE and AGA guidelines, the main indications for ESD in early BE neoplasia are high-grade dysplasia and cancerous lesions >15 mm, fibrotic non-lifting lesions that are not amenable to EMR resection, and suspected submucosal invasion <500 μM (Table 20.3) [4, 23]. In SCC, ESD has been shown to have higher en bloc resection rates than EMR for even smaller lesion sizes >10 mm and is the preferred approach for early SCC [18].

Preoperative Assessment

The preoperative assessment for ESD involves estimating the risk of LNM, depth of invasion, and defining the lateral borders of the tumor. Depth of invasion can be predicted using endoscopic features such as tumor size, redness, uneven surface, and margin elevation, which form the basis of the Japanese classification of gastric carcinoma or the Paris classification in the West [31–33]. Endoscopic ultrasound (EUS) can be useful to assess local lymph node involvement and rule out an invasion of muscular propria. The lateral borders

of SCC are delineated by a combination of narrow-band imaging that enhances the mucosal resolution by selecting specific wavelengths of light and chromoendoscopy with Lugol's iodine. The use of Lugol's iodine to delineate borders of dysplastic lesions is based on the diminished amount of glycogen in dysplastic tissue, causing a lack of iodine staining in dysplastic areas [34]. For SCC, Lugol chromoendoscopy (LCE) was previously the gold standard technique in lateral border delineation. More recent studies have identified LCE may not be as sensitive as NBI and is a time-consuming procedure associated with significant patient discomfort [35]. Gruner et al. compared NBI and LCE in a randomized trial and showed NBI is more specific than LCE in general practice and also that a combined approach could improve early cancer detection [36]. NBI is also able to detect microvascular structures of the esophageal mucosa, such as intrapapillary capillary loops (IPCL), by enhancing the magnification. IPCLs are further classified into four groups—V1, V2, V3, Vn based on their microvascular pattern. IPCL V3 is seen in M2/M3 lesions when irregular vessels lose their loop configuration due to deeper invasion of the mucosa. IPCL Vn indicates destruction of the IPCL and has the highest specificity for ESCC. Magnification endoscopy with NBI can be used to determine tumor invasion depth [37, 38]. For EAC, despite the recent advancements in imaging modalities such as confocal laser endomicroscopy (CLE), wide-area transepithelial epithelial sampling (WATS-3D), and volumetric laser endomicroscopy (VLE), virtual chromoendoscopy using NBI remains the gold standard in preoperative imaging [39–41].

ESD Equipment

The specialized equipment needed for ESD includes distal attachments, lifting solutions, ESD knives, coagulation devices, and high-performance electrosurgical generators.

Distal Attachments

Distal attachments are clear, plastic hollow cylinders or caps that are attached to the distal tip of the endoscope [42]. Caps have important mechanical functions. They aid in mucosal visualization by maintaining a distance between the endoscope lens and tissue. Caps can stabilize, push aside tissue, provide tamponade, and allow for counter-traction necessary for the endoscope to enter into the submucosal space. They also provide stability and housing for endoscopic knives to allow for precise cutting [42]. Straight soft distal attachments work well for gastric and esophageal ESD.

Lifting Solutions

Lifting solutions are used to expand the submucosal layer creating a safe plane for dissection. The ideal lifting solution for ESD needs to be affordable, provide a soft, long-lasting lift to facilitate dissection, and not interfere with the histologic assessment of the specimen. Viscous fluids are preferred in ESD, as it allows for more sustained elevation and decreased need for reinjection. In Japan, Glycerol and Sodium Hyaluronate (MucoUP; Johnson and Johnson, Tokyo, Japan) are commonly used for ESD but are not commonly commercially available in the USA. In the West, off-label solutions were commonly mixed and used for ESD. Hydroxyethyl starch (6% HES), sold as Voluven (Fresenius Kabi Norge AS, Oslo, Norway) is a colloidal volume expander that provides excellent submucosal elevation and is widely available. HPMC (diluted 2.5% hydroxypropyl methylcellulose), a viscous solution used in creating artificial tears is an off-label, non-toxic solution that produces a long cushion duration when used for lifting. Mehta et al. compared certain off-label solutions such as Voluven, HPMC, Eleview, and 6% HES with conventional lifting solutions such as normal saline, hyaluronic acid and demonstrated superiority with Eleview and 6% HES [43]. Currently, viscous fluids devel-

oped for EMR are commercially available in the West. ORISE gel (Boston Scientific, Marlborough, USA) and Eleview (Cosmo Pharmaceuticals, Dublin, Ireland) [44] are FDA-approved, viscous synthetic submucosal lifting solutions that have shown to have a long duration of lift and good cushion forming ability. These fluids usually contain a blue color dye to highlight the submucosal layer and improve the visibility of the lesions. Despite these advantages, the newer synthetic fluids come with their restrictions, bubbling obscuring the field of vision during dissection has been described with the use of Eleview. Olivas et al. recently described the presence of granulomas in the submucosa of patients who undergo interval surgical resection after ESD with ORISE gel [45, 46]. ORISE gel in the submucosa has histology similar to mucinous tumors and over time solidifies to a hard amorphous eosinophilic appearance that resembles amyloid deposits [47]. Tissue staining with mucicarmine, PAS stain, and Congo red can be used to differentiate such histological artifacts from amyloid and mucinous tumors. Knowledge of these fluid-related artifacts is important to avoid misdiagnosis and prevent additional resection procedures [48].

ESD Knives

There are now a large variety of ESD knives available on the market. The evidence differentiating knives is limited and the choice is often operator dependent. The main different types of knives include the Needle-type, Insulation-tip (IT), Hybrid/waterjet, and Scissor/grasping type. IT knives have an insulated ceramic ball at the end of the knife and an electrode to the proximal side of the ceramic tip. IT knives allow for fast dissection, although the plane of dissection is not always directly visualized and may have to be estimated based on the contour of the muscle layer. The IT knife tunneling technique has been described for esophageal ESD in Japan and recently in the West as a safe and effective technique for esophageal ESD [49, 50]. Needle-type knives cut with the tip of the knife

and lack an insulated component. Needle-type knife dissections are generally slower but allow for direct visualization of the dissection plane. While most knives can be used for gastric ESD, the IT nanoknife rather than the IT2 knife should be used in esophageal ESD, as the smaller backside chip (electrocautery blade on the backside of the ceramic ball) is smaller on the IT nano and safer to use in esophageal ESD.

Coagulation Devices

Intraprocedural and delayed bleeding is commonly encountered with ESD. Control of bleeding and unimpaired visualization during ESD is vital to procedural success. Coagulation devices are used to prophylactically cauterize visible vessels in the floor of the ESD defect and have been shown to decrease bleeding [51]. After the bleeding site is identified, a soft coagulation current is precisely applied to the bleeding source to limit tissue damage, reduce the risk of immediate and delayed perforation. If the site of bleeding is small, the tip of an ESD knife is usually sufficient to deliver soft coagulation avoiding the need for accessory exchange. Coagulation is performed with hemostatic forceps like monopolar coagulation grasper (Olympus, Center Valley PA, USA), bipolar HemoStat-Y (PENTAX, Tokyo, Japan), and hot biopsy forceps (Olympus, Tokyo, Japan). Hemostatic clips are generally not preferred during ESD as they can obstruct the dissection plane for further ESD.

Esophageal ESD Technique

Esophageal ESD has its unique challenges. The narrow lumen of the esophagus limits scope maneuverability and gravity counter-traction, the thin wall of the esophagus increases the risk of perforation, and due to the loose mucosa of the esophagus, lesions tend to distally retract and lose orientation during dissection. The techniques of performing esophageal ESD are largely aimed at overcoming these challenges (Fig. 20.1).

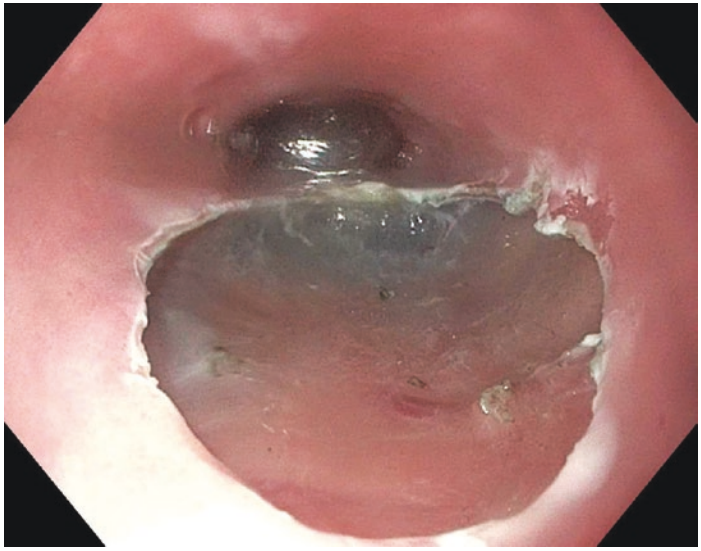

Figure 20.1 Post-esophageal ESD

Marking

Marking involves careful demarcation of the lesion before starting the procedure to ensure the borders of the lesion remain clear during injection and dissection. It is easy for the borders of the lesion to become obscured during dissection or submucosal expansion, so marking before dissection is vital. Due to the thin wall of the esophagus, markings must be done carefully to avoid perforation. Markings can be made with either argon plasma coagulation (APC) or using the tip of a needle-type ESD knife. For early Barrett's neoplasia, markings are generally made 5 mm outside the visible borders of the lesion, as borders can be diffuse, and there can be subepithelial spread of cancer beyond the visible borders of tumors. For SCC markings are generally made closer to the tumor to limit the amount of esophageal mucosa resected to limit the risk of post-ESD stricture.

Esophageal ESD Techniques

Clip Line Traction

Clip line traction is a simple and safe technique to provide counter-traction during ESD. This technique uses a dental floss thread tied to the tip of an endoclip which is applied to the proximal edge of the lesion. The thread is pulled proximally outside the mouth causing gentle pressure and traction allowing optimal visualization of the submucosal layer to direct dissection during ESD. The clip line traction method reduces mean dissection time, mean number, amount of injection during esophageal ESD and decreases the likelihood of muscle exposure [52–55].

Tunnel ESD

Tunnel ESD (ESTD) is a newer technique where the submucosa under the lesion is tunneled through proximal and distal mucosal incisions while keeping the lateral borders intact. This allows for improved visibility of the submucosal space due to the counter-traction maintained by the scope in the tunnel. A meta-analysis by Li et al. included 414 patients from 6 studies and showed the submucosal tunnel improved visibility with a low perforation rate [49, 56–59]. A study by Huang et al. showed ESTD shortened the procedural time by about 10 min compared with conventional ESD. However, one meta-analysis suggested ESTD might be associated with higher stricture rates.

C-Shaped Incision: IT Tunneling Technique

C-shaped incision IT tunneling technique is a technique used to overcome the challenges of esophageal ESD. The technique is primarily used in native non-fibrotic lesions, as IT tunneling does not work in fibrotic lesions. First, a distal and proximal mucosal incision is made. Next, a mucosal incision is made on the gravity-dependent lateral border, and the other lateral border is left intact. This allows the lesion to retract away from the water pooling gravity-dependent side, expos-

ing the submucosa for dissection. Keeping the other lateral border intact allows the lesion to keep its orientation during dissection. The loose submucosa of the esophagus allows entry of the entire ceramic tip of an IT knife into the submucosa, and dissection is performed with the backside chip (electrocautery knife on the back of the ceramic tip). This allows for safe and efficient dissection. Once submucosal dissection is complete, the remaining lateral mucosal border is dissected, completing en bloc resection. Mehta et al. recently confirmed the safety and efficacy of the C-shaped incision IT knife tunneling technique in the West for esophageal ESD of non-fibrotic lesions [49, 60].

Gastric ESD Technique

Similar to esophageal ESD, the steps of gastric ESD include marking of lateral margins, circumferential incision, and submucosal dissection (Figs. 20.2 and 20.3).

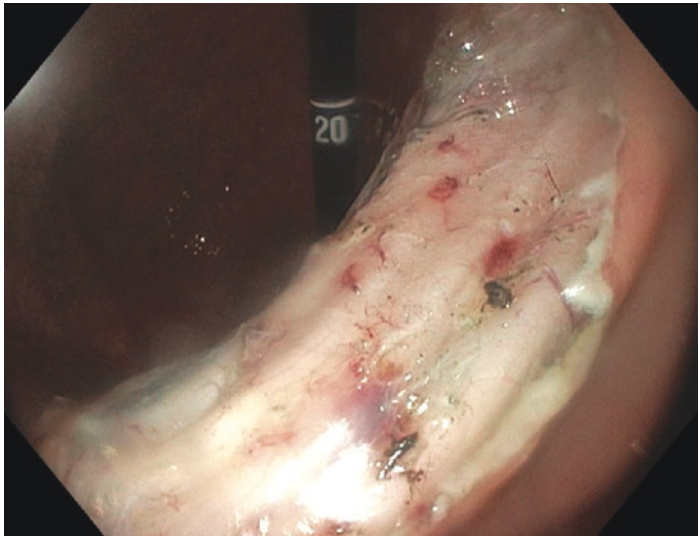

Figure 20.2 Post-gastric ESD resection defect on incisura of stomach

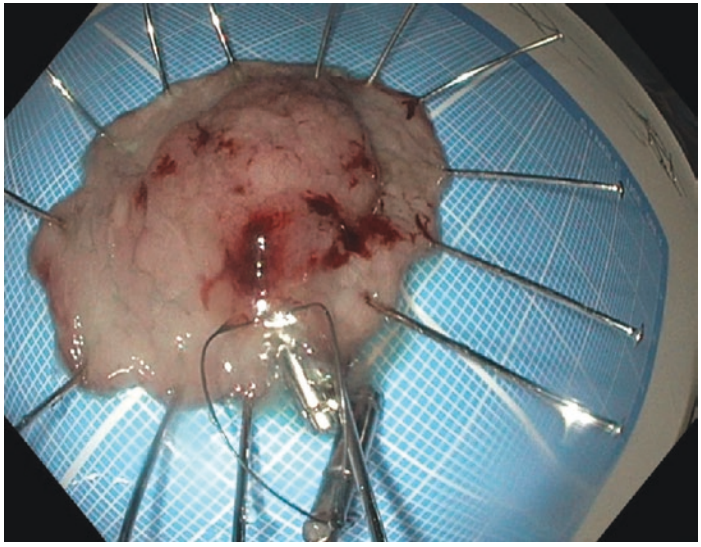

FIGURE 20.3 ESD resected gastric lesion

Marking

Superficial gastric lesions are marked along the lateral margins about 5 mm away from the tumor border. This is to ensure visualization of the lesion is not lost during fluid injection and dissection. Additionally, early gastric cancers can have subepithelial spread and a liberal 5 mm marking allows for the capture of such tumors. Marking is done with APC or the tip of a needle-type knife.

Circumferential Incision

First, a lifting solution is injected around the lesion. Using a needle-type knife, an initial incision is made into the submucosal layer. Finally, mucosal incisions are extended circumfer-

entially around the lesion causing it to separate from the surrounding gastric mucosa. Sometimes, only a partial circumferential incision is performed based on the location of the lesion in the stomach.

Submucosal Dissection

The submucosal layer underlying the tumor is expanded with an injection of a lifting solution. The endoscope bearing the ESD knife is advanced beneath the mucosa and the submucosal layer is dissected. The endoscopist must bear in mind to perform the dissection parallel to the muscular plane to avoid muscular injury.

Retraction Technology to Assist Esophageal and Gastric ESD

The technical complexity of ESD has limited its widespread use. Lack of appropriate traction due to the single-handed nature of the dissection procedure is one of the important limitations of ESD and many novel methods are being developed to provide appropriate traction during ESD.

Clip Line Traction

Multiple retrospective study and a recent trial evaluating the efficacy of dental floss clip line (DFC) traction found similar treatment outcomes with significantly shorter procedure times for lesions located in the upper or middle stomach along the greater curvature. Perforation was also found to be lower in the DFC-ESD group (0.3% vs. 2.2% $P = 0.4$) [61, 62]. The major limitation with clip line traction is that the direction of traction is only toward the oral side.

Water Pocket

Harada et al. [63] evaluated a novel technique for gastric ESD that involved creating a local water pocket (WP) to provide a better view of the dissection field. The study concluded that the overall procedure time was significantly lower in the WP-ESD group compared to conventional ESD. Interestingly, the efficacy of WP-ESD was noted to be dependent on the lesion location, subgroup analysis of WP-ESD in the upper third of the stomach was found to show no difference compared to the conventional ESD.

Tunnel ESD

As described above, ETSD is a safe, fast, and effective way of providing efficient traction for the removal of larger superficial gastric and esophageal lesions with a mild increase in the risk of esophageal stricture formation [64].

S-O Clip

The S-O clip (ZEON Medical, Tokyo, Japan) traction offers a unique way of providing counter-traction in a distal direction. The device consists of a spring with one side attached to the clip that is placed on the proximal mucosal flap requiring traction, the other end of the spring is attached to a nylon loop which is hooked on a regular clip and anchored to the proximal gastric wall opposite to the lesion. Hashimoto et al. describe the technique in a propensity-matched analysis which showed a significantly shorter procedural time with no differences in treatment outcomes [65].

Traction Wire

Mehta et al. recently described the use of a novel traction wire consisting of a nitinol wire loop attached to endoscopic clips on both ends in a live porcine model. The clips are

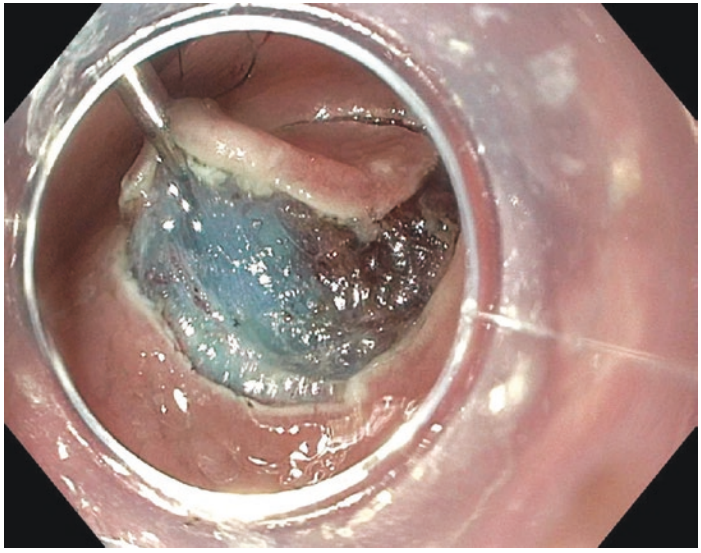

Figure 20.4 ESD with traction wire

attached to opposite sides of the lesion and the nitinol wire progressively bends into its pre-configured shape allowing traction in the horizontal plane between the two clips at the edges of the lesion [66]. This method offers the advantage of being able to apply traction in any direction (Fig. 20.4). There was an overall reduction in mean procedural time and an increase in dissection speed in both the stomach and esophagus in comparison with traditional ESD reference times in similar porcine models [67].

Adverse Events

Bleeding

ESD bleeding can be intraprocedural, immediate (<48 h), or delayed (within 4 weeks after ESD). As discussed earlier, intraprocedural bleeding is managed using coagulation

devices thereby allowing optimal visualization for a successful ESD. Significant post-procedural bleeding is commonly defined as a >2 g/dL drop in hemoglobin from pre-procedural baseline or a change in hemodynamic status. Bleeding is more frequently encountered in the proximal stomach due to larger vessels in the submucosa. In the stomach, the rates of post-ESD bleeding have been reported with a lot of heterogeneity ranging from 1.3% to 13% [68]. Coagulation of visible submucosal gastric vessels in the post-ESD site is recommended to decrease the incidence of delayed bleeding [69]. Coagulation using diathermy can carry a risk of thermal injury. Subramaniam et al. demonstrated the use of a topical novel hemostatic peptide (Purastat) to reduce diathermy use and control bleeding in patients undergoing ESD. The authors of the RCT also found complete wound healing at 4 weeks in 48.8% of patients in the Purastat group versus healing in only 25% of patients in the diathermy group [70]. Administration of proton pump inhibitors or novel potassium-competitive acid blockers [71, 72] after gastric ESD for 4–8 weeks decreases the rate of post-ESD bleed. Delayed bleeding rate following esophageal ESD occurred only around 3.1% (95% CI:2.4–3.8%), possibly due to fewer submucosal vessels and the narrow lumen serving as a physiologic tamponade [19]. PPI administration following esophageal ESD is not recommended unless there are coexisting features of reflux esophagitis [19]. Routine second-look endoscopy has no role in preventing delayed bleeding following upper GI ESD [73].

Perforations

Perforations are adverse events of ESD and appropriate identification and management are necessary for successful ESD [74]. The risk of perforation is 0–6% in esophageal ESD and 1.2–5.2% in gastric ESD [5, 75]. A retrospective study comparing patients undergoing ESD for superficial esopha-

geal SCC under conscious sedation versus general anesthesia (GA) found better outcomes and lower rates of perforation in patients undergoing procedural GA [76]. Carbon dioxide is absorbed faster and is the preferred over the air to avoid complications related to perforations. Perforations are typically small defects compared to the size of the ESD knife tip. When a defect is identified, it is often recommended to apply an end clip slowly after the lesion is dissected. Conservative management is usually sufficient for complications such as mediastinal emphysema, pleural effusions, and pneumothorax, as shown in a retrospective review of 306 patients who underwent esophageal ESD [77].

Stricture

Strictures are most commonly seen following esophageal ESD and may sometimes occur in the gastric cardia and antrum [78]. The risk factors for stricture formation include mucosal resection area, location, and circumference. Due to recent advances in ESD, larger superficial tumors are being resected, which often lead to stricture formation. A study evaluating ESD resection of Barrett's neoplasia, with a mean resection size of 52.5 mm found post-ESD strictures in 60% of cases [79]. Stricture rates range around 66–100% and require about 6–23 endoscopic balloon dilations for symptom control [17]. Oral prednisone and local triamcinolone are the present first-line options for the prevention of esophageal strictures [17]. However, despite the use of steroids, strictures do occur, and further strategies are under investigation for the prevention and treatment of post-ESD strictures [16]. A comparative study combining steroid injection and polyglycolic acid (PGA) shielding effectively lowered the post-ESD stricture rate. Further studies comparing steroids and combination with a tissue shielding agent will help identify the true benefit of these innovations [16, 80].

Conclusion

ESD is now a well-established procedure in the minimally invasive management of early upper gastrointestinal cancers. ESD has numerous advantages over the traditional EMR technique, especially in lesions larger than 2 cm, while avoiding the mortality and morbidity of the surgery. Over the years, ESD has consistently shown higher rates of en bloc resection, curative resection, histopathological accuracy, and lower recurrence. ESD is the procedure of choice for patients with large superficial cancers of the esophagus and stomach with a very low risk of LNM. Patients must be educated on the risks of adverse effects such as bleeding, perforation, and strictures. The future of ESD includes technological advancements in ESD tools and retraction devices, novel endoscopist training strategies, and the development of techniques to prevent adverse events and decrease the technical difficulty of ESD.

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Chapter 21
Endoscopic Submucosal Dissection in Colon and Rectum

Gizem Kaya, Ilker Ozgur, and Emre Gorgun

Introduction

This chapter will discuss advanced endoscopic resection techniques known as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD). These procedures will be presented in detail step by step with technical aspects, indications, and complications. The section will also present and describe the equipment and its application for the specific techniques, future technology developments, and innovations in endoluminal surgery.

Background

Colorectal cancer (CRC) is the third most common cause of cancer death in both men and women in the USA [1]. Like several other developed countries, the USA has a well-established screening program for colorectal cancer [2]. A remarkable increase in non-malignant polyps and early-stage

G. Kaya · I. Ozgur · E. Gorgun (✉)
Department of Colorectal Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: gorgune@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_21

colorectal neoplasia is expected with the expansion of screening programs [3]. In the USA, 30,000 patients with large colon polyps undergo surgical procedures such as colectomy or proctectomy every year.

However, according to our recent study, for greater than 92% of these surgical resections, final pathology does not reveal malignancy [4]. Furthermore, organ resections place them at risk for both surgical and post-surgical complications. While oncological colorectal resection is overtreatment for the majority of these benign polyps, bowel resections may also be associated with major complications and even mortality.

Advanced polypectomy techniques such as endoscopic mucosal dissection (EMR) and endoscopic submucosal dissection (ESD) have been developed in Asia with the purpose of organ preservation with low complication rates [5]. Especially in Japan, ESD plays an important role in the management of non-malignant and early malignant colorectal lesions. It is first established in the treatment of gastric cancers since thick gastric walls allow for safer dissections [6]. ESD procedure is a minimally invasive approach that enables *en bloc* resection of the tumor for further histopathological assessment with organ preservation. Additionally, ESD provides shorter hospital stay, less to no post-procedure pain, less bodily trauma, faster recovery, and fewer postoperative complications compared to surgery [7]. Despite its well-known popularity in Asia, ESD is still a relatively uncommon procedure in Western countries [8]. Although there is growing interest for ESD all around the world, its general acceptance remains very low due to technical challenges and long training time for performers [9]. In addition to its steep learning curve, some of the other reasons for low adaptation rates include increased procedure time, procedural risks, and lack of proper reimbursements [10]. However, considering the increasing incidence of non-malignant colorectal lesions, refinements of newer advanced endoscopic tools, and more training courses, popularity of ESD and its application is expected to grow [11].

Both ESD and EMR procedures consist of instillation of an injectate under the aimed lesion to provide an elevated cushion for both preventing perforation and allowing good visualization and safe dissection during the procedure. Lifting the lesion and the polyp-bearing mucosa with an appropriate injectate creates submucosal lift and provides a lift for safe resection. The EMR procedure consists of removal of the lesion with simple snaring after adequate and proper submucosal lifting, whereas submucosa beneath the lesion is dissected with special tools such as endo-knives during the ESD procedure. The ESD procedure starts with marking the perimeter of the lesion using cautery, subsequently followed by injection of lifting agent into the submucosa. After injection of the submucosal plane, a circumferential mucosal incision is created with a special knife followed by submucosal dissection and complete removal of the lesion in one piece. This provides removal of wider and possibly deeper, scarred lesions. ESD was developed to alleviate removal of lesions that are challenging to remove with regular snaring. The procedure aims to obtain R0 resection with *en bloc* removal of the specimen for further histopathologic assessment. Therefore, ESD is preferred for lesions highly suspicious for superficial submucosal invasion that cannot be optimally removed by EMR.

ESD was initially used for the upper gastrointestinal system and stomach. Even though the anatomy and physiology of the lower gastrointestinal system differs than the upper, ESD gained popularity in the treatment of colorectal lesions. The thinner wall of the colon compared to the stomach wall, irregular colonic folds, flexures and tortuosity, and peristaltic movements of the colon further destabilize the scope position for ideal dissection, which are the main causes of ESD difficulty in the colon [12]. If ESD is compared to EMR, it is reported to not only have a higher perforation risk and longer procedural duration compared to EMR, but also have a higher *en bloc* resection, especially for larger lesions, and lower recurrence rate [13]. The lesion characteristics (such as surface morphology, lesion granularity, pit patterns, etc.), size, location, and the experience level of the endoscopist play a role in the selection of the appropriate procedure [14].

Indications

Current Japanese and US Guidelines both recommend ESD for lesions larger than 20 mm with appropriate features for endoscopic *en bloc* removal. ESD is also recommended for lesions with underlying fibrosis, sporadic localized lesions with ulcerative colitis, and local residual lesions after prior EMR. The US Multi-Society-Task Force on Colorectal Cancer indicates an ESD procedure for the lesions larger than 20 mm which have high suspicion of limited submucosal invasion, depressed morphology, and irregular or nongranular surface pattern that should be managed by an advanced endoscopist, while snare polypectomy is proposed for lesions smaller than 10 mm [15]. Curative resection is described as R0 resection of colon polyp with <1000 μm of submucosal invasion, and with favorable histologic characteristics. Unfavorable histologic features were defined as poorly differentiated lesion, lymphovascular invasion of the lesion, <2 mm margin distance, and invasion of the stalk [16].

Periprocedural Management

Previous colonoscopy reports, especially with colored images, should be evaluated before the procedure. This assessment is essential and guides the endoscopist to evaluate the lesion(s) in detail, determine and plan the flow of the process as well as additional equipment requirement.

Among advanced endoscopic imaging techniques, focal interrogation with narrow-band imaging is used to predict the risk of invasion. The focal interrogation with band narrow-band imaging is especially helpful to assess the surface morphology in detail. The lesion's outlining margins and pit patterns are interpreted for submucosal invasion risk [17, 18].

Routine principles of care for colonoscopy are followed for all patients and pre- and peri-operative assessment is vital for successful outcomes. Patients are prescribed peroral Neomycin and Metronidazole with mechanical bowel prepa-

ration. For bowel preparation, a day before the procedure 4 L polyethylene glycol (PEG) is preferred. Questioning medical history and current medications is crucial. If the patient is taking any anticoagulants, they should be stopped 2–7 days depending on mechanism of action before the procedure with consultation to ordering physician. Endoscopy suites or operating room settings can be chosen based on the patient age, comorbidities, and lesion characteristics. Operating rooms may be preferred for patients with multiple comorbid conditions or lesions that are large and are located within challenging places in the colon. If combined endo-laparoscopic approach or use of an endolumenal platform is anticipated, these cases should also be performed in the operating room. Patients should be kept under observation for at least 4 h after the procedure especially if any concerns and may be discharged the same day after starting oral intake. Sedation is delivered either with conscious sedation or with propofol due to its long-term use ability and quick recovery profile. As part of the standard evaluation after ESD, a follow-up colonoscopy is a must at 6 months for surveillance to rule out recurrence.

Injectate Types and Injection Techniques

The main purpose of the injection process is to create a submucosal space and create a surgical plane for the procedure and subsequent dissection. The created space within the submucosal layer will reduce the perforation risk and transmural thermal injury via separating the lesion from the deeper muscularis propria layer. Injections should be performed in a stepwise manner while aiming to form even elevation beneath the lesion that will facilitate safe dissection.

The injectate material should be long-lasting which is crucial for an effective and safe procedure. Several injectates are currently available in the market. Hyaluronic acid is widely used in Japan. It contains glycosaminoglycan, a substance naturally found in connective tissues. This biological material

is not allergic to humans. However, hyaluronic acid is not commonly used in the USA due to its high cost. Some other agents such as dextrose 50, succinylated gelatin, hydroxypropyl methylcellulose, and hydroxyethyl starch have been used for several years. But none of these solutions have been documented as safe and effective as hyaluronic acid [19, 20]. The Federal Drug Agency approved two new premixed compositions named Eleview® and ORISE™ Gel Submucosal Lifting Agent (Boston Scientific). These composites propose excellent cushion forming ability and longer lifting period. They are premixed solutions that consist of methylene blue dye and colloid agents which improve visualization and highlight tissue planes. Indigo carmine and methylene blue are used for colorization to achieve better visualization and differentiate tissue layers. They aid to identify lateral and deep margins of the lesion. Their special role is to differentiate the submucosal layer from the muscle layer. In the submucosal plane solutions with long-lasting features are preferred as reinjections will extend the procedure duration.

In addition to these solutions, diluted adrenalin (1 mL of 0.1% of adrenalin) and hydroxyethyl starch solution mixed with methylene blue or other dyes are some of the alternatives that have been used. Since it does not remain in tissue for an adequate period saline is one of the solutions that especially should be avoided [21].

The purpose of the injection of the solution is to accomplish a balanced and adequate lift of the lesion. First, start the injections around the perimeter of the lesion to keep a safe margin of the lesion while injecting the mucosa. An injection needle should be placed tangentially to the mucosa. If tissue elevation is not observed, entry into the wrong plane should be suspected. The needle should be adjusted before the continuation of the procedure. Subsequent injection should be continued only after correct positioning of the needle. The shape and the location of the lesions play an important role for the whole process and the amount of injectate. It is crucial to start the injection on the far aspect of the lesions that are located on a fold or behind a haustra. The deployment from

the distal part (anal side) might cause losing the view of the lesion. If adequate lift cannot be achieved even though there is certainty of correct plane assessment, then this could be a sign of deep invasion into the submucosa or fibrosis from previous biopsy or resection. It is proposed to suspend the procedure in case of suspicion of deep invasion. Nevertheless, we recently reported that the non-lifting signs are probably due to previous interventions [22]. In that case, there is no need to stop the procedure.

Materials and Devices

To overcome technical demanding difficult aspects of the ESD, over the past 20 years several types of equipment and innovative technological devices have been established.

One of the challenging aspects of the ESD is that the entire procedure is performed with a single endoscope which causes the absence of a second hand providing traction on the lesion and subsequently the absence of better visualization during the entire procedure. Distal end caps have special importance to provide desired traction between submucosal space and lesion to facilitate dissection. Caps consist of two main shapes: transparent and cylindrical. Hoods are a sort of cap that aid to elevate mucous membranes after an initial incision to guide submucosal dissection. The attached cap at the end of the endoscope provides fixing of the endoscope at a constant distance from the mucosa and guides the endoscopist for better visualization of the lesion which is crucial to prevent complications. Caps improve the visibility, time, and safety of the procedure. Besides that, there are newly designed caps with shorter and smaller stature that allow the endoscopist to slide into the submucosa and accomplish adequate upward traction at the same time [23, 24].

There are several types of knives to dissect the lesion and the endoscopist should know the advantages and disadvantages of each one to improve dissection safety (Table 21.1). There are three main types of knives: Needle type, Insulated

Table 21.1 The knife types and their special features

	Knife types	Features	Advantages	Disadvantages
Needle Type Knives	Dual Knife™ (Olympus, Tokyo, Japan)	– Monopolar	– Easy to use	– Perforation
				– Poor control
	Speedboat–RS2™ (Creo Medical, Chepstow, United Kingdom)	– Bipolar	– Prevents unnecessary tissue damage by less energy delivery	– Possible muscle injury
		– Microwave coagulation		– Fibrosis
Insulation Tip Knives	IT Knife™ (Olympus, Tokyo, Japan)	– Used for gastric lesions	– Facilitates cutting	– Sometimes unable to visualize the lesion
			– Perfect tool for submucosal dissection	
	IT Knife™ 2 (Olympus, Tokyo, Japan)	– Used for gastric lesions	– Facilitates cutting	– Sometimes unable to visualize the lesion
			– Perfect tool for submucosal dissection	
	IT Knife™ nano (Olympus, Tokyo, Japan)	– Shorter knife length for narrower parts of alimentary tract	– Facilitates cutting	–Sometimes unable to visualize the lesion
		– Used for esophagus and colon	– Perfect tool for submucosal dissection	

Hybrid Knives	Hybrid Knife® (ERBE USA, Marietta, GA)	– Central capillary within the cutting knife work as a waterjet	– Expedited procedure process	– More challenging to perform
			– Easier submucosal injection	
			– No need to change tools during procedure	
	ORISE Pro Knife™ (Boston Scientific USA, Marlborough, MA)	– ORISE Pro Knife™ allows ORISE Gel Injection through the tip of the electrode during dissection	– No need to device change	– Expensive
			– Provides long lasting mucosal elevation	

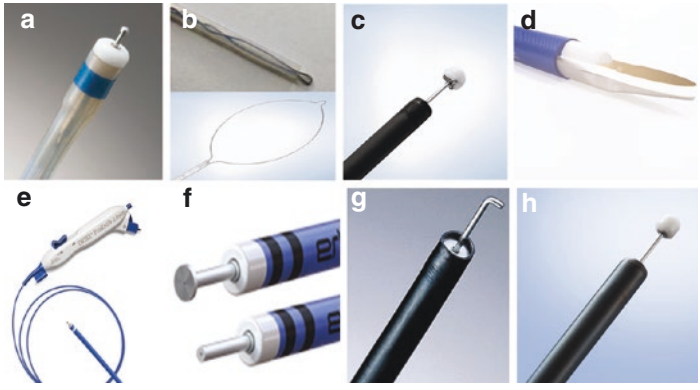

FIGURE 21.1 ESD knives; (**a**) Dual Knife; (**b**) Snare for Hybrid ESD; (**c**) IT Knife 2; (**d**) Speedboat; (**e**) ORISE ProKnife; (**f**) Hybrid Knife (ERBE); (**g**) Hook Knife; (**h**) IT Knife nano

(IT) type, and Hybrid type. There is no standardization for equipment depending on the type of lesion, and the right instrument preference depends on the availability and prioritized comfort level of the endoscopist.

The most commonly used needle-type knife is Dual Knife™. The Dual Knife™ (Olympus, Tokyo, Japan) (Fig. 21.1a) is an electrosurgical knife designed with a disc-like cutting part to facilitate marking and allow incision and dissection in all directions. This disc-like feature provides better and faster hooking of the lesion and the round surface promotes hemostasis by coagulation. The important feature of this knife is its short cutting length which allows dissection over areas with fibrosis. The tip length of the knife is adjustable and when closed it can be used for marking and hemostasis; while opening the knife in full length enables the use for incision and dissection. Olympus has features that offer options such as larger electrode thickness and longer blade

and this makes it compatible and preferred for the ESD procedures.

Hybrid Knife® (ERBE USA, Marietta, GA) (Fig. 21.1f) consists of a central capillary within the cutting knife that works as a waterjet. The pressurized water jet enables the penetration of mucosa and submucosa thus provides submucosal lift without needle puncture. There are three types of knifes that are approved by FDA and available on the US market: O-type, I-type, and T-type. Hybrid Knife® expedites the procedure by providing a single tool for both injection and dissection with no need to change instruments. It promotes location maintenance and avoids unnecessary withdrawal of the scope and instrument exchange.

IT Knives™ (Olympus, Tokyo, Japan) (Fig. 21.1c) are the first devices invented for ESD. It works by pulling the device against the submucosal space. It is usually used for gastric lesions. But shorter IT Knives known as IT knife nano™ are developed for colorectal ESD procedures. It has a longer blade compared to needle-type devices which allow the endoscopist to achieve better horizontal dissections. IT Knife nano™ (Fig. 21.1h) harbors a disc-shaped electrode for precise dissection at thin walled organs.

The Hook Knife™ (Olympus, America) (Fig. 21.1g) is designed as an L-shaped hook that provides fine incision and dissection maneuvers both horizontally and vertically. The shape of the Hook Knife™ provides hooking and retraction maneuvers of the lesion which is especially helpful for fibrotic lesions. The unique turn and lock system of Hook Knife™ provides certainty by locking the cutting wire to prevent perforation.

The Speedboat-RS2™ (CREO Medical LTD, UK) (Fig. 21.1d) is one of the newly designed ESD knives. It consists of an electrosurgical generator, a retractable 26-gauge needle, dual-energy capabilities with bipolar radiofrequency cutting, and hemostasis with microwave coagulation. The Speedboat-RS2™ prevents thermal injury to muscularis pro-

pria with its insulated surface. It prevents tissue damage by delivering less energy when compared to monopolar devices. Its optimized shaft design provides controlled rotation [25].

ORISE ProKnife™ (Boston Scientific USA, Marlborough, MA) (Fig. 21.1e) is a new electrosurgical knife available to use with ORISE Gel Submucosal Lifting Agent which provides long-lasting mucosal elevation. Thus, ORISE ProKnife™ allows ORISE Gel injection through the tip of the electrode during dissection without the need for device replacement. The injection channel is 23–25-gauge wide and ORISE Gel can be injected easily through the tip of the electrode. It has a T-shaped electrode body and has a variety of electrode shaft length options: 1.5, 2.0, or 3.00 mm. We recommend using knifes 1.5 or 2.0 mm in length to perform procedures on the colon. It has a locking feature that provides safety and procedural efficiency by fixing the length of the electrode during the procedure and prevents nursing fatigue.

One of the most important tools of endoscopic resection procedures is a power generator for electrosurgery. The generators have multiple power setting modalities with both monopolar and bipolar features. Electrocautery is used for two main purposes: polyp removal by cutting the lesion (snare closure) and coagulation by using thermal energy. Cautery energy works at the cellular level by causing heat production and reducing tissue resistance which subsequently causes tissue disruption, coagulation, and hemostasis.

In case of bleeding from vessels smaller than 2 mm during the procedure, forced, swift, or soft coagulation modes can be applied to achieve hemostasis. For vessels larger than 2 mm the special hemostatic forceps, the Coagrasper Hemostatic Forceps™ (Olympus, Tokyo, Japan) is widely preferred. The Coagrasper utilizes monopolar energy and can be used with the purpose of hemostasis. It works by grasping a bleeding point or vessel and subsequently applying monopolar coagulation. The device has varying options of cup shapes and opening widths with an excellent rotational function. The Coagrasper delivers both mechanical and energy-based hemostasis to the tissue which allows the endoscopist to iso-

late a vessel from healthy surrounding mucosa and thermal coagulation usage only whenever needed. If coagulation could not be achieved via the Coagrasper, the endoclip can also be used.

Through-the-scope clips (TTS) are typically used for lesions smaller than 2 cm with perforation or bleeding. Recently over-the-scope clip system (OTSC®, Ovesco Endoscopy, Tubingen, Germany) has been introduced for the closure of lesions with full-thickness defect or lesions larger than 2 cm. The OTSC clip, also known as the bear claw clip, not only helps to close large defects, but it also provides hemostasis. It has higher efficacy effects for the ESD procedure compared to TTS clips [26–29].

Endoscopic Mucosal Resection

After injecting the fluid, the EMR procedure continues with piecemeal or en bloc snaring of the lesion. The main purpose of the endoscopist should always be *en bloc* removal but when it is not possible or practical, repeating snaring can be performed. However, as more and more the pieces snared, the quality of histopathologic examination is decreased.

There are many shapes and sizes of snare options available, depending on the lesion size and location. Endoscopists should assess the best snare shape/size fit for the lesion. The endoscopist's main purpose should be to allow 2–3 mm normal mucosal margin while snaring. For lesions with suspected fibrosis or submucosal invasion, the endoscopist should start a mucosal incision using a 1 cm margin instead. When the lesion is completely covered in the snare, then the snare should be closed tightly (Fig. 21.1b). If piecemeal resection is the chosen method, then the snare should be aligned according to the resected margin edge and then the endoscopist can continue snaring until complete lesion removal can be accomplished.

Hybrid ESD is known as simplified ESD, ESD with snaring, EMR with circumferential incision, or Knife Assisted

Snare Resection. Hybrid ESD is differentiated from ESD or EMR by performing circumferential mucosal incision and partial submucosal dissection with the use of snare for the resection step. While conventional ESD is described as a circumferential incision in an *en bloc* resection manner without using any snare device, Hybrid ESD is described as partial submucosal dissection followed by snare-assisted resection. This procedure has advantages over conventional ESD such as shorter procedure time, but it is associated with lower *en bloc* resection rates. Hybrid ESD is usually performed as a bridge for learners between EMR and ESD [30, 31].

While EMR is usually preferred for complete resection of lesions less than 20 mm in diameter, it is accepted not to be able to completely resect lesions larger than 20 mm in diameter. Endoscopic piecemeal mucosal resection (EPMR) is often used for polyps larger than 20 mm which are resected in two or more pieces. As a disadvantage, it usually cannot provide complete pathological diagnostic data with an increased risk of submucosal infiltration. Patients are usually exposed to more frequent follow-up endoscopies due to a higher rate of incomplete resections. Furthermore, EPMR usually results in submucosal vessel trauma which may bleed during or after the intervention [32–35].

Endoscopic Submucosal Dissection

Endoscopic submucosal dissection can be defined simply as an *en bloc* resection of mucosa with surgical principles. It is usually performed with a needle knife through the endoscope and considered a better technique when compared to EMR, as it results in higher *en bloc* resections and lower local recurrence rates.

ESD consists of two main steps: circumferential mucosal incision and submucosal dissection. Injection of the lifting solution should be around the perimeter of the lesion. The submucosal injection is applied at multiple points lateral to the marker points to elevate the lesion and detach it from the

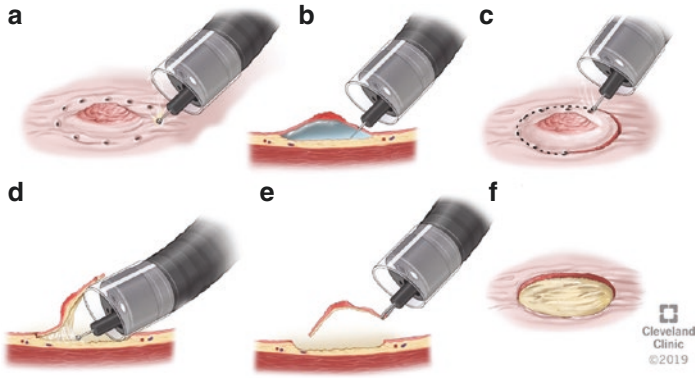

FIGURE 21.2 Stepwise demonstration of ESD: (**a**) Marking, (**b**) Injection, (**c**) Mucosal cut, (**d**) Submucosal dissection, (**e**) Collection, (**f**) Hemostasis and control

muscular layer. The standard steps of the procedure with injection and tissue elevation are followed by marking the borders of the lesion circumferentially with a needle knife (Fig. 21.2). After that, the electrosurgical knife is used for the incision of mucosa followed by circumferential or semi-circumferential cut around the lesion. The incision should be started from the distal end of the lesion and the dissection should be extended within 2–3 mm of normal mucosal margins. In lesions with suspected fibrosis or submucosal invasion, the procedure should be started with a wider and clearer mucosal border incision, such as 1 cm instead of 2–3 mm. The endoscopist should start dissection in a parallel or horizontal direction rather than a tangential way or a perpendicular way to prevent perforation. The distal disposable cap is crucial to provide traction, which shortens the duration and provides better visualization, and prevents dissection in the wrong plane. After dissection has begun, it should be proceeded deep into the submucosa, where visualizing the submucosal plane is key. If elevation or vision loss occurs that may obscure the procedure, submucosal injection should be repeated. The endoscopist should follow the steps described until the full *en bloc* resection is completed. Cleaning the field after dissection is important and allows the endoscopist

to visualize the resected area and observe any possible defects. Coagulation forceps can be helpful for hemostasis while potential injury to the muscular layer via thermal energy should be kept in mind. Hemoclips can be used instead of coagulation forceps to prevent delayed bleeding. Any full-thickness defects created during the procedure may be closed with multiple clips, or over-the-scope clips may be deployed for large holes as well.

Lesions located in the cecum, hepatic or splenic flexure, near the anal verge and at the mouth of the appendix are often more challenging [36, 37]. Later described platforms or assisting traction devices may help to overcome such issues.

Patients can start to drink clear fluids after the first day of the procedure and then progressed as appropriate. Patients can be discharged on the same day, but for challenging procedures or patients with comorbidities the discharge may be postponed after adequate observation which is at least for 4 h.

Lesions in patients with inflammatory bowel disease (IBD) are usually highly fibrous due to chronic inflammation. Thus, they often have higher incomplete resections and perforation rates. A recent, novel pocket-creation method (PCM) has been developed for such lesions. Endoscopists apply the pocket-creation method by creating a large submucosal pocket with a small-caliber tip transparent hood (ST hood) without performing circumferential incision, which assists traction without using other special tools [38].

Complications of Advanced Polypectomy

While ESD is accepted as a minimally invasive treatment procedure for colorectal polyps, it is still associated with major complications such as perforation, bleeding, and minor complications such as electrocoagulation syndrome or fibrosis. Polyp location, difficulty in maneuvering, insufficient traction, and presence of fibrosis play a role for complication occurrence. The existence of fibrosis is a risk factor for perfo-

ration. It can result from previous endoscopic intervention or tumor invasion. Full-thickness perforations usually result from deep resection and require immediate intervention. Even in experienced centers, perforation has been reported in 2.7–5.7% of ESD procedures [39–41]. As soon as the perforation occurs, the patient should be turned to the antigravity side of the defect to prevent peritoneal contamination. Subsequently the endoscopist should wash amply the surrounding and aspirate all feculent fluid. Also, it should be kept in mind that delayed perforations may occur due to coagulation necrosis or any significant injury to the muscle layer. Immediate perforations are more common than delayed perforations [42]. Although we do not routinely use imaging techniques such as abdominal CT or X-ray, these are often used to confirm the diagnosis. The diagnosis is usually based on the overall clinical presentation including abdominal pain, abdominal distension, or fever, rather than laboratory values or imaging outcomes of the patient. Simple clip closure and over-the-scope clips are commonly used for the closure of small defects. If the patient does not improve despite clipping, if the defect is too large for the clips, or if the patient has developed peritonitis, emergency surgical procedures should be performed. In any case of perforation, patients should receive intravenous antibiotics and be monitored regularly for vital signs and inflammatory markers. Most perforations within 24 h can be managed with laparoscopic suture closure techniques (Fig. 21.3).

During ESD, minimal bleeding is expected but endoscopists should always be careful since bleeding is the most common complication of the ESD procedure. Up to 7% of patients may have immediate bleeding during the procedure [43]. Immediate bleeding is defined as bleeding causing a reduction in hemoglobin by >2 g/dL within the first 24 h of the procedure. Endoscopic clips and snare coagulation are common tools to control bleeding. Overall, cleaning of the resected field has a crucial role to discover any possible ongoing bleeding at the site. Delayed bleeding is described as bleeding that causes a reduction in hemoglobin by >2 g/dL

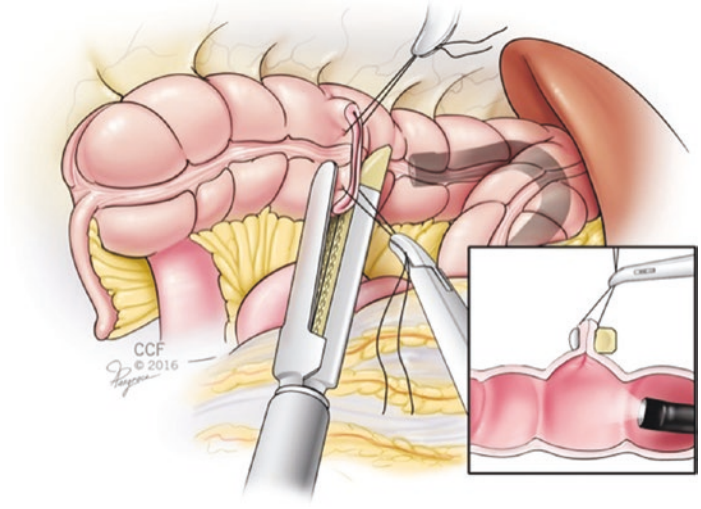

FIGURE 21.3 Suture closure for the perforated bowel wall

after the first 24 h of the procedure and is usually observed 2–7 days after the procedure. Polyps located near the rectum are an independent risk factor for delayed bleeding. Other risk factors for bleeding include polyp size larger than 30 mm, polyps located distally, the use of antiplatelet agents except for aspirin, three or more arterial bleeding episodes during ESD, long procedure time, and malignant lesions [41, 44–48]. Most commonly, delayed bleeding is managed with supportive care and endoscopically. If persistent, exploration and resection is indicated.

Post-ESD coagulation syndrome is a complication of ESD resulting from electric energy trauma to the muscular layer of the bowel wall. The patient presents with localized abdominal pain in the area of dissection with no evidence of perforation, fever, and leukocytosis. Patients are treated with bowel rest, anti-inflammatory drugs, and antibiotics. Risk factors associated with post-ESD coagulation syndrome are polyps located at the right side of the colon, lesions larger than 40 mm, female gender, and prolonged procedure time [49–51].

Besides the described complications, routine colonoscopy procedure complications can be expected too, such as splenic injury, post-polypectomy syndrome, mesenteric hemorrhage, diverticulitis, appendicitis, and pancreatitis [52].

Updates in ESD and Future Directions

Considering ESD requirements such as additional training periods, expert-level endoscopy skills, and familiarization with the techniques of the ESD procedure, all of these contribute to the unpopularity of ESD in western countries. Innovative technological approaches have been developed to overcome this problem. Despite the technically challenging parts of the ESD procedure, continued development of devices and techniques allows us to perform safe and efficient ESD procedures for colorectal lesions. These maneuvers were developed to guide endoscopists by stabilizing the procedure area and to allow them to integrate surgical maneuvers such as traction-counter traction. Several new methods of creating a stable "platform" or workspace in the colon and rectum are developed to enable ESD's technically challenging parts with more ease. ESD with Double Balloon Endolumenal Intervention Platform (DiLumen™, Lumendi, Westport, CT) is an innovative new technique approved by the FDA to remove polyps larger than 2 cm or for polyps located in anatomically difficult locations. It reduces sigmoid colon looping and shortens the colon which is an important advantage for lesions located at anatomically difficult locations. In addition, the Double Balloon Endolumenal Intervention Platform has advantages such as endoscope stabilization, tissue manipulation capability, usability with any standard colonoscope consisting of a tight-fitting arm body, and secure fit to a standard endoscope. It consists of a flexible over-sheath with two manually inflatable balloons (fore and aft balloons). Double Balloon Endolumenal Intervention Platform works by stabilizing the colon with an aft balloon and creating a therapeutic zone for submucosal

dissection. One of the front balloon features is used to create traction with the help of stitches and clips, thereby speeding up the dissection step. In the Double Balloon Endolumenal Interventional Platform application, after the first half of the lesion is dissected, an endoclip is used and the balloon lowering is initiated in front of the scope and clipped to the lesion. This method enables the endoscopist to retract the dissected portion and accomplish better disclosure of the submucosa with the facilitation of the dissection. DiLumen™ body consists of two 6-mm working channels to provide integration of graspers and scissors and fitting over the colonoscope. These instruments have special importance by allowing the endoscopist to perform retraction and cutting [53, 54].

Robotic-Assisted Flexible Endoscopes are another developing device created to perform endorobotic submucosal dissection allowing endoscopists to use both hands with left-right and up-down movement features and better visualization. Challenging parts of ESD are usually caused by the dynamics of conventional endoscopy. Such as, it has a limitation for visualizing the submucosal dissection plane as it is a one-handed procedure that can provide only single-axis dissection. This causes an inability to see lesions from different angles. Robot-assisted flexible endoscopes provide a three-dimensional view with a better depth of vision. The main goals is to improve safety, precision, time, and adverse effects of the procedures. The challenge of the endorobotic submucosal dissection procedure is to synchronize the movement of both hands [55–57].

ORISE Tissue Retractor System™ (Boston Scientific, Marlborough, MA) is another platform commonly used. It has a cage-like body with two instrument channels that can be inserted over a standard colonoscope. This platform allows the endoscopist to stabilize the intraluminal space and insert endoscopic instruments to retract the lesion. As part of the standard procedure, after dissection is started, the platform is presented with the colonoscope and the cage-like part is opened after the proper position is taken. All these steps assist the endoscopist by stabilizing the dissection area and

using separate instrument channels to allow forceps to be used for precise and active real-time retraction [58].

Learning Curve

While there is an accepted stepwise training process for ESD in Japan, there is no accepted learning guideline for ESD training in the USA. This is due to the unfamiliarity of devices used in ESD in Western centers, the high number of gastric cancers in Japan compared to the USA, the differences in endoscopy practice, and the long learning curve before the ESD procedure can be performed confidently and independently [6].

In Japan, trainees begin with observing, then assisting, and finally performing. They usually start with lesions in the gastric area. A trainee should perform 20–30 gastric ESD before being able to perform colorectal ESD in Japan. Trainees begin with rectal or simple colon cases first. Large lesions and lesions located in the flexure should be avoided at the beginning of the training [59, 60].

One of the most important questions is: "How many cases are required to reach proficiency in ESD?" Unfortunately, there is no certain answer for that because the length of the learning curve depends on many factors, such as endoscopist's skills, prior experience, and location of target lesions. From Japanese guidelines, 30–40 cases are required to reach proficiency to perform gastric ESD [61]. In the case of colorectal ESD, the proficiency number is 30–80 cases. According to the results of recent studies, the threshold is 50 cases for rectosigmoid and right colon lesions, while at least 80 cases for left-sided lesions [62]. Korean studies recommend performing ESD in at least 100 patients to be able to perform ESD in colorectal lesions for endoscopists with no previous gastric ESD experience [63]. Proficiency can be achieved after 250 cases in the USA, according to recent studies explained by lower case complexities compared to Japan and avoiding ESD approaches for larger lesions or lesions

located at the difficult sites. Adequacy for the minimum resection speed is assessed out of 150 cases for the stomach, 170 cases for the esophagus, and 280 cases for the required colon [9].

Recently, animal models, video conferencing systems, and simulations have been developed to increase the effectiveness of ESD education. A live animal model trains the endoscopist to more equal conditions to human ESD. It guides endoscopists about how to use hemostatic devices. The Virtual Endoluminal Surgery Stimulator is one of the ESD stimulators that teach endoscopist techniques during the ESD procedure, thereby increasing the endoscopist's adaptation to the ESD procedure. The American Society for Gastrointestinal Endoscopy (ASGE) organized an international matching program to make ESD a well-known procedure. It connects participating mentors and institutions with ASGE member endoscopists who want to learn how to perform ESD procedure [64–68].

Conclusion

ESD is an innovative minimally invasive treatment choice for early colorectal carcinomas and precancerous lesions. ESD allows a significantly higher rate of *en bloc* resection while providing organ preservation. It may replace surgical intervention and possible complication risks of these surgeries. ESD is a procedure that requires a high degree of endoscopic control and expertise. Various tools such as knives, coagraspers, caps, and generator options have been developed and improved to facilitate the procedure. The procedure is associated with complications such as perforation, bleeding, and electrocoagulation syndrome. The possibility of these complications depends on the site of the lesion, endoscopist's skills, and the patient's comorbidities. Considering the increasing incidence of non-malignant neoplasia and early colorectal cancers, ESD may become increasingly common in

the future [11].DisclosuresGizem Kaya, MD, has no financial disclosures.

Ilker Ozgur, MD, has no financial disclosures.

Emre Gorgun, MD, serves as a consultant for Boston Scientific and DiLumen.

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Chapter 22
Peroral Endoscopic Myotomy (POEM)

Matthew M. Snyder and Eric S. Hungness

Abbreviations

DES	Distal esophageal spasm
DI	Distensibility index
EGD	Esophagogastroduodenoscopy
EGJ	Esophagogastric junction
EMR	Endoscopic mucosal resection
EPT	Esophageal pressure topography
ES	Eckardt score
ESD	Endoscopic submucosal dissection
FLIP	Functional lumen imaging probe
GERD	Gastroesophageal reflux disease
GERDQ	Gastroesophageal reflux disease questionnaire
HRIM	High-resolution impedance manometry
HRM	High-resolution manometry
IDQ	Impaction-dysphagia questionnaire
LES	Lower esophageal sphincter
NOTES	Natural orifice translumenal endoscopic surgery

M. M. Snyder · E. S. Hungness (✉)
Department of Surgery, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: matthew.snyder@northwestern.edu; eric.hungness@nm.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_22

POEM	Per-oral endoscopic myotomy
TBE	Timed barium esophagram
VSI	Visceral sensitivity index

Indications

Achalasia

Achalasia is a rare disease characterized by failure of swallow-induced relaxation of the lower esophageal sphincter (LES) and loss of coordinated peristalsis in the esophageal body. It is the most common primary esophageal motor disorder with an annual incidence historically estimated at 1 per 100,000 individuals [1]. With the advent of the widespread use of high-resolution manometry (HRM), newer studies suggest that actual incidence could be 2–3× higher [2]. Initially described in 1674 by Sir Thomas Willis, our current understanding of the etiology of achalasia has developed thanks to histopathologic analysis over the last two decades. Immunohistochemical studies have suggested an auto-immune response, potentially triggered by a neurotropic virus such as herpes simplex virus 1 in genetically susceptible hosts, with selective loss or impairment of ganglions in the myenteric plexus resulting in unopposed cholinergic stimulation of the distal esophagus and LES [3]. Presenting symptoms include dysphagia to solids and liquids (>90%), regurgitation of undigested food and saliva (76–91%), weight loss (35–91%), and chest pain (25–64%). Patients may also report respiratory complications of aspiration such as nocturnal cough and pneumonia and heartburn and esophagitis secondary to stasis [4]. There is no known cure for achalasia; current treatment options aim to palliate symptoms through elimination of outflow obstruction at the EGJ.

Emerging Indications

Based on case series reporting excellent early results, POEM operators have applied the minimally invasive technique to esophageal motor disorders other than type I and type II

achalasia, including type III achalasia, distal esophageal spasm (DES), Jackhammer (hypercontractile) esophagus, and hypertensive LES [5, 6]. POEM has also been utilized as a salvage operation following failed Laparoscopic Heller Myotomy (LHM). In general, EGJ outflow obstruction caused by high LES pressure responds favorably to the division of the obstructing muscle fibers. In contrast, symptoms such as chest pain, attributed to esophageal body contraction (DES and type III achalasia), have lower rates of symptom remission following myotomy [7].

History/Background

In the 100 years since Dr. Heller first described the "transabdominal, extra mucosal cardioplasty performed onto the anterior and posterior walls of the cardia," the procedure has been transformed by laparoscopy, modified in length, and augmented by anti-reflux procedures [8]. In the last 10 years, however, the complementary fields of natural orifice translumenal endoscopic surgery (NOTES) and endoscopic submucosal dissection (ESD) have expanded from simple proof-of-concept studies to a wide variety of fully incisionless operations in use today. Early animal models demonstrated the feasibility of both safe access to the submucosal space using the mucosal flap technique and endoscopic myotomy [9, 10]. Based on these techniques, Dr. Haruhiro Inoue performed the first human POEM procedure in Japan in 2008 and presented his results at the 2009 Digestive Diseases Week in Chicago with subsequent publication in Endoscopy in 2010 [11]. Following his landmark publication, the procedure as described by Inoue grew exponentially with an estimated number of POEM cases exceeding 2000 worldwide by the end of 2012, when the global experience in POEM was summarized in the international POEM survey (IPOEMS) as part of the NOSCAR conference in July 2012 [7]. Current estimates approximate that well over 10,000 POEMs have been performed worldwide. However, no such global survey has been re-created.

Patient Selection

Symptom Assessment Questionnaires

Validated, disease-specific questionnaires can help establish the diagnosis of achalasia, assess disease severity, and establish baseline values to allow postoperative evaluation of treatment effect. The most widely used and reported instrument for achalasia is the four-item Eckardt score that evaluates the frequency of occurrence of chest pain, regurgitation, dysphagia, and amount of weight loss on a 0–3 scale [12]. Higher scores represent increasingly severe disease, while post-intervention scores less than or equal to three are associated with treatment success [13]. While simple to obtain, the ES does not measure disease impact on the overall quality of life and is limited by patient subjectivity. More extensive and sensitive surveys include the Mayo Dysphagia Questionnaire-30, Achalasia Disease-Specific Quality of Life measure, Visceral Sensitivity Index, and EORTC QLQ-OES18 [14].

Physiologic Tests

High-Resolution Manometry

Esophageal manometry has long been considered the "gold standard" for the diagnosis of idiopathic achalasia. Over the last decade, High-Resolution Manometry (HRM) has begun to replace conventional manometry (CM) as the diagnostic test of choice given its relative ease of interpretation and superior diagnostic accuracy [2]. The improved HRM catheters, utilizing 36 or more pressure sensors at 1 cm intervals, accompanied by the development of esophageal pressure topography (EPT), or Clouse plots, have allowed easier and more reliable manometry analysis. A prospective randomized control trial comparing HRM to CM showed a twofold increase in achalasia diagnosis (26% vs. 12% $p < 0.01$) with a 97% sensitivity and a false positive rate of only 3% [15].

Pandolfino et al. proposed the Chicago classification based on manometric profiles, dividing patients into three subtypes of achalasia [Fig. 22.1] with well-described prognostic implications [16, 17]. Type I, or "classic" achalasia, is defined by absent peristalsis and impaired EGJ relaxation in response to swallowing, quantified as a 4-s integrated relaxation pressure (IRP) >10 mmHg. Type II achalasia is diagnosed by the presence of pan-esophageal pressurization (>30 mmHg) and is associated with the best outcomes following myotomy. Type III achalasia, associated with premature, spastic contractions of the distal esophagus (two or more swallows with a distal latency of <4.5 s) and impaired EGJ relaxation, has the least reliable response to myotomy or pneumatic dilatation [17].

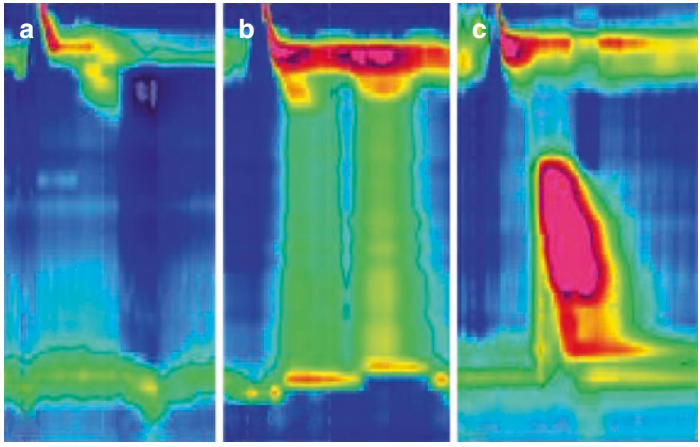

FIGURE 22.1 High-resolution manometry. Distinct manometric patterns are observed in the subtypes of achalasia according to the Chicago classification. In the setting of elevated 4-s integrated relaxation pressures, (**a**) type I patients are recognizable by the absence of peristalsis, (**b**) type II patients exhibit pan-esophageal pressurization at the 30 mmHg isobaric contour, and (**c**) type III patients are defined by a spastic distal esophageal contraction with a distal latency less than 4.5 s

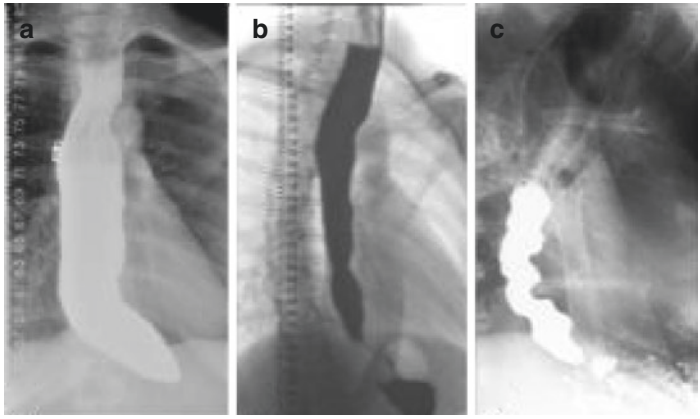

FIGURE 22.2 Timed barium esophagram. Characteristic findings in achalasia include (**a**) increased esophageal width as seen in a patient with type I achalasia, (**b**) so-called "bird's beak" appearance of the contrast column as it tapers in the distal esophagus of a patient with type II achalasia and (**c**) retained contrast with a "corkscrew" appearance seen in type III achalasia and other spastic disorders of the esophagus such as DES

Timed Barium Esophagram (TBE)

TBE [Fig. 22.2], comprised of chest radiographs obtained 1, 2, and 5 min after ingestion of 200–250 mL of dilute barium contrast, is useful for evaluation of both esophageal body and EGJ anatomy (classic appearance of the "bird-beak" esophagus). TBE quantifies the barium column's baseline height, degree of esophageal emptying, and esophageal width. TBE also allows detection of the sigmoid esophagus (representing so-called "end-stage achalasia"), hiatus hernia, and epiphrenic diverticula.

Esophagogastroduodenoscopy (EGD)

EGD is required as part of the pre-operative work-up of all patients before treatment for achalasia to rule out pseudoachalasia (EGJ outflow obstruction secondary to an infiltrat-

ing malignancy). If the index of suspicion remains high for pseudo-achalasia (older patients with prominent weight loss and a short duration of symptoms) despite a negative EGD, adjunctive studies such as endoscopic ultrasound or computed tomography scan should be performed [18]. EGD also allows for the assessment of retained solids or liquids, stasis or reflux esophagitis, and candidiasis.

EndoFLIP

The functional lumen imaging probe, or EndoFLIP (Medtronic, Minneapolis, MN), is a novel diagnostic catheter that utilizes impedance planimetry, with sensors positioned at 0.5–1 cm intervals within an infinitely distensible balloon to generate a geometric representation of the lumen of the esophagus and LES [Fig. 22.3]. When combined with a pres-

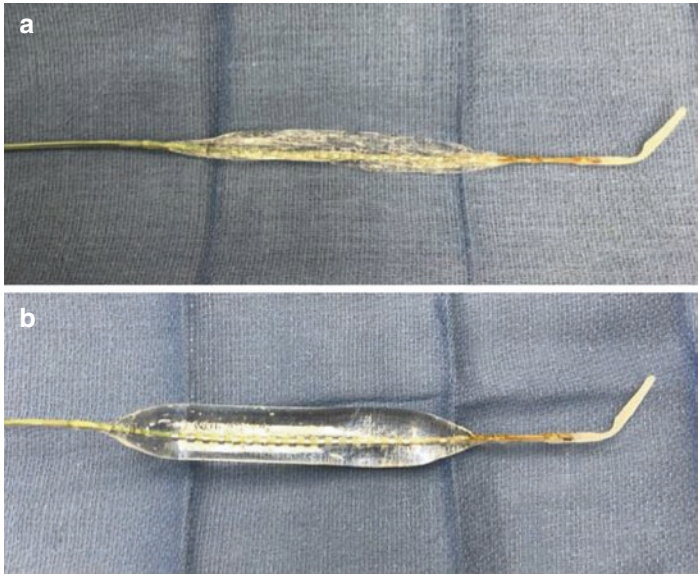

Figure 22.3 EndoFLIP Catheter (Medtronic, Minneapolis, MN). EndoFLIP catheter filled with 0 cc (**a**) and 60 cc (**b**) fluid

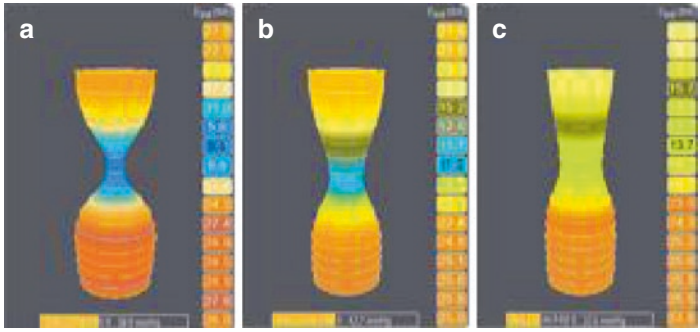

FIGURE 22.4 Intraoperative EndoFLIP. The lower esophageal sphincter is identified on EndoFLIP by the characteristic "hourglass" shape (**a**) following induction of general anesthesia during a POEM procedure. Increased distensibility is noted after (**b**) creation of the submucosal tunnel, with a doubling of the minimum diameter and (**c**) completion of myotomy; final EndoFLIP measurements revealed a further increase in diameter and a nearly 50% pressure decrease at the EGJ

sure sensor in the distal portion of the balloon, the FLIP allows quantification of the EGJ response to volumetric distention, calculated as the distensibility index, or DI (DI = cross-sectional area/intra-balloon pressure) [Fig. 22.4] [19]. Normal EGJ-DI has been defined as greater than 2.8 mm^2/mmHg with a maximal EGJ diameter greater than 18 mm [20].

Teitelbaum et al. [21] demonstrated in their study that intraoperative FLIP analysis can be used to predict postoperative outcomes following POEM [21]. We routinely perform EndoFLIP during POEM. Our updated protocol involves the insertion of the endoFLIP under endoscopic guidance for initial EGJ DI and maximal diameter measurement following induction. Subsequent measurements are taken following the creation of the submucosal tunnel and after the myotomy. Although the relationship of intraoperative measurements and postoperative outcomes has not been reliably demonstrated across subsequent studies, it does provide objective data to the surgeon during the myotomy. It has the potential to act as an effective calibration tool.

Contraindications

Patient Factors

Patients should undergo evaluation in a pre-operative clinic in coordination with anesthesiology and additional workup as indicated. The less invasive nature of the POEM procedure minimizes the list of comorbidities that preclude the procedure. Absolute contraindications to POEM include the inability to tolerate general anesthesia, secondary to prohibitive cardiopulmonary disease, uncorrectable coagulopathy/thrombocytopenia, and the presence of advanced cirrhosis, with or without evidence of esophageal varices. Additionally, the POEM procedure relies on access to the submucosal space, so extensive fibrosis secondary to external-beam radiation to the mediastinum, extensive mucosal ablations, or prior EMR generally prohibit the operation. Published reports have included patients ranging in age from 3 to 97 years old [7]. Prior treatments that can cause inflammation and/or fibrosis of the submucosal space, such as botulinum toxin injection, pneumatic dilation, prior LHM, or prior POEM can all contribute to the difficulty of the dissection and in some cases increase the rate of inadvertent mucosotomies or duration of the procedure. While none of the prior treatment modalities, other than esophagectomy, represent absolute contraindications to POEM, the added complexity should preclude such cases from being attempted during the initial learning curve [22].

Technical/Training

Safe conduct of the POEM procedure relies on the availability of all necessary equipment, adequately trained and well-coordinated support staff, and sufficient pre-clinical training. Prior experience with EMR/ESD techniques and/or NOTES procedures has been reported as helpful, as have simulations using live animals, ex vivo models, and cadavers. Most operators reported having expert proctoring during the initial human cases (median 2, range 1–7) [7].

Pre-operative Care

Before surgery, a multidisciplinary team including gastroenterologists and minimally invasive surgeons should evaluate the patient.

Patient Instructions

Pre-operatively, the patient is prescribed daily oral fluconazole 100 mg for 7 days. They are instructed to maintain a clear liquid diet for 48 h before surgery and remain NPO 12 h before surgery. Some centers report conducting routine EGD 1–3 days pre-operatively to screen for candidiasis, while others evaluate at the start of the procedure. Management of peri-operative medications should be performed in consultation with the pre-operative clinic and patients primary care provider. In general, we continue beta blockers peri-operatively and Aspirin when indicated for a history of stent placement, coronary artery disease, or coronary artery bypass graft. Prophylactic Plavix and Aspirin are typically held for 5 and 7 days pre-operatively, respectively. Decisions regarding the management of therapeutic anticoagulation are made on an individual basis.

Anesthetic Considerations

Pre-operative and intraoperative coordination with the anesthetic team is crucial to the safe conduct of the POEM procedure. Issues of particular importance include positioning and securing the endotracheal tube as far laterally as possible and potentially utilizing a preformed, right-angled Oral RAE™ tracheal tube (Moore Medical). Given the inherent risk of aspiration, all airways should be secured utilizing Rapid-Sequence Intubation (RSI) protocols. In addition, the anesthesia team should be aware of the potential for unplanned extubation given the frequent passage of the endoscope through the oropharynx, with the equipment necessary for

re-intubation readily available. It is also helpful to discuss blood pressure management, specifically maintaining the systolic blood pressure below 120 mmHg, if feasible, as this is anecdotally associated with fewer bleeding complications.

Room Set-Up and Equipment

For a list of equipment recommended for POEM, see Table 22.1. Sequential compression devices are utilized for thromboprophylaxis, and a second-generation cephalosporin or comparable pre-operative antibiotic (Ancef at our institution) is given. After successful induction of general anesthesia

Table 22.1 Equipment checklist

Room set-up	Forward viewing, high-definition gastroscope with 2.8 mm working port (GIF-H190, Olympus)
–	Clear cap with ¼″ tape to secure at the end of the gastroscope
–	Carbon dioxide (CO_2) insufflation system (Olympus)
–	High-frequency electrosurgical generator
Intraoperative tools	Bite-block
–	60–90 mL syringes with saline for irrigation +/− simethicone
–	Indigo carmine injection solution with normal saline
–	Dilute bacitracin irrigation
–	¼″ red tape to mark insertion depth for endoscopic instruments
–	Sterile toothbrush for cleaning knife

(continued)

Table 22.1 (contiued)

Endoscopic instruments	Endoscopic injection/sclerotherapy needle
–	Triangular-tip endoscopic submucosal dissection knife (Olympus)
–	Coagrasper hemostatic forceps (Olympus)
–	Resolution 360 (Boston Scientific) hemostatic clips
–	OverStitch (Apollo Endosurgery) endoscopic suturing system

and secured positioning of an endotracheal tube, the patient is positioned supine, flush with the head of the OR table, the right arm is supported on an arm board, and the left arm is appropriately padded and tucked next to the torso. The bed should be lowered and step stools positioned at the head of the bed as needed to minimize strain and fatigue on the part of the operator. An endoscopy tower, equipped with a forward viewing, 2.8 mm single-channel, high-definition flexible gastroscope (GIF-H190; Olympus America, Inc., Center Valley, PA), with carbon dioxide (CO_2) insufflation, is positioned near the midpoint of the OR table and the cautery foot pedal is placed within reach of the operator. A minimum of one assistant is required to coordinate the operation of the injector and triangular-tip ESD knife and should be positioned to the operator's left. To the operator's right, a second assistant can stabilize the endoscope at the mouth, allowing simultaneous manipulation of the deflection wheels and the injector or cautery knife. The second assistant can also assist with the passage of intraoperative measurement devices such as the endoFLIP catheter. A time-out should be performed before the procedure to confirm patient identity, procedure, availability of endoscopic equipment (clips, coagulation forceps, etc.) and ensure that the endoscopy tower utilizes CO_2 insufflation and that correct electrocautery levels are set.

Operative Technique [Fig. 22.4]

Diagnostic Endoscopy

Once the anesthesiologist is satisfied with the positioning and security of the endotracheal tube, the abdomen is prepped and draped to provide access if Veress needle decompression of a capnoperitoneum is required. A bite-block is placed to facilitate the passage of the endoscope [Fig. 22.5a]. Thorough clearance of impacted food is required for complete assess-

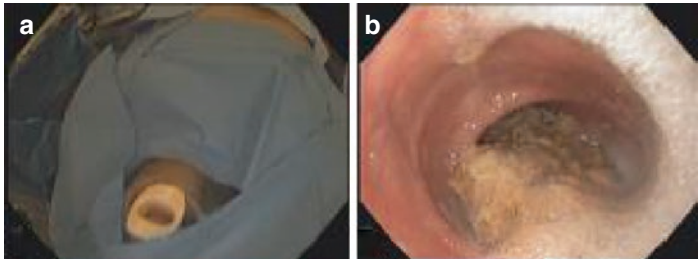

FIGURE 22.5 (**a–f**) Operative steps for POEM. Patients are (**a**) prepped and draped with the abdomen exposed, and a bite-block is placed to facilitate passage of the endoscope. Findings during initial EGD can include (**b**) impacted food and (**c**) copious frothy sputum that should both be cleared to allow for the detection of (**d**) active candidiasis. Identification of the (**e**) squamocolumnar junction provides an approximation distance to the EGJ. A combination of dilute indigo carmine is injected to (**f**) elevate the mucosa. (**g–l**) Operative steps for POEM. The submucosal space is accessed through (**g**) creation of a longitudinal mucosotomy. The submucosal tunnel is extended distally with a combination of (**h**) dilute indigo carmine injection for marking and hydro-dissection and (**i**) cautery to divide the tissue of the submucosa. Withdrawal from the tunnel and retroflexion in the stomach allow (**j**) endolumenal verification of adequate extension onto the gastric cardia. Starting 6–7 cm proximal to the EGJ, (**k**) a selective myotomy of the inner, circular muscle layer is performed to 2–3 cm distal to the EGJ. After ensuring hemostasis and irrigation of the submucosal tunnel with dilute bacitracin, (**l**) endoscopic clips are used for mucosotomy closure

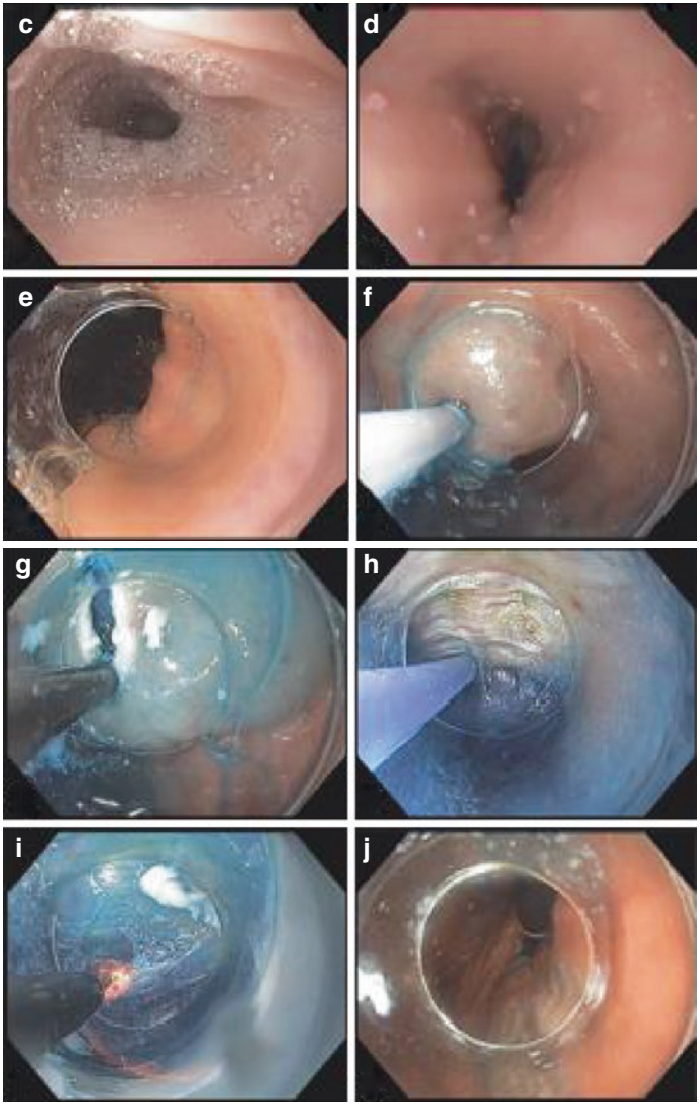

FIGURE 22.5 (continued)

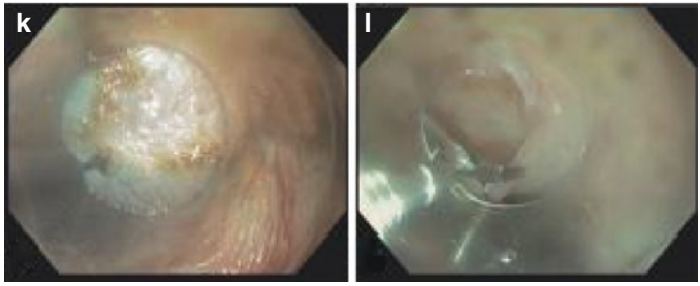

FIGURE 22.5 (continued)

ment of the esophageal mucosa [Fig. 22.5b] and to minimize soilage of the submucosal tunnel. Placement of a 16- or 18-French orogastric tube can facilitate clearance, as can the availability of 60–90 mL flushes or a power-flush system for the working port. It is not uncommon to encounter copious frothy sputum in the esophagus [Fig. 22.5c], a condition that resolves quickly with irrigation using dilute simethicone. Initial EGD is performed to assess for the presence of active candidiasis [Fig. 22.5d], an indication to abort the procedure and reschedule the myotomy pending resolution of the infection. Following a visual inspection of the esophagus and stomach, note should be made of the location of the esophagogastric junction as determined by the distance from the incisors to the squamocolumnar junction [Fig. 22.5e] using the external markings on the endoscope for reference. In the absence of a hiatal hernia, the SCJ is typically located between 38 and 42 cm from the incisors.

Mucosal Lift and Mucosotomy

In the case of a standard length myotomy (extending 6–7 cm proximal to the EGJ), the mucosotomy should be made 12–14 cm above the EGJ. Most operators performing POEM

report creating an anterior submucosal tunnel in the 1–2 o'clock position [7]. An endoscopic needle is inserted just below the mucosa, and a 3–4 cm wheal is raised using 10 mL of a solution containing indigo carmine and 0.9% saline [Fig. 22.5f]. A longitudinal mucosotomy is created (using a few drops of liquid to create a meniscus to assess positioning relative to the most anterior aspect, designated 12 o'clock). Mucosotomy length should be just large enough to accommodate the clear cap on the endoscope (approx. 2 cm) [Fig. 22.5g], as excessive length will add time and cost to the procedure during clip closure of the mucosotomy.

Creation of the Submucosal Tunnel

After the initial mucosal lift, subsequent injections during the creation of the submucosal tunnel should be diluted dye without epinephrine to limit total exposure to the adrenergic agent. Distal progression of the submucosal tunnel is facilitated by alternating hydro-dissection to enlarge the submucosal space [Fig. 22.5h] and cautery to divide the thin fibers connecting the mucosa to the inner, circular muscle layer [Fig. 22.5i]. Careful advancement of the endoscope and slight posterior deflection of the cap can be used to put the submucosal fibers on stretch and guide dissection. Frequent reference to the fluid meniscus can help prevent spiraling as the tunnel is carried distally on the esophagus. Extra care should be taken near the EGJ as this area is prone to inadvertent mucosotomy given the increased muscle tone and anecdotally described "stickiness," attributed to prior episodes of inflammation or previous treatment modalities. Beyond the EGJ, switching back to an injection solution containing both dye and dilute epinephrine can aid in demarcating the distal extent of the submucosal tunnel. To confirm adequate extension onto the gastric cardia, the endoscope can be withdrawn from the submucosal tunnel and passed into the stomach lumen to obtain a retroflex view of the EGJ [Fig. 22.5j].

Anterior Myotomy of the Circular Muscle Layer

Using the endoscopic markings, the selective myotomy of the circular muscle layer should be initiated 6 cm proximal to the EGJ for a standard length of the myotomy. Variations in myotomy length have been suggested when treating conditions that predominantly affect the esophageal body, such as type III achalasia or jackhammer esophagus; in these cases, the myotomy can be started just proximal to the spastic segment, ensuring at least 2–3 cm of mucosal flap coverage in the submucosal tunnel [23]. Once the plane between the inner circular muscle layer and the thin, outer, longitudinal muscle layer is accessed, the triangular-tip ESD knife can be used to hook the circular muscle fibers and extend the myotomy distally [Fig. 22.5k]. Full-thickness myotomy or splaying of the thin, outer longitudinal muscle fibers is common, especially around the EGJ. The myotomy should be extended 2–3 cm distal to the EGJ onto the gastric cardia. After the myotomy, after assuring hemostasis in the tunnel, irrigation is performed with dilute bacitracin solution.

A variety of intraoperative techniques have been described to evaluate for adequacy of myotomy in relieving esophageal outflow obstruction at the level of the EGJ. These range from purely subjective, based on laparoscopic inspection or ease of passage of the endoscope during EGD post-myotomy, to quantitative but time-consuming, in the case of intraoperative manometry. Several centers in the US employ the EndoFLIP device, described earlier, for intraoperative assessment of myotomy adequacy as measured by an increase in EGJ distensibility index and obtaining a Schatzki diameter of at least 12 mm [19].

Closure of Mucosotomy

The mucosotomy is closed with approximately 5–10 endoscopic clips depending on the size of the mucosotomy. We routinely use Resolution 360™ (Boston Scientific,

Marlborough, MA) clips given the 1:1 torque ratio that helps facilitate precise placement [Fig. 22.5l]. Care should be taken to ensure the eversion of the mucosal edges during clip placement. Alternative closure methods have been described utilizing proprietary endoscopic suturing devices such as the OverStitch or X-Tack (Apollo Endosurgery, Austin, TX, USA) to allow a running closure of longer mucosotomy defects.

Troubleshooting

Retained Debris

It is relatively common to find extensive debris and food particles during the initial diagnostic endoscopy of a POEM. Typically, standard irrigation and suction via the endoscope are enough to clear the esophagus. However, if large debris persists, the use of an endoscopic over-tube (Guardus® Overtube, STERIS, Mentor, OH) can stabilize access to the esophagus and permit multiple passes of the endoscope for foreign body removal [Fig. 22.6]. Additionally, we have found the Roth Net® standard retriever (STERIS, Mentor, OH) useful in snaring large food debris [Fig. 22.7]. Rarely, the procedure has to be aborted and rescheduled because the debris burden is too great.

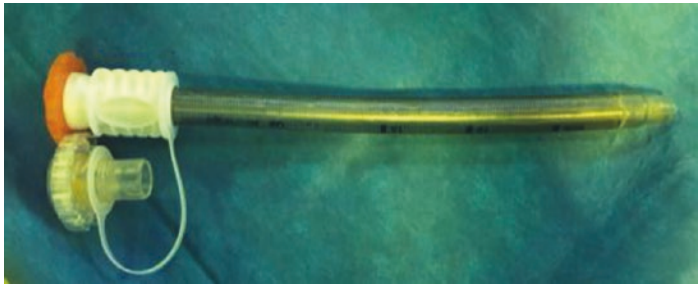

FIGURE 22.6 Guardus® Overtube-Esophageal (STERIS, Mentor, OH)

FIGURE 22.7 Roth Net® Standard Retriever (STERIS, Mentor, OH)

Avoiding Complications

Implications of COVID-19 Pandemic

The COVID-19 pandemic has created unique challenges to surgical endoscopy. However, surgical endoscopy can and has been safely performed since the onset of the pandemic. Current surgical guidelines recommend mandatory testing of all patients within 24–48 h of their planned surgery and are screened for any high-risk symptoms or contacts on the day of surgery. Any patient with a positive test or symptom screen should be rescheduled and advised to quarantine per local guidelines. Given that upper endoscopy is a high-risk, aerosolizing procedure, it is recommended that the operating surgeon and assistants wear personal protective equipment that consists of, at minimum, N95 respirator mask, protective eyewear/shield, surgical gown and hat, surgical gloves, and shoe covers regardless of the patient's COVID-19 status [24]. Care should be taken to don and doff PPE appropriately. The anesthesiology team should take similar care during intubation and extubation.

Aspiration

Pre-operative dietary restriction to clear liquids in preparation for the procedure and use of a rapid-sequence intubation protocol by the anesthesia team (limited pre-oxygenation/bag-masking) can help minimize the risk of aspiration during induction. If needed, awake fiberoptic intubation in the upright position can be utilized in extra high-risk patients.

Capnothorax

Given the frequency of full-thickness myotomy or splaying of the outer, longitudinal muscle fibers, the development of unilateral or bilateral capnothorax and capnoperitoneum is common [7]. No data supports routine postoperative chest radiographs, assuming CO_2 is utilized for insufflation in place of air. Capnothorax progressing to tension physiology or hemodynamic compromise is exceedingly rare. Still, the instruments should be available and staff capable of performing an emergent needle or tube thoracostomy if needed. Self-limited subcutaneous emphysema is also common with expected resolution within 24 h post-operatively. In addition, roughly 50% of POEM cases are accompanied by the development of some degree of capnoperitoneum secondary to CO_2 tracking from the mediastinum or full-thickness gastric myotomy [7]. Care should be taken to distinguish capnoperitoneum (diffuse abdominal distension) from an over-insufflated stomach (isolated epigastric fullness). Capnoperitoneum accompanied by hemodynamic instability or impaired ventilation is an indication for decompression with a Veress needle (typically in the left upper quadrant, just inferior to the costal margin) or laparoscopic port. While not necessarily a complication, the relative frequency with which insufflation-related events are encountered highlights the necessity of utilizing CO_2 insufflation during POEM.

Bleeding

Based on the global POEM experience to date, bleeding, if it occurs, is most commonly encountered during dissection across and distal to the EGJ. As previously discussed, even mild hypertension will compound the bleeding risk inherent to the increased vascularity in the submucosal space of the EGJ and gastric cardia. Mild bleeding can typically be controlled with the application of monopolar electrocautery. Brisker bleeding, or unavoidable division of larger bridging vessels, should be approached with coagulation forceps. Submucosal tunnel bleeding that obscures endoscopic visualization can occasionally be temporized by removal of the endoscope from the tunnel and application of direct pressure with the scope or cap from the esophageal lumen for 10–20 min. Alternative techniques include hemostatic clip application and judicious injection of dilute epinephrine. Case reports have suggested the option of utilizing tamponade devices such as Sengstaken-Blakemore, Minnesota, or Linton Tubes (All Bard Medical) to staunch brisk bleeding. Given the disastrous consequences of this in the setting of a partial or full-thickness myotomy, these high-pressure balloons should not be considered as part of the endoscopic armamentarium when approaching bleeding during the POEM procedure. Additionally, it is recommended that the use of postoperative ketorolac (Toradol) be limited.

Full-Thickness Perforation

Entry into the mediastinum at the level of the mucosotomy, either during initial access of the submucosal space or subsequently, should prompt close attention to mucosal closure technique, including consideration of alternative methods of closure such as endoscopic suturing [25] or utilization of larger clips. Blunt dissection of the submucosal space has

been described in animal models and human case series to expedite tunnel creation and decrease procedure duration. This technique is associated with increased rates of inadvertent mucosotomy, particularly in the area just proximal to the EGJ, where relative tethering of the mucosa can occur and predispose the proximal tissue to perforation when approached blindly. Significant mucosal defects that occur before myotomy creation should prompt consideration of aborting the procedure and/or attempting submucosal tunnel and myotomy in an alternate position on the esophagus (i.e., posterolateral). Small mucosal defects and those that occur during or after myotomy should be closed from the lumenal side with endoscopic clips or sutures. Note that mucosal injuries, especially in the region of the EGJ can lead to the development of strictures and recurrent dysphagia.

Postoperative Care

Patients are extubated in the operating room and transferred to the post-anesthesia care unit (PACU) after the case. During the initial recovery phase in the PACU, patients are given standing intravenous anti-emetics and analgesia as needed. Once the patient is sufficiently recovered from anesthesia and not experiencing chest pain, fever, or tachycardia, sips of clear liquids are initiated. In the absence of concerning symptoms or signs that suggest leak, patients are given a tray of clear liquids and advanced to a full liquid diet as tolerated. Discharge typically occurs in the afternoon of the first postoperative day (POD#1). Select patients may discharge on the same day provided sufficient recovery has occurred and the patient is tolerating a full liquid diet without adverse effects. Patients are discharged on twice-daily proton-pump inhibitors that are continued until physiologic testing is performed at 6 months to assess for the presence or degree of gastroesophageal reflux. Many centers advocate routine imaging (water-soluble or thin barium esophagram) on POD#1, with some centers performing second-look EGD before diet ini-

tiation or hospital discharge [7]. During our initial experience, the postoperative care pathway included obtaining a POD#1 esophagram, but the lack of impact on patient management and low leak rate has led to the abandonment of asymptomatic screening of all patients post-operatively. There are descriptions of postoperative computed tomography scans of the chest being routinely obtained; however, following the same logic that led to the abandonment of routine esophagram use, there is no clear evidence to support the cost or radiation exposure associated with routine screening CT scans.

Follow-Up

Patients should be seen 2–6 weeks post-operatively to evaluate treatment response and detect potential early failures. In the absence of recurrent symptoms, full physiologic testing with TBE, HRM, EndoFLIP, and pH-impedance is postponed until the 6-month follow-up appointment. TBE, in particular, has been shown to have significant prognostic value following pneumatic dilation in detecting patients with symptomatic relief that are at increased risk for early treatment failure [26]. Patients are seen again at 1 year and then annually for life, completing validated questionnaires and intermittent physiologic testing to track long-term outcomes. Long-term follow-up protocols can also incorporate routine or symptom-triggered screening for esophageal malignancy.

Review of Existing Literature

Efficacy

Studies addressing short-term outcomes for POEM have consistently demonstrated excellent results. Meta-analysis on existing short-term POEM outcomes found that 82–100% (mean of 90%) of patients reported symptomatic improve-

ment [27]. The IPOEMS reported an overall treatment success of 98% at a mean follow-up of 9.3 months, with 40% of patients having failed prior treatments [7]. Additionally, Teitelbaum et al. reported sustained symptom relief in 83% of their patients who underwent POEM to treat achalasia without the need for reoperation at the 5-year follow-up mark [28]. This is the longest follow-up series to date and demonstrates that POEM can result in durable long-term symptom relief with outcomes equivalent to, if not superior to, LHM or PD. Given that no prospective, randomized trials directly comparing POEM to LHM have been published, further research in this area is warranted.

Rates of GERD

Richards et al. demonstrated in 2004 that in the absence of a concurrent fundoplication, complete division of the lower esophageal sphincter and gastric sling fibers during Heller's cardiomyotomy results in debilitating reflux [29]. Neither Partial nor complete fundoplication is performed following POEM, and concern has been raised regarding the potential for higher long-term rates of GERD. While long-term data is forthcoming, based on visualization of erosive esophagitis on EGD or abnormal pH studies during short-term follow-up (<1 year), the estimated prevalence of GERD following POEM may be in the range of 20–46% [7]. Comparable rates have been reported in patients undergoing LHM with anterior (Dor) fundoplication in multicenter, prospective, randomized trials [30, 31]. Similar to the argument put forth by proponents of anterior (Dor) fundoplication, the lack of posterior mediastinal dissection and preservation of the phreno-esophageal ligament during POEM may mitigate the absence of a surgical anti-reflux barrier. Preservation of the angle of His may also contribute to the anatomic anti-reflux barrier when the 1–2 o'clock position is used for myotomy during POEM, as the natural course of the esophagus (clockwise rotation and right-to-left sweep) favors dissection onto the lesser curve and division of the clasp fibers with the maintenance of the sling fibers.

Conclusion

POEM is a safe and effective procedure for the treatment of achalasia and other esophageal dysmotility disorders. Combining the efficiency of endoscopy with the effectiveness of surgical myotomy, POEM offers the advantage of shorter recovery, less hospitalization, and a wider patient demographic while maintaining excellent short-term outcomes with durable long-term results.

Acknowledgments We recognize Joel M. Sternbach, MD, MBA, the primary author of this chapter in the first edition, for their excellent work that we have updated and revised.

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Chapter 23
Intramural Surgery Per Oral Endoscopic Myotomy for Zenker's Diverticulum (Z-POEM)

Alisan Fathalizadeh and Michael Klingler

Intramural Surgery Per Oral Endoscopic Myotomy for Zenker's Diverticulum (Z-POEM)

Zenker's diverticulum (ZD))is an outpouching that occurs within Killian's triangle which constitutes an area of anatomic weakness just above the upper esophageal sphincter. This triangle is formed by the pharyngeal constrictors superiorly and the transversely oriented cricopharyngeus (CP)) inferiorly. High pressures are generated in this space when there is improper relaxation of the cricopharyngeus during swallowing, which can lead to the development of a pulsion-type false

A. Fathalizadeh
Digestive Disease and Surgery Institute, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: Fathala@ccf.org

M. Klingler (✉)
Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: Klinglm@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_23

esophageal diverticulum [1]. Generally, ZD is rare with a prevalence of 0.01–0.11% with most occurring during the fifth to seventh decades of life [1–3]. Patients may describe symptoms largely attributed to trapped food, excess secretions, or air becoming trapped in the diverticulum. Patients may also experience the need to clear their throat periodically or following meals. Additionally, patients may regurgitate undigested food, putting them at risk for aspiration and subsequent pneumonia. The diverticulum may spontaneously empty and cause coughing or belching noises as air is evacuated, also known as esophageal borborygmi. Dysphagia is the most common symptom, which may cause patients to change their diet with notable resultant weight loss. The diagnosis of ZD is established through a thorough history and physical exam followed by imaging studies such as a contrast esophagram or via an upper endoscopy [1, 2].

Historically, treatment of ZD was performed through an open approach with a left cervical incision in order to remove the diverticulum and divide the cricopharyngeus. This approach was associated with a higher rate of complications such as vocal cord paralysis, esophageal leakage, or mediastinitis. The treatment approach to ZD has evolved from an open surgical to a rigid endoscopic approach, and most recently, to a flexible endoscopic approach. Although no prospective randomized trials have been performed to demonstrate the superiority of one approach, based on the morbidity and long hospital stays associated with the open approach, the minimally invasive approach is generally preferred [1, 4]. Flexible endoscopic diverticulotomy was first introduced in 1982 with the first series reported by Mulder and colleagues [5]. This approach was initially intended for patients who were poor surgical candidates unable to tolerate general anesthesia or those with unfavorable anatomy or neck extension for rigid scopes [4]. Over time, minimally invasive approaches became favored as there is a lower associated morbidity in this group of older patients with many pre-existing comorbidities. The minimally invasive approach provides a shorter surgery time, the possibility of performing the procedure without general anesthesia, a shorter hospital

stay, and earlier oral food intake [2]. In both the rigid and flexible endoscopic approach, the main goal is to divide the common wall or septum of the diverticulum to achieve a cricopharyngeal myotomy (Fig. 23.1). This combines the diverticulum with the esophageal lumen which may improve pharyngeal motor function and reduce symptoms of dyspha-

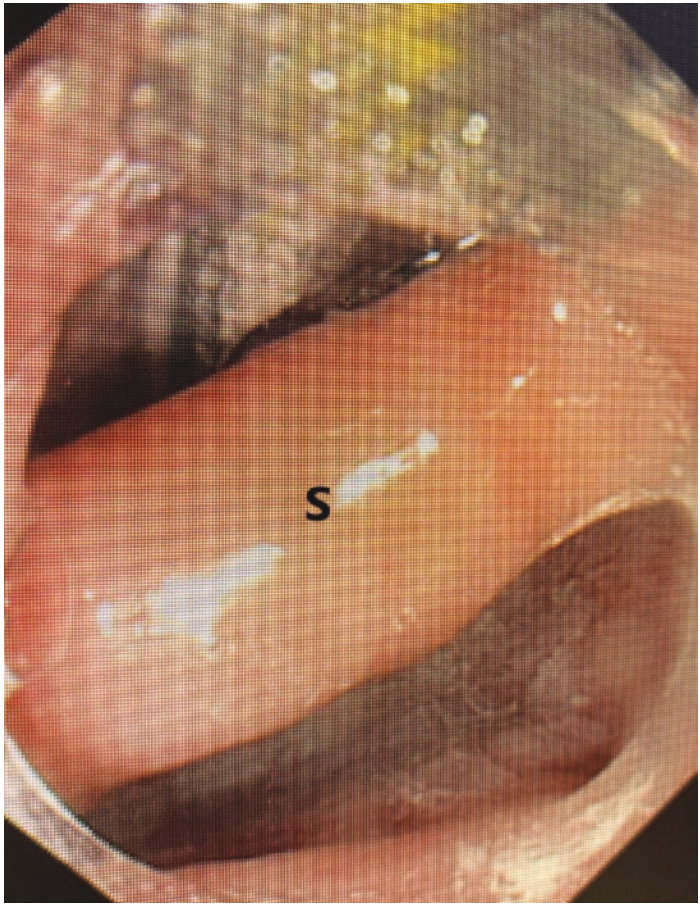

FIGURE 23.1 Septum (S) created between the true esophageal lumen and the false diverticulum containing an NGT and colorful wire to improve visualization

gia and regurgitation [4]. When performed by an experienced surgeon or gastroenterologist, patients experience between an 85 and 100% long-term success rate with regard to symptomatic relief [1, 4]. Patients not experiencing relief can undergo a revised minimally invasive approach or an open approach [1].

With the advent of new accessories and techniques, endoscopic options for treatment of ZD include but are not limited to endoscopic stapling, CO_2 laser, and submucosal tunneling with the use of various devices including argon plasma coagulation, needle knife, monopolar or bipolar forceps, hook knife, clutch cutter, stag beetle knife, or harmonic scalpel [2]. By using the principle behind per oral endoscopic myotomy (POEM) for treatment of achalasia, Li and colleagues first described the per oral endoscopic myotomy for Zenker's diverticulum (Z-POEM)) [6]. It was initially developed to decrease the risk of perforation with flexible endoscopic techniques which have been reported as high as 6.5% [7]. In addition, this tunneling technique may decrease the risk of diverticulum recurrence, which is notably higher compared to an open repair. Various tunneling techniques have been described, including Zenker's per oral endoscopic myotomy (Z-POEM), submucosal tunneling endoscopic septum division (STESD), or mucosal incision with muscular interruption (MIMI), which will be described further below.

General Technical Principles

The patient is taken to the operating room or endoscopic suite where the procedure is to be performed. After informed consent is obtained, anesthesia is provided. General anesthesia may be used to improve the ease of the procedure for the patient and the proceduralist. It is recommended for general anesthesia to be administered using rapid sequence intubation (RSI) due to the high risk of aspirating contents of the diverticulum [4]. Alternatively, if the patient cannot tolerate general anesthesia or if the proceduralist prefers, the proce-

dure may be performed under conscious sedation with monitoring by the anesthesia team. Antibiotic prophylaxis is administered. The patient is either placed in the left lateral decubitus or supine position. Carbon dioxide insufflation is used throughout the procedure due to its rapid absorption by the soft tissues and to minimize any postoperative subcutaneous emphysema. Initially, a standard upper gastrointestinal (GI) endoscopy is performed to evaluate the septotomy with an Olympus GIF-HQ190 gastroscope (Olympus Co., Japan) with a 2.8-mm working channel. Any residual food in the diverticulum should be removed if able. A transparent cap or a diverticuloscope may be used on the endoscope to assist with the procedure. A beveled (or non-beveled) silicone-based endoscopic cap (Barrx™ RFA Cleaning Cap, Covidien, Mansfield, MA) may be used [8]. The bevel may assist with exposure by pulling the flap away from the working area. Alternatively, a soft, flexible diverticuloscope (Cook Medical, Indiana, USA) may be used and is placed over the endoscope and advanced to 20 cm from the incisors in order to straddle the common wall between the true esophageal lumen and the diverticulum. The short blade is placed into the diverticulum and the long blade into the esophagus. A nasogastric tube or visible colorful wire (Jagwire™, Boston Scientific, MA) can also be used to reference the true esophageal lumen, which may not be easily visible during the procedure.

Flexible Endoscopic Septum Division

In the flexible endoscopic septum division (FESD) technique, once the septum is exposed, the diverticular septum is cut using various available endoscopic devices. The cutting device is used to create a mucosotomy over the cricopharyngeus muscle and carried down until the septum is completely divided [9]. The use of a Dual Knife (Olympus Co., Japan, with the following electrocautery settings: Endocut I mode, effect 1, soft coag effect 2; generator VIO® 300D; ERBE, Tubingen, Germany) has been described [10]. A midline inci-

sion is performed from the esophageal lumen toward the diverticulum with a medium length of 1.5 cm. Once the myotomy is complete the mucosa is closed with a series of endoscopic metallic clips (Resolution 360 Clips, Boston Scientific, Marlborough, MA) [10]. The endoscope is passed into the esophagus to assess for resistance.

Submucosal Tunneling Technique: Z-POEM [Q]

The first description of the Z-POEM technique involved four major steps: (1) Mucosal incision, (2) submucosal tunneling, (3) septum division, (4) mucosal closure. This differs from the FESD technique whereby the whole septum is directly divided [4]. Once the septum is visualized and in center view, the submucosa overlying the cricopharyngeus muscle is injected with 3–5 mL of a mixture of saline, epinephrine, and methylene blue (or 1% indigo carmine) (Fig. 23.2). The methylene blue may also be injected into a syringe of pre-packaged Orise gel© (Boston Scientific, Marlborough, MA) to darken the solution which can then be used for the submucosal injection. This dye is used as needed throughout the procedure. Once a submucosal bleb is created, a mucosotomy is performed over the middle of the septum with any of various tools as previously mentioned. The use of a HybridKnife and VIO® 300D generator with setting EndoCut Q 3-1-1 has been described (Erbe USA, Marietta, GA). The endoscope is inserted into the submucosal space and the space is dissected in a proximal to distal direction with the HybridKnife (setting forced Coag/Effect 2/50W) on both sides of the septum past the diverticulum and onto the circular and longitudinal fibers of the esophagus. Next, a myotomy of the entire length of the cricopharyngeus is performed using the HybridKnife with setting (EndoCut Q 3-1-1) [4]. The endoscope is withdrawn from the submucosa into the esophagus. Once hemostasis is confirmed, the mucosal defect is closed with Endoclips (Resolution 360 Clips, Boston Scientific, Marlborough, MA).

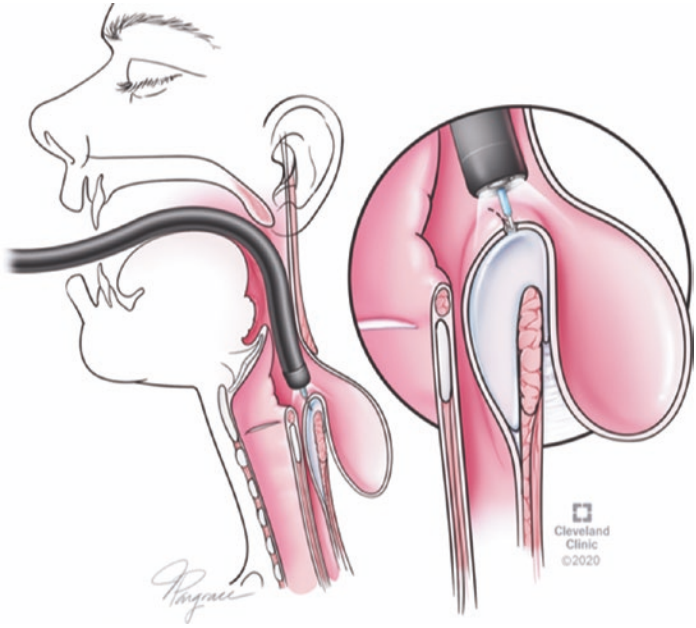

FIGURE 23.2 Submucosal bleb created with an endoscopic injection needle

For difficult mucosal closures, the endoscopic overstitch suture device (Apollo Endosurgery, Austin, TX) can be employed. The nasogastric tube and/or guidewire is removed and the endoscope is passed into the esophagus to assess for any residual resistance at the cricopharyngeus.

Endoscopic Mucosal Incision and Muscle Interruption (MIMI)

In the mucosal incision and muscle interruption (MIMI) technique, a solution of blue dye as previously described is injected directly into the submucosa overlying the cricopharyngeal septum, in comparison to the Z-POEM technique whereby the injection and overlying incision are made in the

hypopharynx and a submucosal tunnel is created to reach the septum. A 1–1.5 cm longitudinal incision is made in the mucosa overlying the cricopharyngeus with a triangle-tip (TT) knife (KD-640L, Olympus, Tokyo, Japan) on cutting current (Endocut effect 2-1-2) (Fig. 23.3). Using ERBE Vio 300 electrosurgical generator (ERBE, Tübingen, Germany), the submucosa on both sides of the cricopharyngeal septum are dissected bluntly with the endoscopic cap and the TT knife using coagulation current (Spray coagulation, 50 W, effect 2) until the base of the diverticular septum is clearly identified (Figs. 23.4 and 23.5). The cricopharyngeus muscle is then

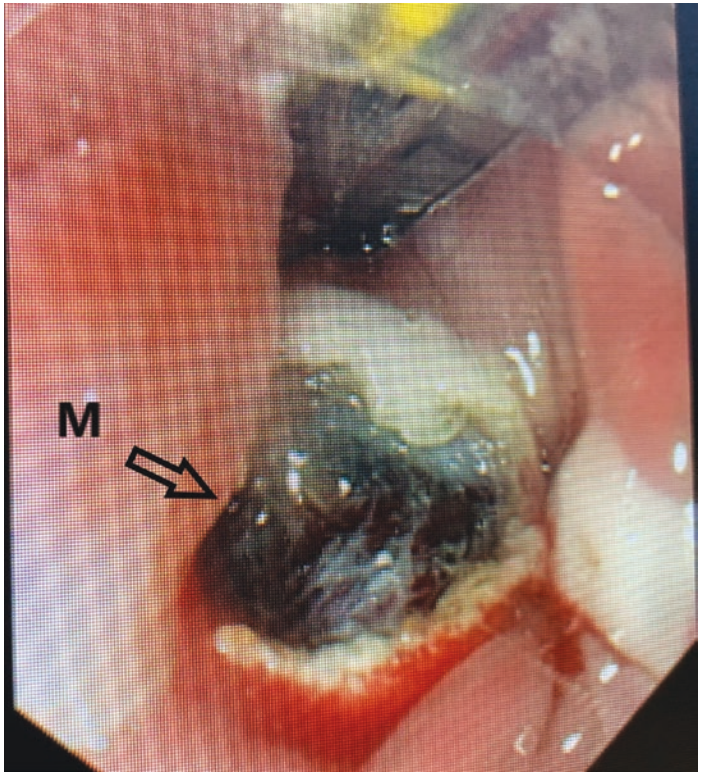

Figure 23.3 Mucosotomy (M) created along the septum

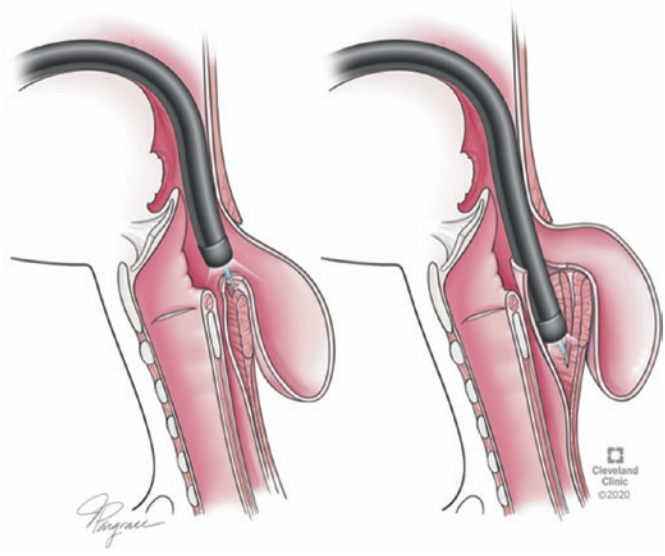

FIGURE 23.4 Creation of mucosotomy and submucosal tunnel

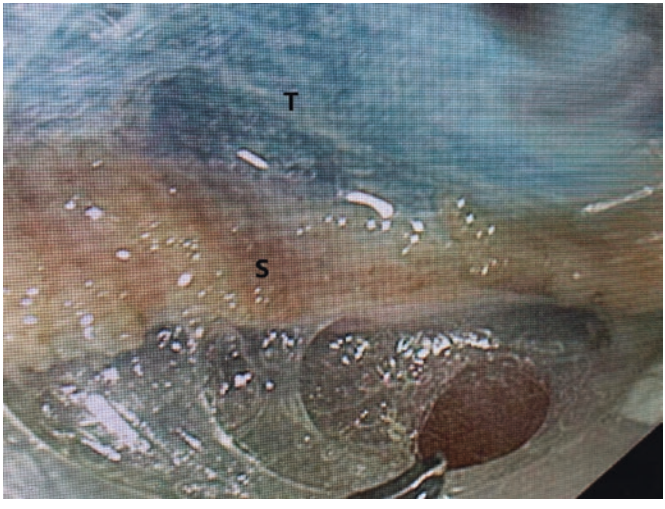

FIGURE 23.5 Demonstration of submucosal flaps with septum in the center and tunnel (T)

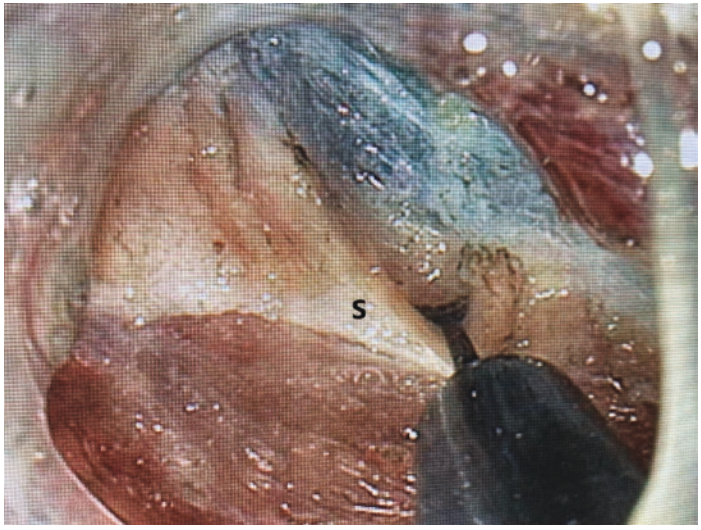

FIGURE 23.6 Cricopharyngeal myotomy

divided along its length with the TT knife using coagulation current or Endocut with the settings as above until the base of the septum is clearly divided (Fig. 23.6). The esophagus is examined for any signs of perforation or hemorrhage and the tunnel is closed with endoscopic clips. The endoscope is passed into the esophagus to assess for any residual resistance at the cricopharyngeus [8] (Fig. 23.7).

Postoperative Care

Once the patient has recovered from anesthesia, they may initially be kept *nil* per os (NPO) with maintenance fluids on the day of the procedure. They are subsequently placed on a pureed or soft diet for two weeks to prevent dislodgement of the endoscopic clips. Patients may be either discharged home the same day or kept overnight for observation based on the individual surgeon's comfort and preference. Some may choose to perform a follow-up esophagram before diet

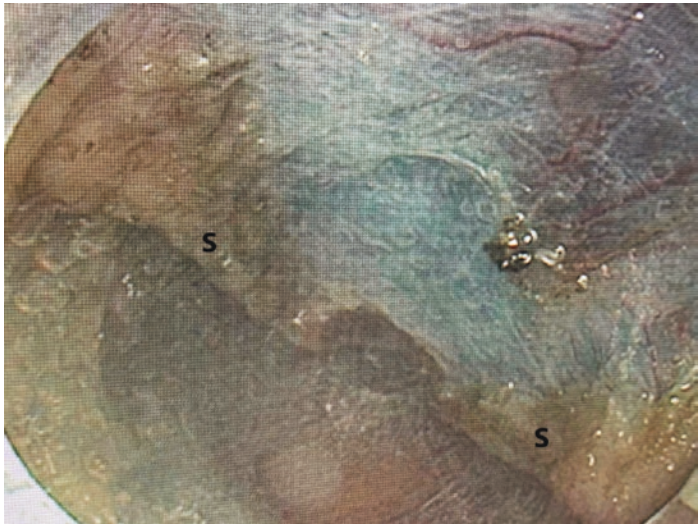

FIGURE 23.7 Submucosal tunnel view after complete myotomy

advancement, particularly if there is clinical concern for complication or perforation such as the presence of crepitus. Patients are discharged home when clinically stable and able to tolerate oral intake [8]. Additionally, the individual surgeon may opt to continue antibiotics for up to 7 days postoperatively [11]. There is no clear evidence suggesting that postoperative esophagram or prolonged antibiotic use is correlated with improved clinical outcomes.

Outcomes

Partially due to the rarity of ZD, studies evaluating the appropriate management options and treatment outcomes are largely published as case series or retrospective observational studies. Systematic reviews and meta-analysis suggest endoscopic approaches have shorter recovery time with lower perioperative morbidity, however, not enough evidence is available to support one approach over the other [12–15].

Earlier studies in the endoscopic management of ZD employed techniques such as endoscopic staplers and $C0_2$ lasers. Such studies demonstrated regurgitation and dysphagia improvement in 96% and 86% of patients enrolled with a 12% rate of complications and 18% rate of recurrence treated mostly endoscopically [16].

A study evaluating the aforementioned FESD approach involving 31 patients demonstrated symptomatic relief in all patients with a 70% decrease in the diverticulum size. Three patients had intraprocedural hemorrhage managed endoscopically and five developed a recurrence treated with subsequent endoscopic approach. Overall, the technique was found to be safe and effective [10]. A subsequent meta-analysis confirmed the safety and efficacy of FESD. Twenty studies were included and the results demonstrated pooled success, adverse events, and recurrent rates of 91%, 11.3%, and 11%, respectively [9].

Despite heterogeneity particularly in instrumentation of flexible endoscopic cricopharyngotomy, multiple meta-analyses have demonstrated comparable outcomes to open or rigid endoscopic approaches [13]. A meta-analysis including 115 studies, of which twenty-nine were flexible endoscopic studies, demonstrated no difference in mortality, infection, or perforation. Bleeding and recurrence, however, were more likely after flexible endoscopic repair compared to rigid endoscopic repair. Flexible endoscopy has the advantage of not requiring neck hyperextension, which may be a limiting factor in this patient population. The data for flexible endoscopic approaches overall demonstrates high rates of technical success and clinical response with low complications and recurrence. In a review by Jain and colleagues [17], 997 patients from 23 studies who underwent flexible endoscopic cricopharyngotomy for ZD, a composite technical success rate of 99.4% and clinical success rate of 87.9% were noted. A composite failure and recurrence rate of 10.0% and 13.6%, respectively, were noted. Close to half of the failure and recurrence groups were managed with repeat endoscopic intervention [17]. The study also evaluated the use of diver-

ticuloscope versus cap which demonstrated comparable success rate. The use of a diverticuloscope resulted in higher clinical success rate compared to cap usage (86.8% vs. 75.4%). However, use of the diverticuloscope had twice the risk of symptom recurrence (16.5% vs. 9.5%) but a lower perforation rate than cap usage (2.3% vs. 10.3%). Bleeding and perforation occurred in 6.6% and 5.3%, respectively, with most managed nonoperatively and 0.9% of the perforations requiring invasive management. The study demonstrated the same safety and efficacy of ZD treatment regardless of diverticulum size or prior treatment [17].

A variety of instruments have been implemented in the endoscopic treatment of ZD. A meta-analysis specifically evaluating the use of the needle knife technique included thirteen studies. Overall complication, bleeding, and perforation rates were 13%, 5%, and 7%, respectively. Recurrence occurred at a rate of 14%. Diverticula greater than 4 cm demonstrated pooled adverse event rates of 17%, while diverticulum less than 4 cm had pooled adverse event rates of 7%. Further studies are needed to evaluate if any specific instruments or tools improve outcomes in the management of ZD [18].

As a novel procedure, the data behind Z-POEM is largely presented in the form of case reports generally demonstrating the overall safety and efficacy of the procedures. Smaller case studies involving 5 patients demonstrated Z-POEM can be safely performed entirely endoscopically with little associated pain or complication rates with short-term follow-up having excellent functional and symptomatic results [M]. A multi-institutional study by Yang and colleagues included 75 patients and reported overall technical and clinical success rate of 97.3% and 92%, respectively. In two patients, the septum was unable to be located due to failure in tunneling [19]. Adverse events were noted in 6.7% of patients. A recent meta-analysis evaluated the management of all esophageal diverticula. In analyzing the patients that had ZD treated with Z-POEM, the pooled rates for technical success were 95%. Adverse events were noted at a rate of 6% [20].

In a new variation to the Z-POEM, Klingler and colleagues describe the aforementioned MIMI approach whereby the mucosal incision is made directly over the diverticulum. This technique may theoretically decrease the risk of technical failure in the tunneled approach in not being able to identify the septum after tunneling as previously described [19]. Nineteen patients undergoing the MIMI approach and seven patients undergoing the non-tunneled approach were included. The mean ZD size was larger in the MIMI group compared to the non-tunneled group (2.8 cm vs. 1.9 cm, $p = 0.03$). Clinical success was achieved in 89.5% MIMI patients and 100% in non-tunneled patients with no significant differences in the two groups. Dysphagia scores improved in both groups; however, this difference was only significant in the MIMI group ($p \leq 0.001$). Recurrence occurred in 2/17 (11.7%) MIMI patients and 3/7 (42.9%) non-tunneled patients ($p = 0.094$). One patient with a very small (<2 cm) ZD suffered a perforation requiring open surgery in the MIMI approach. Overall, this novel approach was found to be safe and effective, but care should be taken with this approach in patients with a small ZD or a prominent cricopharyngeal bar [19].

Recurrence after treatment of ZD is not infrequent and generally occurs at a frequency of 11–14% [9,17]. Recurrences have been managed with open surgery and repeat endoscopic treatments; however, the optimal approach is not clearly understood. The matter of managing these recurrences with Z-POEM was investigated by Sanaei and colleagues [21]. Thirty-two patients with persistent or recurrent symptoms after prior endoscopic and/or surgical interventions for ZD were included. In this group, Z-POEM was technically successful in all but two patients (93.8%) with clinical success in 96.7%. A reduction in the median dysphagia score from 2 to 0 ($p < 0.001$) was noted. Four adverse events (12.5%) including two inadvertent mucosotomies and two leaks on postoperative esophagram were noted [21].

Future Developments

The management of Zenker's Diverticulum, as in many aspects of surgery, has evolved to be progressively less invasive. With the new era of robotic endoscopy, there may be a role in the management of ZD in the future [22]. The repertoire of tools used in endoscopy is also constantly evolving. A variety of endoscopic options may be implemented in the treatment of ZD with newer technologies being developed or refashioned for use in the treatment of ZD. One particular study evaluated the use of needle knife versus bipolar forceps on pig models. The bipolar forceps were found to be safe and effective with a theoretical added benefit of bonding the mucoso-muscular tissue edges, therefore, potentially decreasing the risk of subsequent perforation. Future studies in human models are necessary to delineate the added benefit [23].

It is thought that the flexible endoscopic approach may not be suitable for diverticula that are too large or too small. In a study evaluating prognostic variables for clinical success in flexible endoscopic septotomy for ZD, it was found that septotomy length less than 2.5 cm or ZD size greater than or equal to 5 cm were independent predictors of failure to achieve symptom relief. For very large diverticulum, open surgery has historically still been the main consideration, however, as described by Wong and Ujiki [4], endoscopic diverticulopexy is a potential alternative to be further studied and evaluated. This approach was completed on a patient with a pre-treatment 6.2 cm ZD that returned with recurrence of dysphagia. A dual-lumen scope and overstitch device with 2-0 DemeLENE sutures (DemeTECH, Miami, FL) were used. The apex of the diverticulum was identified, grasped with a helix device, brought into the jaws of the device, and then brought into the true lumen of the esophagus. It was then pexied to the lateral wall of the esophagus. This was repeated until the entire diverticulum was attached to the lateral wall. Fluoroscopy confirmed no lumenal obstruction,

perforation, or bleeding. As the technology continues to develop, the potential endoscopic options to manage diagnoses such as ZD will continue to evolve to improve patient outcomes while minimizing patient risk.

Ultimately, endoscopic cricopharyngeal myotomy has been found to be a safe and efficacious procedure with favorable outcomes for the treatment of Zenker's diverticulum [24]. Given the variability in instrumentation and techniques across different centers, large-scale prospective studies using standardized techniques with long-term follow-up are needed to better delineate optimal interventions in the treatment of ZD.

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Chapter 24
Intramural Surgery: Per Oral Pyloromyotomy

Megan Lundgren and John Rodriguez

Development of the Per Oral Pyloromyotomy

It would be remiss to discuss per oral pyloromyotomy without a discussion of Dr. Inoue and his first report of the per oral endoscopic myotomy in a human in 2008 [1]. It is the submucosal tunneling technique that he utilized for achalasia, following its first demonstration in a pig model by Parischa et al. 3 years before [2]. Inoue presented this technique with video at a SAGES conference, and since that time POEM has been shown to be as effective as laparoscopic heller myotomy for at least the short-term relief of dysphagia, revealed in a systematic review and meta-analysis completed in 2017 by Schlottmann et al. [3]. Similarly, in 2012 Kawait et al. demonstrated the gastric per oral endoscopic myotomy in a

M. Lundgren (✉)
General Surgery, Penn Highlands Healthcare, DuBois, PA, US

J. Rodriguez
General Surgery, Digestive Disease Institute, Cleveland Clinic, Abu Dhabi, UAE
e-mail: Rodrigj2@clevelandclinicabudhabi.ae

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_24

pig model, revealing that the pylorus could be accurately identified and divided using the submucosal tunneling technique [4]. One year later, in 2013, Kashab et al. reported on the first human model of per oral pyloromyotomy. His group showed that not only was this minimally invasive access technique to the pylorus safe in humans, but that the gastroparesis cardinal symptom index and the gastric emptying study after division of the pylorus via the submucosal tunnel were significantly improved [5]. This incisionless, device-less option for the treatment of gastroparesis, is offering some of these patients' relief—with low complication rates.

The Nature of the Problem: Gastroparesis

Gastroparesis is a likely-underdiagnosed condition. Patients who suffer from the disorder are frequently misdiagnosed, and it may take substantial time to navigate the healthcare system for diagnosis and ultimately treatment. Patients typically present with a multitude of symptoms—in varying combinations. The most common categories of symptoms include: early satiety, nausea/emesis, and fullness/bloating. The Gastroparesis Cardinal Symptom Index was validated by Revicki et al., and it attempts to quantify the symptoms of gastroparesis (Table 24.1) [6]. This index is a tool to quantify pre-treatment scores for gastroparesis, which can be compared with post-treatment scores. POP has been shown in multiple studies to improve the Gastroparesis Cardinal Symptom Index—in particular the scores related to early satiety, bloating and emesis. Healthcare utilization and costs associated with gastroparesis have increased overtime.

Gastroparesis can be a confusing diagnosis—and the fact that there are multiple etiologies can be misleading. Idiopathic gastroparesis is most common. Diabetic gastroparesis and post-surgical gastroparesis follow. If patients present with symptoms potentially consistent with gastroparesis and have diabetes or have had a prior foregut surgery, such as an antireflux procedure or an esophagectomy, this can be a clue to

Table 24.1 The gastroparesis cardinal symptom index

Symptom subscale	Symptoms	Scale (none to very severe)
Nausea/vomiting	Nausea	0–5
	Retching	0–5
	Vomiting	0–5
Fullness/early satiety	Fullness	0–5
	Inability to finish meal	0–5
	Fullness after a meal	0–5
	Loss of appetite	0–5
Bloating/ distention	Bloating	0–5
	Visibly larger belly	0–5

the etiology and the diagnosis. Patients with gastroparesis may be underweight and severely malnourished, or of normal weight or overweight/obese. They may present with a single symptom, such as pain after eating, or multiple symptoms. Patients often undergo initial treatment with conservative dietary measures, pro-kinetic and anti-nausea medications, feeding tubes, and unfortunately may be dependent on narcotic pain medications related to chronic visceral pain. To complicate the diagnosis even further, a certain percentage of gastroparesis patients also have global transit issues and may concentrate more on their bowel function/constipation symptoms.

Sanaka et al., after a review of the National Inpatient Sample Dataset, reported a remarkable increase in gastroparesis-related admissions in the last 16 years by 300%. It is a small minority of patients with gastroparesis who are medically refractory to conservative management who make up 50% of hospitalizations for gastroparesis [7]. As rates of obesity and type two diabetes increase globally, delayed gastric emptying and gastroparesis rates may follow.

The Evidence

A recent meta-analysis on per oral pyloromyotomy includes 11 studies and 332 patients. The authors, Adler et al., used a comparable group of laparoscopic pyloroplasty including 7 studies and 375 patients. The authors concluded that per oral pyloromyotomy achieves a significant reduction in clinical symptoms and demonstrates improved gastric emptying, with comparable outcomes to surgical pyloroplasty in medically refractory gastroparesis patients. Both groups of patients had 11% adverse event rates. Bleeding was the most common adverse event with per oral pyloromyotomy, whereas surgical site infection was most common with laparoscopic pyloroplasty [8].

The largest patient series to date is from the Cleveland Clinic, including 100 consecutive patients. This is a prospective registry review of patients after per oral pyloromyotomy from 2016 to 2017. In this series, 85 of the patients were female and 56 suffered from idiopathic gastroparesis, with the majority of the remaining patients having diabetic and post-surgical gastroparesis. In this series, the short-term results were excellent. Significant changes were noted in terms of objective and subjective measures of gastroparesis symptoms and gastric emptying. The mean gastroparesis cardinal symptom index prior to POP was 3.8, which improved to 2.4, or an absolute difference of 1.4 points—which was statistically significant. Changes in gastric emptying were also statistically significant. The mean percent retention at 4 hours was 39.9% prior to POP, which improved to a mean of 16.3% at 90-day follow-up [9].

Pre-operative Work Up

A patient who presents with epigastric pain, bloating, nausea, vomiting, and early satiety must first have an upper endoscopy to rule out mechanical obstruction from mass or ulcer. Following this, the most specific technique for diagnosis of

gastroparesis is the 4-h solid phase gastric emptying study. A gastric emptying study is the ingestion of a radiolabeled solid meal (typically scrambled eggs, bread, and water) with subsequent measuring of radioactivity in the stomach at intervals post ingestion. Normal gastric emptying is defined as 37–90% retention at 1 h, 30–60% at 2 h, and 0–10% at 4 h. If there is greater than 60% retention of radioactivity at 2 h or >10% retention at 4 h this is considered to be delayed gastric emptying. The percent retention at 4 h is used to define severity of delayed emptying: 10–20% mildly delayed, 20–35% moderately delayed, and >35% as severely delayed gastric emptying.

An important adjunct to the gastric emptying study in the workup for gastroparesis is the transit study—using a wireless motility capsule. If a patient has a global motility disorder, diagnosed using the transit study times through the small bowel and colon, management is altered. Basic electrolyte and nutritional laboratory workup should be completed. In the authors practice, if a patient has a positive GCSI and abnormal gastric emptying study, a per oral pyloromyotomy is offered. If a patient is presenting after previous intervention for gastroparesis such as gastric stimulator, a per oral pyloromyotomy is still an option for intervention—whether the patient desires to keep the stimulator or not.

The Set Up

In the author's practice, per oral pyloromyotomy is completed under general endotracheal anesthesia in either the operating room or the endoscopy suite. The patient is typically placed in the supine position. The patient is intubated. A bite block is placed.

The following are the necessary instruments to have in the room prior to procedure start (Fig. 24.1a–c):

1. Standard diagnostic endoscope
2. Distal cap for the scope

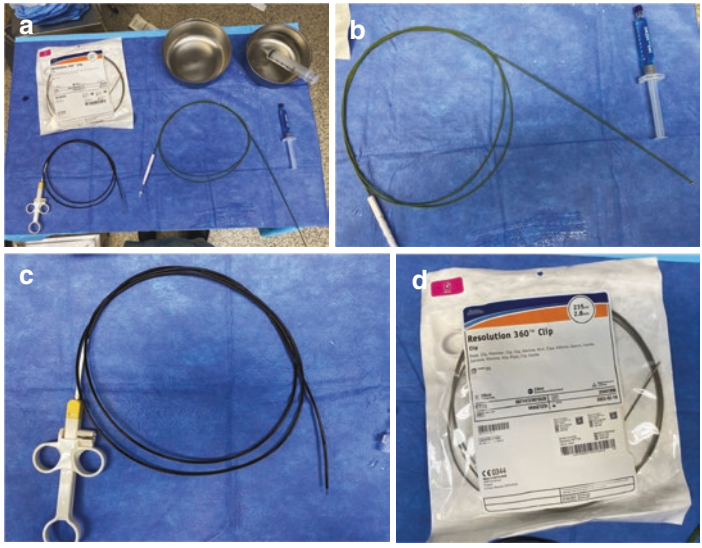

FIGURE 24.1 (**a**) Arrangement of procedural table, set up for per oral pyloromyotomy. (**b**) Injection needle and blue gel for creation of a mucosal bleb. (**c**) Electrosurgical knife for mucosotomy and mucosal tunneling. (**d**) Hemostatic clip for closure of the mucosotomy

3. Electrosurgical endoscopic knife
4. Electrosurgical unit (settings shown in Fig. 24.2)
5. Injection needle with retractable tip
6. Endoscopic clips
7. CO_2 insufflation
8. Blue dye and Sterile water for injection

The cap should be placed with the bevel on the side of the working channel of the endoscope. The cap should be taped to the endoscope using electrical tape to avoid the cap loosening or falling off during the procedure.

The surgeon advances the endoscope in to the stomach, insufflates it fully, and performs a diagnostic endoscopy. Barring any prohibitive findings, such as a stomach full of undigested food, the procedure can begin.

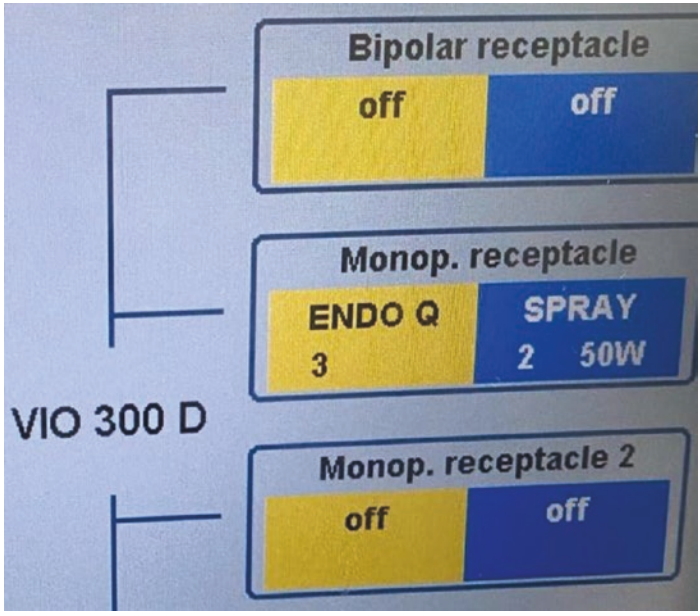

FIGURE 24.2 Electrosurgical unit settings

Step by Step Per Oral Pyloromyotomy

Step 1 (Fig. 24.3a)—Submucosal Injection: an injection needle is used to deliver a submucosal injection of a solution containing blue dye. The site of injections is chosen based on the anatomy of the stomach. The authors prefer a site along the lesser curve 3–5 cm proximal to the pylorus, however, if anatomy or prior pyloroplasty or per oral pyloromyotomy dictate it, a greater curvature site can be used. In general, the shape of the stomach will determine the site. In patients with a J-shaped stomach, this maneuver may need to be performed in a semi-retroflexed position. The site of the initial injection must be distal to the incisura angularis. The goal of this step is to form a bleb that will separate the mucosa from the muscular layers of the stomach to avoid a full thickness perforation at the site of the initial incision. The current

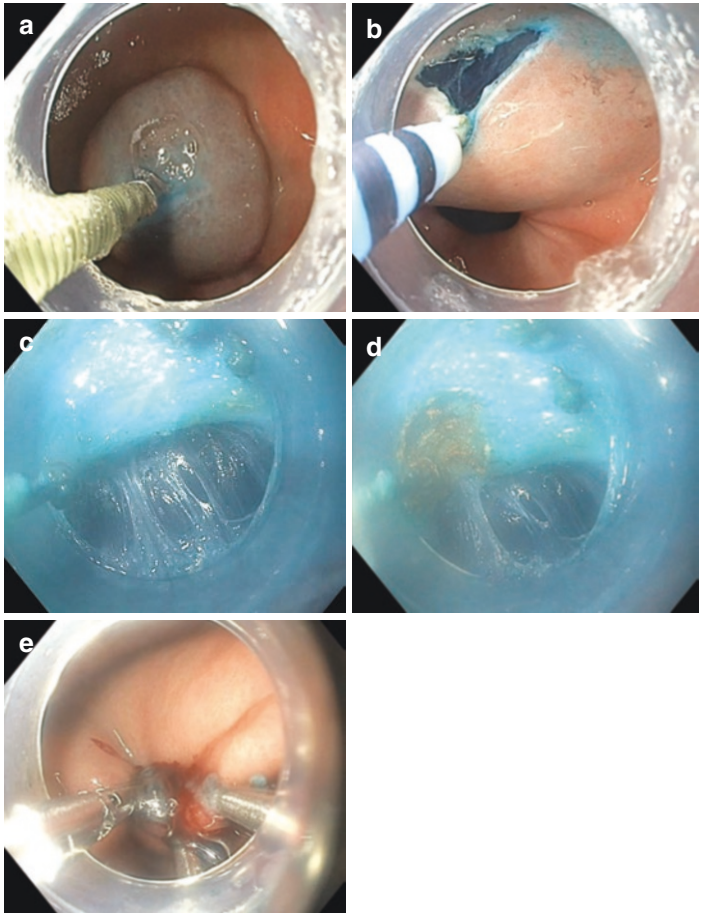

Figure 24.3 (**a**) Submucosal Injection of blue dye 3–5 cm proximal to pylorus. (**b**) Completed mucosotomy using TT knife on cut current, with a downward stretch on the inferior mucosal flap to assist with accommodation of the endoscope in the next step. (**c**) Tunneling through the submucosal fibers (bottom of photo) until the pylorus is clearly visualized (top of photo). (**d**) Beginning of Myotomy—The pylorus muscle is transected with the TT knife using cut or coagulation mode. (**e**) The mucosotomy is closed using hemostatic clips, at least three, starting from one corner moving toward the other

authors prefer a darker solution of methylene blue and sterile water. Saline should not be used as it can crystallize on the endoscope camera and this decreases visualization. Premixed gel solutions are commercially available and tend to dissipate slower in the submucosal plane. Solutions that dissipate more slowly are especially useful in training situations. A tip when forming the bleb is to pull back slowly while injecting the solution to allow dissection between the submucosa and muscular interface, without allowing the injection needle to exit the mucosa.

Step 2 (Fig. 24.3b)—Mucosal Incision: Once the bleb is formed, a transverse incision is made using an endoscopic knife connected to an energy source with cut current. The incision should be large enough to accommodate the diameter of the endoscope being used. Obviously, the larger the mucosotomy, the more endoscopic clips will be required at the end of the procedure, and this should be kept in mind. It is important to maintain an even or level lower mucosotomy flap as the transverse mucosotomy is made, being sure that the incision is not made obliquely toward the pylorus, this again will affect the ability to close the mucosotomy well with clips. The mucosa of the stomach can be of variable thickness. It is important to ensure a complete mucosa incision before extending the incision laterally. In many cases, the submucosa will be adhered to the mucosa and will not allow for mucosal separation after the initial incision. The beveled cap can be used to place tension and simultaneously utilize the electrosurgical knife with spray coagulation to divide these fibers. The endoscope is then completely inserted into the submucosal plane to develop the tunnel.

Step 3 (Fig. 24.3c)—Tunneling: once the endoscope is inserted into the submucosal plane, tunneling toward the pylorus is performed. The critical step is achieving proper orientation in the submucosal plane before proceeding with distal dissection. The blue dye will stain the submucosal plane while the mucosa and muscularis will not uptake dye. Once the muscle fibers are identified, dissection is continued distally at the junction of the muscularis and submucosa. It is

critical to avoid any mucosal injuries during this dissection. With trainees, a reminder to avoid "burying the knife" is helpful to avoid a full-thickness perforation. The orientation of the muscle fibers in the antrum follows a cone shape, with the apex being the pyloric sphincter. The tunnel dissection ends just distal to the pylorus. The mucosa of the duodenum becomes perpendicular to the tunnel just distal to the pylorus. Therefore, further dissection is unnecessary and likely to result in mucosal injury. An injury will appear as a dark-colored space. It should be noted, however, that the procedure can be safely completed despite a small full-thickness injury, because of the submucosal tunnel and mucosotomy closure.

Step 4 (Fig. 24.3d)—Division of the Pylorus: after the tunnel is completed, the pylorus should be clearly visualized. The pylorus can then be divided using the electrosurgical knife. This step can be achieved in several ways based on individual preference. Using cut current will result in the clean division of the muscle fibers with minimal charring of the tissue. This is preferred by the authors. The downside is a higher potential for bleeding if small vessels are encountered during the division of the pylorus. Coagulation current is highly effective as well but can result in more charring of the muscle fibers. This can make visualization somewhat difficult. Complete division is achieved once the circular fibers that compose the pyloric sphincter are completely divided. One can usually visualize a subtle change in the orientation of the muscle fibers that compose the gastric wall. In some cases, build-up of blue dye can be seen dissecting between the pylorus and gastric wall.

Step 5 (Fig. 24.3e)—Closure of the Mucosotomy: once division of the pylorus is completed; the endoscope is withdrawn from the tunnel and the pylorus visualized from the lumen of the stomach. In most cases, widening of the pylorus with a somewhat oval-shaped opening can be immediately seen. Hemostasis within the tunnel is ensured and closure of the mucosotomy is performed. Hemostatic clips are a great and simple tool to re-approximate the mucosal edges. It is during this step that an even, lower mucosotomy flap is helpful, as

the hemostatic clips need to be able to catch this flap to result in a solid mucosotomy closure. The authors prefer to start at a corner and proceed from one end to the next. This usually requires between three and five hemostatic clips.

Technical Pearls

1. It can be helpful to have a second surgeon available to control the scope, while the other surgeon controls the needle knife during dissection. This is especially important during training, as well as cases performed at difficult angles.
2. It is best to mix the blue dye with sterile water, rather than saline, which can crystallize and obstruct visualization.
3. Create an even lower mucosal flap during mucosotomy.
4. Use the beveled cap and intermittent, low-volume CO_2 insufflation to create tension in the submucosal tissue and muscle fibers.
5. Coagulate submucosal vessels as you tunnel.
6. Avoid burying the needle knife during tunneling beyond the superficial tissue being divided and during myotomy.
7. Hemostatic clips can close the mucosotomy, as well as control minor bleeding from the mucosal edges.

Post-operative Management

The patients should be counseled both pre- and post-operatively that, temporarily, the gastroparesis symptoms can worsen after the procedure due to edema and inflammation at the surgical site. If a full thickness injury occurs and the mucosotomy closure is complete, then the patient can be sent home after a recovery period. The abdomen should be palpated to rule out significant pneumoperitoneum and decompressed with a 14-gauge angiocatheter if present on exam. It is reasonable to keep the patients overnight and potentially perform an upper gastrointestinal contrast study to ensure the mucosotomy closure and the tunnel are preventing leakage. This may be preferred early in one's experience. Otherwise, it is safe for a per oral pyloromyotomy procedure

to be a same day discharge after an uneventful recovery in the post-anesthesia recovery unit. Diet post operatively varies between endoscopists and institutions; however, 2 weeks of a full liquid diet is our practice. The authors discharge patients with a prescription for a mucosal protective agent such as sucralfate and a proton pump inhibitor. A post-operative gastric emptying study and gastroparesis cardinal symptom index should be performed at around 4–6 weeks and 1-year to assess the success of the procedure objectively.

Future

Further study is required to determine the long-term efficacy of the per oral pyloromyotomy. Some of the questions that remain to be answered will be the longevity of the outcomes, the frequency of need of a repeat per oral pyloromyotomy or a secondary procedure such as a pyloroplasty, a stimulator placement, or a subtotal gastrectomy with Roux-en-Y reconstruction, and the learning curve for performing a per oral pyloromyotomy. With continued advances in the field of intramural surgery, the procedure itself will likely also evolve.

Disclosure Megan Lundgren, MD has nothing to disclose.

John Rodriguez, MD has consulting relationships relevant to this topic including Cook, Gore, Medtronic, Boston Scientific, Johnson & Johnson.

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Chapter 25
Per-Oral Endoscopic Tunneling for Restoration of the Esophagus (POETRE)

Jordan N. Robinson, Bola Aladegbami, and Paul D. Colavita

Complete Esophageal Obstruction

Complete esophageal obstruction (CEO) is a rare clinical entity characterized by total aphagia. It may result from benign or malignant pathology but is most frequently a late manifestation of chemoradiation therapy for head and neck or thoracic malignancy and less frequently prior surgical intervention [1]. The obstructive etiology can be intrinsic or extrinsic. Intrinsic obstruction occurs due to severe esopha-

J. N. Robinson · P. D. Colavita (✉)
Division of GI Surgery, Carolinas Medical Center, Charlotte, NC, USA
e-mail: Jordan.n.robinson@atriumhealth.org; Paul.d.colavita@atriumhealth.org

B. Aladegbami
Division of Minimally Invasive Surgery, Department of Surgery, Center of Advanced Surgery, Texas A&M College of Medicine, Dallas, TX, USA
e-mail: Bola.Aladegbami@bswhealth.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_25

geal stricture, which may be hastened by poor oral intake secondary to extensive disease burden or chemoradiation therapy.

Stricture formation is incited by mucosal damage with subsequent intramural fibrosis and scarring, leading to constriction of the esophageal lumen [2]. When stricture is the result of chemoradiation, esophageal toxicity often proceeds stricture formation. Injury following radiation therapy involves a complex interplay involving direct toxicity, pro-inflammatory cytokines, reactive oxygen species, and several additional factors [3]. Early evidence of esophageal toxicity involves some level of acute superficial mucositis, which progresses to stricture formation and symptoms of dysphagia. Continued progression of esophageal stricture formation can result in complete obstruction and aphagia, leaving patients unable to swallow saliva, placing them at substantial risk for aspiration and poor quality of life [1–3]. Radiation-related factors, including dose, fractionation, and anatomic location of administration, in addition to patient factors such as age, gender, and the preservation of oral intake, all influence the nature and extent of stricture formation and progression to complete obstruction [1–3].

Endoscopic Treatment Options

Re-establishment of a continuous esophageal lumen can be challenging in cases of complete or near-complete obstruction as the disease process often distorts local anatomy making endoscopic identification of the true lumen technically difficult. Dissection without a means to confirm the anatomic location is dangerous, placing patients at risk of esophageal perforation. The inability to intervene endoscopically necessitates surgical intervention, which likely entails a complex resection and free flap reconstruction [4]. When feasible, endoscopic procedures are a far less invasive form of intervention and avoid forms of morbidity inherent to surgical intervention.

Endoscopic procedures to address CEO consist of various forms of rendezvous procedures entailing combined antegrade and retrograde endoscopy, fluoroscopy, and/or the passage of a guidewire. These procedures, which have been successfully implemented in cases of CEO, typically involve obstructed segments less than 3 cm in length [5–8]. Segments of obstruction greater than three centimeters impose a higher risk of perforation with retrograde endoscopic and fluoroscopic guidance due to the requirement to blindly puncture the esophagus [9, 10]. Per-oral endoscopic tunneling for restoration of the esophagus (POETRE) utilizes endoscopic submucosal dissection similar to per-oral endoscopic myotomy (POEM) and combined antegrade-retrograde endoscopic dilation to avoid blind puncture across long segments of esophageal obstruction [10].

Per-Oral Endoscopic Tunneling for Restoration of the Esophagus (POETRE)

History

The foundational components of POETRE are derived from rendezvous endoscopy and the POEM procedure. POEM has its roots in endoscopic mucosal resection and natural orifice transluminal endoscopic surgery (NOTES) [10–12]. The first described endoscopic myotomy was completed by Ortega in 1980 when he divided the mucosa and muscle of the lower esophageal sphincter in a case series of patients with achalasia [13]. Gostout described a technique later recognized as essential for obtaining submucosal access during NOTES procedures in 2004 [11]. This was subsequently adopted by Pasricha and Inoue to perform what would become known as “per-oral endoscopic myotomy” or “POEM” in the first reported lab animal (porcine) case and human case, respectively [12, 14].

The history of rendezvous procedures is more protracted due to the technological requirements to truly complete the

procedure endoscopically. The first documented form of rendezvous procedure is credited to Adams and Hoover, who in 1953 addressed a corrosive stricture of the thoracic esophagus with a thoracotomy and retrograde puncture of an obliterated segment of the esophagus with the tip of a metal suction catheter [15]. The first report of a true endoscopic rendezvous procedure was described by Bueno in 2001 as part of a case series investigating the procedure as an intervention for complex esophageal strictures [7]. Rendezvous procedures have been employed with a high rate of technical and clinical success since for indications including CEO [6]. However, for long segment obstruction (>3 cm), blind puncture places patients at significant risk for esophageal perforation necessitating a more controlled means of re-establishing the esophageal lumen in such cases [9, 10]. Fluoroscopic monitoring and the formation of a submucosal tunnel facilitate the safe traversal of segments of CEO greater than 3 cm.

In 2012, a case report by Babich et al. presented an approach for submucosal tunneling in a retrograde fashion to reduce stricture length and allow for transillumination and safe puncture [16]. The term POETRE was coined by Wagh et al. in a 2014 video presentation and subsequent publication, followed by a four-patient case series by Wagh and Draganov in 2017 [10]. This chapter will highlight the technique of Wagh and Draganov.

Pre-operative Considerations

As with all surgical procedures, a thorough pre-operative history and physical are essential to thoroughly understand the nature of each patient's disease, relevant comorbid conditions and to elucidate cardiopulmonary risk factors. General endotracheal intubation is necessary due to the very high associated risk of aspiration in this patient population. This procedure should also be avoided in hemodynamically unstable patients. Relative contraindications include thrombocytopenia (platelet count <50,000/μL), an international normalized

ratio of greater than 1.5, and a length of esophageal obstruction less than 3 cm in length [10].

Anesthetic Considerations

Given the high risk for aspiration associated with CEO, preoperative and intra-operative coordination with the anesthesia team is critical to the safe completion of the POETRE procedure. As with many endoscopic procedures, the lateral placement of the ETT or nasotracheal intubation is essential to facilitate a minimally obstructed antegrade endoscopy. Anesthesia should be made aware of the possibility of inadvertent extubation during the procedure and should be readily prepared for reintubation throughout the duration of the procedure.

Patient Positioning and Pre-operative Medications

Patients are placed in the supine position. The table should be set in a position that facilitates ergonomic endoscopy throughout the duration of the case. Prophylactic surgical antibiotics should include gram-positive and anaerobic coverage. These should be administered within 30 min of mucosotomy. Carbon dioxide insufflation is recommended for all third space procedures.

Technique

There are six steps to the POETRE procedure: endoscopic assessment, measurement of obstructed segment, saline lift and mucosotomy, submucosal tunnel, navigation across the obstructed segment, and passing of the guidewire with stent placement. POETRE requires gastric access for retrograde endoscopy. Patients with head and neck malignancies will often already have gastrostomy tubes in place for nutritional support. Proximal CEO favors initial retrograde endoscopy and the creation of the mucosotomy distal to the site of

obstruction. The steps of the procedure are identical to the following description in which the submucosal tunnel is formed using the antegrade endoscope.

Step 1: Endoscopic Assessment

Antegrade endoscopy is completed with a standard upper endoscope (GIF-H180/HQ190, Olympus America, Center Valley, Pa). An Ultra Slim-Sight endoscope (GIF-XP160, Olympus America, Center Valley, Pa) can be used for retrograde endoscopy. Cases of extremely proximal obstruction require the dilation of the G-tube tract to 10 mm to allow retrograde passage of a standard endoscope for retrograde submucosal tunneling.

Most cases begin with antegrade endoscopy to evaluate the patient's obstruction and demonstrate CEO. The retrograde endoscope is subsequently inserted into the pre-existing gastrostomy site to evaluate the distal aspect of the esophageal obstruction.

Step 2: Fluoroscopic Measurements

Once both endoscopes are in the esophagus straddling the obstructed segment, multi-planar fluoroscopy is used to assess the length of the obstructed segment. For segments less than 3 cm, POETRE is not required, and the obstruction is traversed with a 19-gauge endoscopic needle under multi-planar fluoroscopy and endoscopic guidance. If the measured segment is greater than 3 cm in length, then POETRE is performed.

Step 3: Saline Lift and Mucosotomy

At this time, the site for the mucosal incision is identified. It should be approximately 5 cm proximal to the blind end of the esophagus. The saline lift is performed by injecting a dilute methylene blue saline solution, with or without epi-

nephrine ("lifting solution") into the submucosal space through a 23-gauge endoscopic injection needle as commonly performed in the POEM procedure. A ~10 mm mucosotomy is then created using a triangle-tip (TT) or hook cautery with a cutting current. The endoscope is then inserted through the mucosotomy and into the submucosal plane. A vented, tapered, or angled dissection cap can be fitted to the endoscope to facilitate insertion into the submucosal space and subsequent tunneling in step 4.

Step 4: Submucosal Tunnel Formation

The esophageal mucosa and submucosa are separated from the underlying circular muscle with spray cautery. Further dissection is achieved with hydrostatic pressure through the injection of the lifting solution every few centimeters. Special care should be taken during the formation of the submucosal tunnel to avoid inadvertent thermal mucosal injury from cautery or shearing from the bowing of the endoscope. The circular fibers of the esophagus should remain parallel to the end of the cap to avoid spiraling within the tunnel. The tunnel is extended to the fibrotic stricture, at which point further guidance is provided by the retrograde endoscope and fluoroscopy.

Step 5: Navigation Across the Obstructed Segment

At this point, the circular fibers direct the orientation of the dissection, which should be perpendicular to these fibers. Transillumination and the mechanical changes imposed by the retrograde endoscope provide further guidance for the dissection. Once the two endoscopes are noted to be in close proximity based on fluoroscopy and mechanical manipulation of the retrograde endoscope, the remaining fibrotic tissue is incised. The retrograde endoscope is then passed into the proximal esophagus, thus restoring continuity through the submucosal tunnel.

Step 6: Passing of the Guidewire and Stent Placement

A guidewire is placed through either endoscope and subsequently grasped by the opposing endoscope to maintain control of the reestablished lumen. One or two fully covered esophageal stents are passed trans-orally to maintain patency of the esophageal lumen, traversing the submucosal tunnel and covering the native esophagus above and below the stricture, including coverage of the mucosotomy site.

Post-procedure Care

A water-soluble contrast esophagram on post-operative day one is completed prior to the initiation of a diet to exclude a post-procedural leak or perforation. Stents are removed 3–4 weeks later.

Results

Technical success is primarily determined reestablishment of esophageal patency and clinical evidence of dysphagia assessed by subjective scoring tools.

Complications

Bleeding

Mild bleeding can be addressed with monopolar electrocautery, while higher volume bleeding may require the application of coagulation forceps. Dilute epinephrine can also be injected to aid with achieving hemostasis. When these measures fail, tamponade via the application of direct pressure with the endoscope should be employed. This is particularly effective for submucosal bleeding without an identifiable source or bleeding that obscures endoscopic visualization.

When this kind of bleeding is encountered, pressure should be held for 10–20 min and reassessed.

Perforation

Inadvertent mucosal injuries, burns, and small perforations can occur during any submucosal technique. Often these are clinically irrelevant and are covered by stent placement at the end of the POETRE procedure. In the case of full-thickness injury surgical repair or external drain placement may be necessary. Pneumoperitoneum, pneumomediastinum, and pneumothorax can occur and are typically not considered complications.

Conclusion

POETRE is a newer modality for the safe reestablishment of esophageal continuity in cases of CEO greater than 3 cm in length. It is a novel intervention that combines the technical features of rendezvous endoscopy and the POEM procedure to safely traverse long segments of CEO. Given the relative rarity of its indication, it has yet to be broadly adopted but is an important modality to safely address difficult cases of CEO endoscopically. Further applications for its use may be elucidated over time.

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Chapter 26
Operating Through the Endoscope: Endoscopic Full-Thickness Resection

Pravallika Chadalavada and Madhusudhan R. Sanaka

Background

Advances in interventional endoscopy led to various techniques that facilitate resection of neoplastic lesions of the gastrointestinal (GI) tract. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) effectively remove neoplastic lesions involving the mucosal and submucosal layers. However, these techniques are suboptimal for lesions extending beyond the submucosa and involving the muscularis propria.

P. Chadalavada
Department of Gastroenterology and Hepatology, Digestive Disease and Surgery Institute, Cleveland Clinic Florida, Weston, FL, USA
e-mail: CHADALP2@ccf.org

M. R. Sanaka (✉)
Department of Gastroenterology and Hepatology, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: sanakam@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_26

The evolution of reliable endoscopic closure techniques and devices has recently introduced EFTR as a promising treatment modality for challenging subepithelial tumors (SET) and epithelial lesions arising from the muscularis propria or those associated with significant fibrosis. EFTR has emerged as a less invasive endoscopic alternative to surgical resection in a group of selected patients.

Suzuki and Ikeda were the first to propose endoscopic full-thickness resection (EFTR) with complete defect closure to treat early GI malignancies [1]. In a Japanese study conducted nearly two decades ago, they reported complete resection of two rectal and one duodenal carcinoid with minimal to no complications. Ever since, EFTR has emerged as a viable technique in managing difficult epithelial and subepithelial lesions not amenable to traditional endoscopic resection methods. This chapter highlights the current techniques and tools available for EFTR and the outcomes from such interventions for treating lesions in various anatomical locations of the GI tract.

Current Techniques Used for EFTR

Two common approaches to EFTR described in literature thus far include: Exposed and Non-exposed EFTR [2].

Exposed EFTR

The concept of exposed EFTR has originated from its technical precursors; per-oral endoscopic myotomy (POEM) and natural orifice transluminal endoscopic surgery (NOTES) that use an analogous principle of submucosal tunnel endoscopy. In exposed EFTR, full-thickness resection of the tumor is initially performed, followed by subsequent closure of the defect. This approach results in a transient exposure of the peritoneal contents to the gut lumen, thus explaining the term “exposed.” Exposed EFTR has been further subcategorized into tunneled and non-tunneled techniques.

Tunneled Exposed EFTR

Tunneled exposed EFTR, as the name implies, includes the creation of a submucosal tunnel. A submucosal tunnel is created by dissecting the submucosal plane through a mucosal incision made a few centimeters away from subepithelial tumors (SET). This submucosal endoscopic dissection technique is used to achieve access to the SET which is then enucleated and extracted through the tunnel. Given the proportionately narrow size of the tunnel, submucosal tunnel endoscopic resection (STER) is most practical for lesions measuring under 3 cm in diameter. Additionally, since the tunnel entry site is quite far off from the actual mucosal defect, a full-thickness closure is not required. STER requires closure of only the mucosal defect to conserve the integrity of the GI mucosa that is usually achieved by deploying endoscopic clips or endoscopic suturing.

Non-tunneled Exposed EFTR

Non-tunneled exposed EFTR uses a similar approach to ESD with fluid expansion and dissection of the submucosal layer for circumferential resection of the SET. This results in an inadvertent disruption of the muscularis propria with a subsequent full-thickness defect. Various techniques have been devised and described in the literature thus far for full-thickness closure of defects created in the muscularis propria (MP) by non-tunneled exposed EFTR. Smaller defects measuring ~2 cm can be closed with cap-mounted clips such as over-the-scope clip (OTSC); Ovesco Endoscopy. Another technique includes a loop-and-clip closure with a detachable nylon loop advanced through a double-channel endoscope to the area of the full-thickness defect. The nylon loop is opened around the defect, followed by the application of endoscopic clips above the loop at several locations. Several endoscopic suturing devices such as Apollo OverStitch suturing device, T tags, endoscopic puncture-suture device, and other associated devices have been utilized and reported as useful tools for defect closures following EFTR [3–6].

Non-exposed EFTR

In non-exposed EFTR, a serosa-to-serosa apposition is first created underneath the tumor by invaginating the bowel segment containing the lesion before performing full-thickness resection. The closure is achieved by fixating the serosal surfaces before the actual resection, avoiding exposure of GI contents into peritoneal cavity by a "lose first-cut later" principle, thus explaining the term "non-exposed."

This technique is conceptually related to surgical wedge resection of gastric tumors that includes retraction of the gastric wall from the serosa with apposition of the two intraluminal mucosal walls. The lesion containing the wedge segment is then isolated by firing staples to achieve closure and facilitate subsequent resection. Similarly, EFTR includes retraction of the tumor-containing bowel segment into the lumen allowing approximation and fixation of the two serosal surfaces. The ensuing intestinal wall duplication isolates the tumor, thus enabling full-thickness resection above the fixated serosal tissue with a snare or other ligation devices [7]. Non-exposed EFTR can be performed by over-the-scope devices (full-thickness resection device (FTRD) Ovesco, Tübingen, Germany) [8] and endoscopic suturing platforms (Overstitch Sx, Apollo Endosurgery, Austin, TX, USA) [9]. Cap-mounted clips are useful for achieving hemostasis by mechanical tamponade [10]. More recently, combined endoscopic and laparoscopic techniques such as laparoscopic and endoscopic cooperative surgery (LECS) and laparoscopy-assisted endoscopic full-thickness resection (LAEFR) have also been reported [11].

Indications for EFTR

There is no evidence-based consensus on the indications of EFTR to date owing to the recent development of the procedure. Currently, the most widely used indications for EFTR include subepithelial GI tumors arising from the muscularis

propria with a diameter ≤5 cm based on endoscopic ultrasound (EUS) or CT imaging [12]. It is also recommended for submucosal tumors not amenable to routine laparoscopic techniques such as those present around the gastroesophageal junction [13]. Gastrointestinal stromal tumors (GIST) are another common indication for EFTR [14–18].

EFTR is also preferred in GI lesions with a high risk of adverse events (i.e., tumors in a diverticulum or near the appendiceal orifice), non-lifting lesions that may be secondary to fibrosis and scarring, small subepithelial lesions such as neuroendocrine tumors, or recurrence of epithelial neoplasms following EMR or ESD [19–21].

Contraindications of EFTR

EFTR is contraindicated in patients who cannot tolerate general anesthesia or those with high surgical risk. This includes patients with severe cardiopulmonary disease, blood dyscrasias, severe coagulopathy, and those on antiplatelet or anticoagulant medications that cannot be interrupted or discontinued. It is also not recommended for patients with mucosal lesions at high risk of lymphatic metastasis or intraprocedural peritoneal dissemination. Submucosal lesions with a high risk of aggressive behavior suggested by preoperative imaging or histology are also not preferred [12].

Preoperative Considerations

EFTR is a complex procedure that requires a multidisciplinary approach with support from anesthesia, surgery, pathology, and critical care departments. Patients selected for EFTR should undergo routine preoperative evaluation, including a prior anesthetic evaluation. EFTR is performed in the operating room or an endoscopy suite under general anesthesia with continuous cardiopulmonary monitoring. Intravenous antibiotics, preferably second-generation cepha-

losporins, should be given 30 min before performing the procedure. Adequate bowel preparation with appropriate dietary modification and oral laxatives is recommended for patients with colonic lesions [22]. A prospective pilot study evaluating colonic EFTRs by Xu et al. [23] suggested selective digestive decontamination (SDD) with erythromycin and neomycin before the procedure. Although there is some data supporting a lower rate of post-operative infections and anastomotic leakage with perioperative SDD in elective gastrointestinal surgery [24], there is no clear evidence on the effectiveness of this practice in preparation for EFTR and requires further evaluation in future studies.

Post-operative Care and Follow-Up

Currently, there are no guidelines on post-operative care after EFTR. Based on the recommendations of various experts, patients should be kept nil per os (NPO) for 1–2 days after the procedure. A gastrointestinal contrast study is typically performed to identify any leak before initiating oral nutrition. Patients should be started on a liquid diet gradually progressing to a regular diet over 48–72 h. Empiric antibiotic prophylaxis should be continued for 3–5 days postoperatively to prevent infection. Select patients with upper GI tract lesions may be prescribed proton pump inhibitors for 4 weeks following the procedure.

Clinical Outcomes of ETFR

Efficacy of EFTR in Upper Gastrointestinal Tract Lesions

Esophageal Tumors

Submucosal tunnel endoscopic resection (STER), in other words, exposed tunneled EFTR, appears to be the current most commonly performed endoscopic technique for resect-

ing esophageal SETs originating from the MP layer. By establishing a submucosal tunnel between the mucosa and MP, STER maintains mucosal integrity of the GI tract and is favored over pure EFTR for tumors located in areas where tunneling is possible. Resection of the esophageal lesions under direct vision by STER also facilitates a finer resection with a lower risk of infections and post-procedural leakage. In a study conducted in Beijing by Du et al. [25], STER proved to be an effective and safe procedure for resection of esophageal SMTs with an overall en bloc resection rate of 81.1% and complication rates of 19.8%. Among the 106 patients with esophageal SETs, only 2 patients had residual tumors with 0% recurrence noted during serial follow-up.

STER for esophageal SETs is not typically associated with severe complications. All complications usually resolve without any intervention or with conservative measures without the need for any surgical intervention. Demographic factors such as age, sex, or location do not affect the rate of en bloc resection and adverse events (AE) in patients with esophageal SETs [26–28]. Although en bloc resection appears relatively easier and safe in patients with smaller SETs, longer surgical time was noted to be an independent risk factor for STER-related AEs [26].

More recently, Chen et al. [29] suggested comparable outcomes between STER and thoracoscopic enucleation for large symptomatic esophageal SETs. Patients who underwent STER had a significantly shorter procedure time and hospital length of stay. Thus, STER appears to be safe and effective for SMTs in the esophageal or esophagogastric junction, however, caution should be exercised while considering this procedure for larger (transverse diameter ≥3.5 cm) and irregular tumors due to a higher risk of AEs and requiring piecemeal resection [30].

Gastric Tumors

Zhongshan et al. first reported a case series of EFTR for gastric tumors with a complete resection rate of 100% and no complications [19]. Most of the initial evidence on EFTR for

gastric lesions is from Asian populations with good clinical outcomes [31–33]. A recent study by Andalib et al. [16] suggested promising clinical and safety outcomes in the western population as well.

Almost a decade ago, Wang and group performed a study on endoscopic resection of intracavitary gastric stromal tumors measuring about 3.5 cm in size. Their study suggested that EFTR is safe and successful for resecting gastric tumors arising from the MP layer with a reported shorter hospital length of stay, lower operative time, and lower post-operative complications such as bleeding and infection when compared to laparoscopic surgery. The authors further suggested that combining titanium clip with nylon ring technique can successfully seal surgical wounds incurred while resecting large irregular lesions or those located in endoscopically less accessible sites.

A systematic review on the endoscopic resection for gastric tumors originating from MP layer suggested high success and low complication rates for EFTR technique [34]. The mean success rate of EFTR was 96.8% with a mean procedure time ranging from 37 to 105 min. The conversion rate to laparoscopy was primarily related to the location and size of tumor suggesting a need for extensive pre-procedural imaging to better delineate the tumor characteristics prior to choosing the resection modality of choice. It is also important to acknowledge that EFTR technique has a steep learning curve and collaboration with the surgical team is necessary, especially for excessively large tumors that are not suitable for endoscopic resection.

Duodenal Tumors

EMR has been the conventional technique for resecting duodenal non-ampullary adenomas with 87–96% complete and 87% en-block resection rates [35–37]. Despite the high success rates, adverse events such as bleeding have been reported in 9–24.5% of the cases [36–39]. While most of these bleeds are intraprocedural, delayed bleeding has also been noted in

almost up to 12% [38]. The rate of perforation is also substantially high with EMR and ranges from 0.6% to 5.0% [37–39]. ESD on the contrary, is associated with an even higher perforation rate (35%) and is no longer recommended for resection of duodenal lesions [40, 41].

EFTR is emerging as an endoscopic alternative for resection of duodenal lesions that were not amenable to resection by the techniques mentioned above. Prospective data from the WALL-RESECT study demonstrated that EFTR of "difficult" colorectal adenomas and gastrointestinal subepithelial tumors is effective and safe using the FTRD [42]. The feasibility of EFTR in duodenal lesions with the FTRD has been reported in a small case series by Schmidt et al. [7]. Another retrospective pilot study by the same group reported an 85% technical success for EFTR with the FTRD in resection of duodenum lesions in 20 consecutive patients [43]. Interestingly, this study evaluated proportionally higher number of difficult cases including six patients with failed prior EMR due to non-lifting sign of the duodenal adenomas. Full-thickness resection was technically successful in all these challenging cases, further emphasizing the role of FTRD in difficult non-lifting lesions.

Collective evidence from the existing case series suggests good technical efficacy and safety of EFTR inpatients with duodenal adenomas. A well-designed randomized, controlled trial comparing EFTR with EMR is needed to clarify the usefulness of this novel technique for treating duodenal lesions.

Efficacy of EFTR in Lower Gastrointestinal Tract Lesions

Colonic Tumors

Not all colonic or rectal lesions are treatable with EMR or ESD, especially those with non-lifting sign due to significant

fibrosis and scarring from prior sampling or incomplete resection. EFTR is a better alternative option for treating such challenging colonic lesions. Due to the recent advancements in the FTRD system that facilitates a single step-clip and cut method, treating such lesions has become much easier. EFTR is also useful for recurrent non-lifting lesions located at tricky anatomic sites such as the intra-diverticular or peri-appendicular locations. Several clinical studies have supported the feasibility and effectiveness of EFTR in resecting colorectal lesions [44–48]. EFTR is a better alternative to ESD or EMR for resection for recurrent colonic adenomas or small SETs. It is a less time-consuming procedure than other treatments such as ESD or laparoscopic surgery [49].

A meta-analysis of 9 studies with clinical data on EFTR for colorectal lesions reported a satisfactory full-thickness resection rate of 89.5%, and R0 resection rate of 84.9%, respectively [50]. Additionally, the authors also found a significantly lower risk of AEs. On pooled analysis, the rate of bleeding and post polypectomy coagulation syndrome was only 2.2% and 2.3%, respectively. Notably, the rate of perforation was only 0.19% with almost no heterogeneity. EFTR with FTRD can safely seal the defects caused by resection [51–53] with an estimate for surgery being 6.3% [50]. In a majority of cases, the reason for secondary surgery was deeper invasion or lymphatic spread of the tumor. As such, thorough evaluation of the extent of invasion should be done prior to performing EFTR to avoid secondary surgeries. Moreover, another meta-analysis evaluating the endoscopic resection of large colonic lesions reported a recurrence rate of 13.8% for larger polyps [54]. A few other major limitations of EFTR include the size of the resectable lesion and the limited endoscopic view that aggravates the advancement of scope through colonic or sigmoid flexures. More studies are needed to further investigate the role of EFTR in large colorectal lesions and to further optimize its indications.

Limitations and Challenges

EFTR is still a technically challenging and complex procedure that is currently performed only in a few tertiary centers worldwide with expertise in endoscopic resection. A few other limitations that need to be addressed before a wider adoption of this novel procedure include the incorporation of newer devices and suturing techniques into daily clinical practice and development of more effective hemostatic devices and staplers. EFTR also requires a thorough understanding of surgical anatomy and a higher expertise in interventional endoscopy. There is limited data on the infection rate, risk of bleeding, accuracy of closure, and peritoneal tumor seeding following EFTR, which makes optimal technique and patients selection challenging. Moreover, little is known about the long-term clinical effectiveness and outcomes of EFTR when compared head-on with other well-accepted resection techniques such as transanal minimally invasive surgery and laparoscopic surgery. Lastly, the lack of current procedural terminology (CPT) codes for EFTR limits reimbursement and may impede wider incorporation of this procedure.

Conclusion and Future Perspectives

Recent advancements in endoscopic devices and techniques have propelled the frontiers of endoluminal resections to transluminal interventions following surgical principles. Introduction of reliable closure devices and optimization of appropriate indications have made EFTR more pragmatic for routine clinical practice as it also significantly contributes to lowering the physical, psychological, and financial burden of patients with lesions involving the GI tract. A recent study by Liu et al. [55] suggested comparable efficacy, tolerability, and clinical outcomes of EFTR with surgical intervention for patients with gastric subepithelial tumors. As such, EFTR is expected to gain wider popularity among advanced endosco-

pists, with emerging data supporting its feasibility and positive outcomes. Well-designed prospective clinical trials are needed for further validation of this evolving technique in the algorithm for the management of gastrointestinal SETs.

Conflicts of Interest All the authors declare that this review was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest.

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Chapter 27
Submucosal Tunneling Endoscopic Resection of GI Submucosal Tumors

Joshua Lyons and Jeffrey Marks

Background

The safe and effective use of endoscopy in the treatment of disease processes that would otherwise be treated with a surgical approach is beneficial for many reasons including less post-procedural pain, improved cosmesis, and lower healthcare costs. One of the first feasibility studies illustrating this concept was published in 2004 and showed that endoscopy could be used to gain access to the peritoneal cavity and perform both diagnostic and therapeutic procedures [1]. These types of procedures are now referred to as natural orifice translumenal endoscopic surgery (NOTES). While these procedures are not yet standard of care, they have led to an awareness of the benefit of gaining access to the submucosal space endoscopically for a variety of surgical purposes.

J. Lyons (✉) · J. Marks
University Hospitals Cleveland Medical Center, Cleveland, OH, USA

Case Western Reserve University, Cleveland, OH, USA
e-mail: Joshua.Lyons@UHHospitals.org; Jeffrey.Marks@UHhospitals.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_27

With endoscopic access to the submucosal space, techniques could be developed for the treatment of various esophageal and gastric pathologies including achalasia and gastroparesis which have quickly evolved over the past decade [2–4]. These techniques offer reduced length of stay, decreased post-operative pain, and avoid the morbidities associated with thoracoscopic or laparoscopic approaches. Due to the promising success of these procedures, endoscopic approaches to other esophageal and gastric pathologies are now being performed. One such procedure is the submucosal tunneling endoscopic resection (STER) of esophageal and gastric submucosal tumors.

Submucosal tumors (SMT) encompass a wide variety of both benign and malignant lesions that are mainly found incidentally but can also present with abdominal pain, GI bleeding, dysphagia and early satiety [5]. Pathologies include benign SMTs like leiomyomas, schwannomas, lymphangiomas, and lipomas, as well as malignant SMTs such as gastrointestinal stroma tumors (GISTs) leiomyosarcoma, carcinoid tumors, and lymphomas. GISTs are the most common GI SMT, while the majority of esophageal SMTs are benign histologically [6]. Diagnosis is mainly done with a thorough and complete evaluation of the upper GI tract with esophagogastroduodenoscopy combined with an endoscopic ultrasound evaluation of the lesion, and occasionally radiographic imaging. Image 27.1**.** Endoscopic ultrasound is able to determine the lesions size, layer of origin, and overall endoscopic appearance. While most lesions <3 cm are generally benign, some pathologies including GI stromal tumors do carry a metastatic potential, and even smaller lesions may be high risk for metastasis or recurrence. Depending on the endoscopic appearance of the lesion, a biopsy can be obtained using fine needle aspiration or “bite-on-bite” biopsy where repeated biopsies are taken effectively digging through the mucosa in order to obtain submucosal mass tissue, Endoscopic tissue forceps biopsies can be challenging and are frequently non-diagnostic due to the submucosal nature of these lesions. Endoscopic ultrasound-guided fine needle aspiration is the

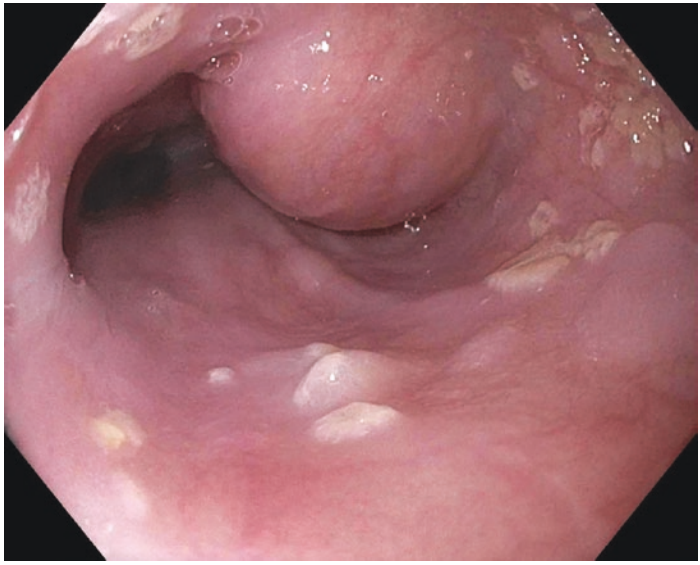

Image 27.1 Endoscopic image of a submucosal mass

most sensitive and specific method for accurate biopsy of SMT. If EUS-FNA is nondiagnostic or unsuccessful, endoscopic mucosal resection can be indicated for diagnosis of SMT.

Small asymptomatic lesions can be safely followed due to the low malignant risk, however if due to patient preference, symptoms, or high-risk features on endoscopic evaluation or pathology including anechoic areas, echogenic foci, irregular borders, or evidence of ulceration, resection [7] indicated [8]. Historically, resection approaches include thoracotomy/thoracoscopy, laparotomy/laparoscopy, and endoscopy. While advances in thoracoscopy and laparoscopy have led to a reduction in the morbidity and mortality of these operations, endoscopy offers the unique ability of avoiding skin incisions and limiting the dissection field thus leading to decreased post-operative pain and lower rates of major complications. Endoscopic mucosal resection has been used in the past but is associated with the potential for perforation and incom-

plete resection. Therefore, STER was developed as an alternative approach for the resection of these lesions.

Description

Submucosal tunneling techniques were shown in 2009 to be a viable and safe endoscopic technique in a porcine model and is now used in clinical practice mainly during POEM and POP [9]. The initial steps of STER are quite similar to POEM and POP. The lesion is identified and a point approximately 5 cm proximal to the lesion is marked and saline (possibly combined with epinephrine or indigo carmine) is injected in the submucosal space to create a submucosal bleb. A 2 cm mucosal incision is made and the longitudinal tunnel formed in the submucosal space by dissecting the submucosal fibers using an endoscopic surgical knife. Image 27.2**.** The tunnel is extended approximately 2–3 cm distal to the lesion which allows for excellent endoscopic visualization and allows for high rates of complete resection. Attention is then turned to resection of the SMT from the involved muscularis propria, which can be performed using a combination of the endoscopic knife, endoscopic cap, and electrocautery. En bloc resection is desired but for larger lesions, piecemeal resection can also be performed. Injury to the mucosa, esophageal adventitia, or gastric serosa is avoided but complete resection is critical and therefore an adventitial or serosal resection can also be performed to ensure complete resection. The tumor is then removed and hemostasis achieved with endoscopic knife or hot forceps. The mucosal incision is then closed with multiple hemostatic clips or an endoscopic suturing device [10]. The anatomic locations best suited for STER are those with fairly straight orientation including the distal esophaus, and distal greater curvature and mid-lesser curvature of the stomach.

Post-operatively, the patients are generally admitted for observation and their diets slowly advanced. Post-operative complications are often able to be managed medically or

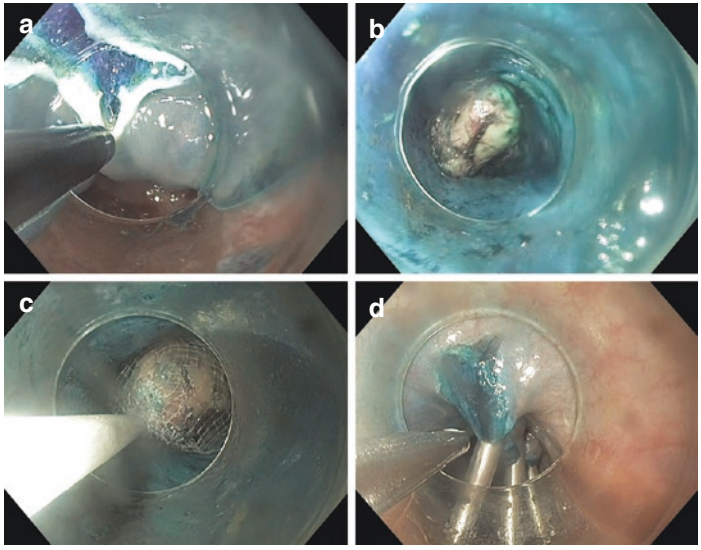

Image 27.2 Submucosal tunneling endoscopic resection of an esophageal gastrointestinal stromal tumor. (**a**) Incising the esophageal mucosa (**b**) dissection of the mass (**c**) Retrieving the specimen (**d**) closing the mucosal defect

endoscopically. Post-operative or intra-operative capnoperitoneum or capnothorax can be managed with needle evacuation or temporary pigtail thoracostomy tube placement. Other potential complications include bleeding, leakage into the tunnel, infection, tumor recurrence, and fistula formation.

Efficacy

Since being described in 2012, STER has been performed on tumors originating from the esophagus and stomach and has shown promising results [11]. A 2017 retrospective case series of 180 patients with SMT who underwent STER with a median follow-up of 36 months showed a 91% complete resection rate and an overall complication rate of 8% which

included pneumothorax, hydrothorax, bleeding, mucosal injury, and esophageal-pleural fistula but these were all managed non-operatively. There was no evidence of local recurrence or distant metastases during the follow-up period [12].

A larger meta-analysis encompassing 16 original studies and 703 patients showed a complete resection rate of 99.8%. Most tumors originated from the esophagus and the majority were leiomyomas. The complication rate varied widely from 0% to 42% with again most being managed non-operatively. The majority of complications noted were pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema but these can frequently be considered inherent to the procedure and not necessarily a complication.

STER is mainly used for smaller (<2 cm) SMTs but it has been proposed that in high-volume centers, larger SMTs could also be resected using STER. A direct retrospective comparison of 166 patients who underwent STER or thoracoscopic resection for esophageal SMTs greater than 5 cm showed no difference in complete resection rates with STER. In addition, STER was associated with significantly lower procedure times and hospital length of stay. There were no recurrences or development of distant metastases in the median follow-up of 2 years [13].

Conclusion

STER is an endoscopic therapy for the resection of SMTs designed to reduce the morbidities associated with more invasive surgical resection techniques. Since its conception, it has been proven to be safe and has demonstrated similar complete resections rates for smaller SMTs and some data showing promising results in larger SMTs as well. This combined with the lack of local recurrence and acceptable complication rates make STER a promising therapeutic approach to the management of SMTs.

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Chapter 28
Thoracic Applications Per Oral Plication of the Esophagus (POPE)

Michael B. Ujiki and H. Mason Hedberg

Abbreviations

DGE	delayed gastric emptying
EGJ	esophagogastric junction
ESG	endoscopic sleeve gastroplasty
GES	gastric emptying scintigraphy
GI	gastrointestinal
LES	lower esophageal sphincter
POEM	per oral endoscopic myotomy
POP	per oral pyloromyotomy
POPE	per oral plication of the esophagus

Introduction

About 5% of patients with achalasia progress to end-stage, meaning despite maximal therapy the esophagus empties poorly and the patient suffers from chest pain, dysphagia,

M. B. Ujiki · H. M. Hedberg (✉)
NorthShore University HealthSystem, Evanston, IL, USA
e-mail: mujiki@northshore.org; hhedberg@northshore.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_28

regurgitation and possibly recurrent aspiration pneumonias. The recommended treatment for end-stage achalasia is surgical resection of the esophagus and replacement with a gastrointestinal (GI) conduit. This is technically challenging and highly morbid undertaking. In some cases, poor esophageal emptying is due to a dilated and tortuous course of the organ, resulting in the pooling of swallowed food and fluid. In this anatomic situation, per oral plication of the esophagus (POPE) may be attempted to delay or avoid esophagectomy. This new procedure employs endoscopic suturing to straighten the esophagus by plicating redundancy. A similar emptying problem can be seen in a neoesophageal conduit after esophagectomy and can be treated in a similar fashion. The following chapter first overviews the two major indications for POPE, poor emptying from megaesophagus or neoesophagus, and describes how to work up and select patients appropriately. Second, the operation is described along with specific technical and clinical considerations.

Megaesophagus

Achalasia

Achalasia is a primary motor disorder of the esophagus characterized by loss of inhibitory ganglion cells in the myenteric plexus. Functional outcome is esophageal body aperistalsis and lack of lower esophageal sphincter relaxation [1]. Most commonly the cause of ganglion degeneration is unknown, or idiopathic. The most common cause of secondary achalasia, or pseudoachalasia, is primary esophagogastric junction (EGJ) malignancy. Other causes include Chagas disease, metastasis, and iatrogenic e.g. a tight Nissen fundoplication [2]. Primary achalasia is chronic, progressive, and lacks a cure. Several options are available for symptom palliation, among them: calcium channel blockers, botulinum toxin injection, pneumatic dilation, and surgical myotomy. Even with treatment, about 5% of patients progress to end-stage achalasia

poor emptying leading to regurgitation, aspiration pneumonia, chest discomfort, and esophageal erosion/ulceration [3, 4]. End-stage achalasia may be due to either a severely tight, scarred, and inflamed EGJ, or megaesophagus, where the organ is dilated to >6 cm and is tortuous or 'sigmoid' in shape [5]. Megaesophagus can result in 'sump' formation - areas where food and oral secretions can pool and fail to drain caudad with gravity. Figure 28.1 shows a barium esophagram of megaesophagus with a sigmoid shape and sump, marked by the arrow.

End-Stage Treatment

End-stage achalasia patients should be worked up with barium esophagram to determine if poor emptying is due to a tight EGJ or sump formation. Obstruction at the EGJ may be improved with repeat myotomy, either endoscopic or laparoscopic. Pseudoachalasia must also be ruled out with endoscopy. If repeat myotomy is not indicated, not technically feasible, or does not improve symptoms, gold standard treatment is surgical resection and replacement with a gastric, colonic, or small bowel neoesophageal conduit. Even when performed in high-volume centers esophagectomy for end-stage achalasia retains one of the highest risks of morbidity and mortality in the realm of GI surgery [6].

Chagas disease is a blood born infection caused by the protozoan *Trypanosoma cruzi*, transmitted by the "kissing bug." The disease is most prevalent in South America, and megaesophagus is the second most common GI manifestation of infection following megacolon. The pathogenesis is the destruction of the enteric nervous system, both excitatory and inhibitory fibers. Interestingly, this results in a slightly different physiology than idiopathic achalasia, where only inhibitory ganglia are lost. Chagasic achalasia patients demonstrate no peristalsis and failure of lower esophageal sphincter (LES) relaxation, but also low basal LES pressure on manometry. Regardless, patients typically present with symp-

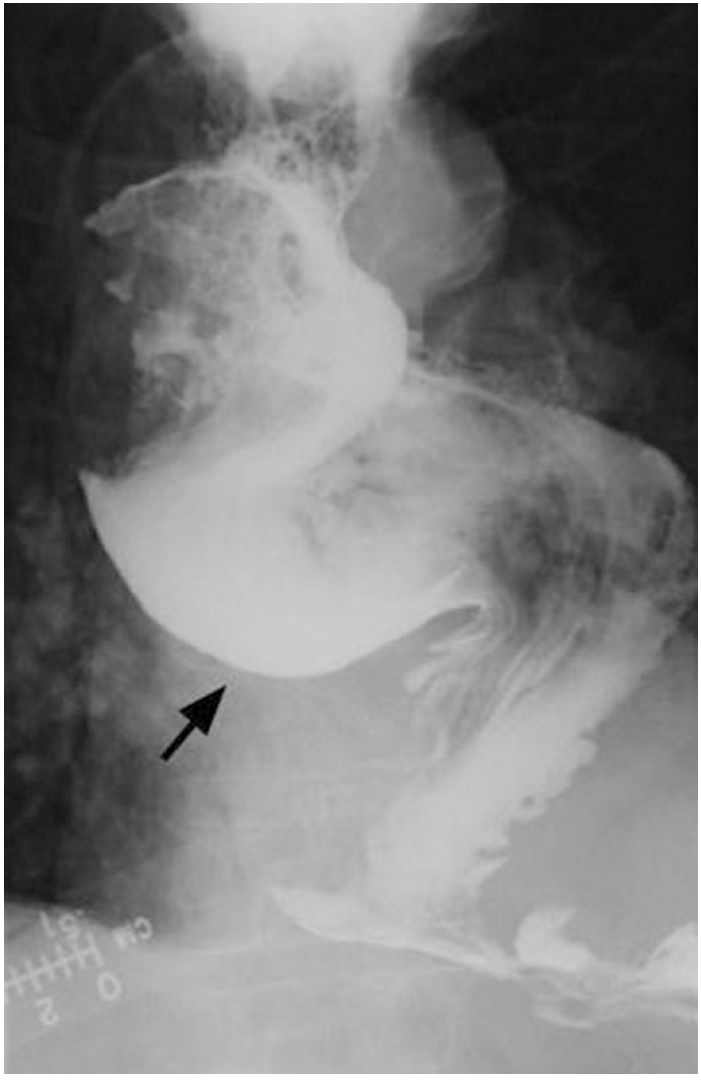


Figure 28.1 End-stage achalasia depicted by a tortuous "sigmoid" esophagus with sump formation (arrow)

toms similar to idiopathic achalasia, have similar radiographic findings, and similarly respond to treatment [7].

Due to the prevalence of Chagas disease, South American surgical literature includes some alternative treatments for end-stage achalasia not well known in North America. As an alternative to esophagectomy, an option for a tight, scarred EGJ is the cardioplasty, antrectomy/vagotomy, and roux-en-y reconstruction. This is also known as the Serra Dória procedure, after the Brazilian surgeon who popularized the operation [8]. It involves a full-thickness incision along the length of the GEJ. The cut edges of the gastric cardia are then folded over and sewn onto the cut edges of the esophagus. This effectively results in an EGJ stricturoplasty. However, it also leaves the patient with no defense against reflux, which is why the vagotomy/antrectomy with roux reconstruction follows. There are current South American case reports of this procedure being performed robotically with favorable outcomes [9].

Surgical alternatives to esophagectomy for megaesophagus with sump formation have also been described. One is a stapled sleeve esophagectomy, where the mediastinum is dissected sufficiently to expose distal esophageal redundancy that can be resected in a manner similar to sleeve gastrectomy. The operation is completed with Heller myotomy and fundoplication [9]. This procedure approaches the esophagus via the abdomen, meaning a mid-esophageal sump as shown in Fig. 28.1 may be difficult to access. Another alternative to esophagectomy is a minimally invasive cervicoabdominal esophageal mucosectomy. This technique invaginates and resects redundant esophageal mucosa in order to narrow and straighten the organ. While this approach is also able to improve symptoms while preserving the esophagus, it is not without its own technical challenges and morbidity and is not commonly performed [10].

Just as endoscopic sleeve gastroplasty aims for a similar anatomic outcome to laparoscopic sleeve gastrectomy, POPE aims for similar anatomic outcome as sleeve esophagectomy or cervicoabdominal mucosectomy. POPE is a fairly new pro-

cedure, first reported in 2018, and currently being investigated by a clinical trial at the Mayo Clinic [11]. As described in detail later in this chapter, an endoscopic suturing device is used to cinch redundant portions of the esophagus, eliminate sumps, and improve emptying. In practice this achieves the same functional outcome as the two surgeries discussed above with a same-day, incisionless procedure. Unpublished experience from these authors shows most patients undergoing POPE experience immediate and significant symptomatic relief, including cessation of recurrent aspiration pneumonia. Typically patients report a few days of chest discomfort and no other complaints.

Given the rarity of megaesophagus, a robust clinical trial comparing POPE, stapled sleeve esophagectomy, and cervicoabdominal mucosectomy would be very difficult. However, we can make some speculations about potential advantages of POPE. Its incisionless approach likely comes with less postoperative morbidity and shorter hospital stays. No incisions means no scarring at surgical access sites; in the case of failure or recurrent symptoms it is likely that POPE would be more easily repeated. Likewise, POPE is less likely to interfere with an esophagectomy should one become necessary later in the disease course. Again, these are speculations, but also reasonable arguments in favor of POPE as a first-line treatment for symptomatic megaesophagus.

Clinical Approach

Patients with end-stage megaesophagus either managed to live a long time without treatment, or received treatment in the past and are presenting with recurrent or persistent symptoms of dysphagia and regurgitation. Symptoms may be due to an inadequately treated LES, an over-treated and scarred EGJ, sump formation, or a combination of these. High resolution manometry will likely resemble a pattern of achalasia: aperistalsis and absent LES relaxation. Manometry findings

alone are not helpful in determining if a redo myotomy is indicated, since a previously treated LES will not relax and basal pressures will vary. Barium swallow is helpful to determine if contrast is being "hung up" at the EGJ and/or in a sump. The dynamic flow of contrast should clearly demonstrate an anatomic reason for the patient's symptoms in order to offer POPE. Ultimately endoscopy and impedance planimetry are the best to evaluate these complex cases. Pseudoachalasia can be ruled out, the LES can be objectively evaluated to assess a prior myotomy, and anatomic evidence of sump formation can be directly visualized.

Cases determined to have an EGJ outlet obstruction, by barium swallow and/or impedance planimetry, either previously had an incomplete myotomy/balloon disruption, or have developed EGJ scarring. We recommend first attempting POEM in these cases if anatomy is amenable. If POEM does not improve symptoms, laparoscopic exploration of the hiatus should be performed with Heller myotomy. In cases where extensive scarring prevents safe surgical myotomy, esophagectomy is indicated. Barium swallow should be performed at each step in this treatment algorithm since persistent symptoms may be due to sump formation not addressed by successful resolution of EGJ outlet obstruction via myotomy.

Patients with good EGJ emptying and contrast pooling in sumps on esophagram are good candidates for POPE. Esophagram is a useful tool to guide endoscopic treatment. Figure 28.2 shows pre- and post-POPE esophagrams. The arrow marks a large mid-esophageal sump that was the target of endoscopic sutured plications. In the preoperative study we can see that distal to the sump the esophagus is fairly straight, and contrast does not pool on its way to the stomach. This patients is a good candidate for a targeted plication of just the mid-esophageal sump. The postoperative study, although taken at a different angle, shows the sump is nearly obliterated, corresponding with improved symptoms for the patient.

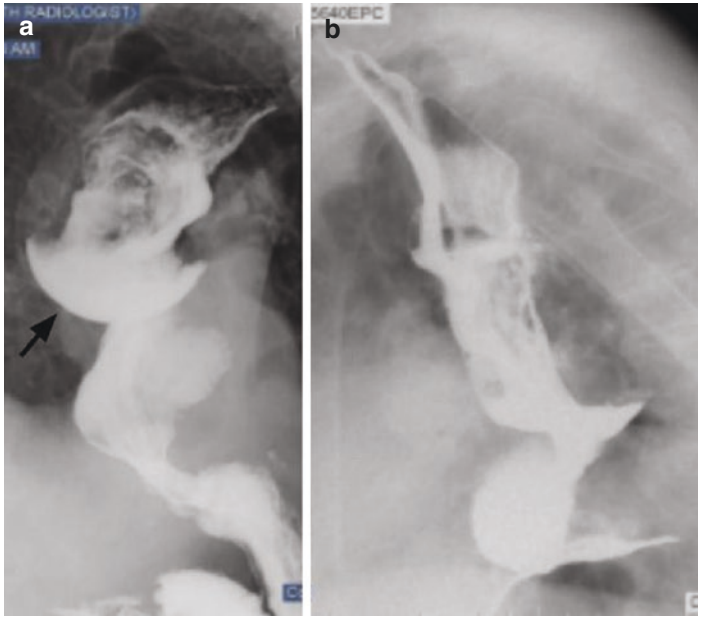


FIGURE 28.2 Esophagrams before (**a**) and after (**b**) POPE. Arrow marks the large mid-esophageal sump targeted by plications during the procedure

Neoesophagus

A progression similar to the development of megaesophagus may occur with the neoesophagus after esophagectomy. Although the stomach, colon, or small bowel may be used as a neoesophagus, stomach is by far the most common conduit. While it is possible that conduits other than stomach could form anatomic sumps amenable to POPE, there is inadequate literate to support a discussion in this chapter. Therefore, the remainder of this section will focus on indications for POPE in patients with a gastric conduit.

Delayed Gastric Emptying

Delayed gastric emptying (DGE) of the conduit after esophagectomy is a fairly common problem affecting 15–39% of patients [12–14]. To empty, the gastric conduit must overcome two hurdles: the pressure gradient from the thorax to the abdomen, and an incompetent pylorus due to the division of the vagus nerves. Technical factors such as torsion, narrow hiatus, or redundant conduit may contribute to DGE. In the early postoperative period DGE increases risk of aspiration, pneumonia, and anastomotic leak. Long-term, it can lead to malnutrition and poor quality of life [15].

There is some debate regarding the management of the pylorus at the time of esophagectomy. Some advocate for pyloromyotomy or pyloroplasty, some botulinum injections, and some prefer no intervention. Up front pyloromyotomy results in higher rates of dumping syndrome, and doing nothing results in higher rates of delayed gastric emptying requiring nasogastric decompression in the postoperative period. Botulinum toxin intraoperatively can decrease immediate pyloric dysfunction and decrease length of stay, although some reports suggest patients receiving the toxin have worse reflux, take more promotility agents, and undergo more endoscopic interventions postoperatively. Regardless of intraoperative preference, a substantial number of patients develop DGE after esophagectomy and ultimately require intervention [16].

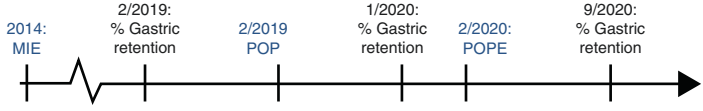
Treatment options for DGE of the conduit include medications, botulinum toxin injection, balloon dilation, per oral pyloromyotomy (POP), and laparoscopic pyloroplasty. Medical and endoscopic interventions are preferred for initial management to improve emptying. Promotility agents such as metoclopramide can be helpful, but if symptoms persist the conduit should be evaluated for delayed emptying. A four-hour gastric emptying scintigraphy (GES) study can be useful in this context. There is no consensus for what 'normal' values should be for the emptying time of a gastric conduit, but these authors feel that a narrow, intrathoracic gastric con-

duit should empty faster than a normal intra-abdominal stomach and that emptying time exceeding typical normal values are actionable. This view is consistent with current literature on the subject [17].

Reconstructing the gastric conduit into a long, narrow tube is known to decrease rates of delayed emptying and reflux esophagitis [18]. However, gastric conduits remain susceptible to dilation and sump formation similarly to megaesophagus. Delayed emptying due to dilation and sump formation will not be addressed by medications or emptying procedures. These cases traditionally require surgical revision or resection and replacement of the conduit [19–21].

Clinical Approach

POPE may be applicable in cases of persistent DGE after adequate pyloromyotomy. Figure 28.3 shows a clinical timeline of a patient's gastric emptying after esophagectomy. Initially, she did well for about 5 years and then began experiencing recurrent hospitalizations for aspiration pneumonia. GES showed delayed emptying, with some improvement in both the test and her symptoms after POP. After another hospitalization for pneumonia, she underwent POPE, and emptying improved further.



	%	Norm
1hr	97	<90
2hr	86	<60
4hr	76	<10

	%	Norm
1hr	77	<90
2hr	52	<60
4hr	46	<10

	%	Norm
1hr	34	<90
2hr	31	<60
4hr	20	<10

FIGURE 28.3 Timeline of a clinical course, from minimally invasive esophagectomy (MIE), to per oral pyloromyotomy (POP), to per oral plication of esophagus (POPE). Tables below show the progression of nuclear gastric emptying results

DGE is a well-known complication following esophagectomy and should be approached in a stepwise manner. These authors consider POP to be the first line treatment for medically refractory DGE given it is incisionless and more definitive than balloon dilation. Intraoperative impedance planimetry can help confirm a successful myotomy. Recording distensibility values at the time of POP can also be helpful to determine if re-do POP is indicated for recurrent symptoms in the future [22].

DGE in the context of an open and distensible pylorus may be due to sump formation or other anatomic outlet obstruction, and outlet obstruction must be ruled out prior to offering POPE. Figure 28.4 shows a CT scan of a patient with a severe gastric conduit outlet obstruction. This patient was suffering from symptoms of DGE and underwent POP with minimal improvement, and presented with this outlet obstruction a few months later. His poor emptying was due to kinking of the duodenum at the hiatus, not an incompetent pylorus nor sump formation. A (neo)esophagram should be

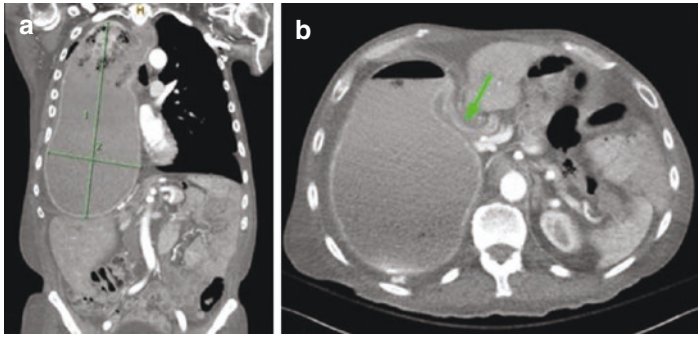


FIGURE 28.4 CT scan demonstrating a gastric conduit outlet obstruction. Cranial view (**a**), shows the stomach filling the majority of the right chest with mass effect directing the diaphragm and liver caudad. There is an outlet obstruction caused by angulation of the duodenum entering the abdomen through the hiatus (**b**, arrow)

obtained for patients with persistent DGE after POP. This will help differentiate anatomic outlet obstruction from sump formation that may benefit from POPE.

Operative Description

Endoscopic suturing is a relatively recent technological advancement used to address GI tract defects such as fistulas and perforations, to prevent endoscopic stent migration, and to revise or remodel portions of the GI tract. For example, endoscopic sleeve gastroplasty (ESG) utilizes endoscopic suturing to functionally achieve the same anatomical result as sleeve gastrectomy without resection or removal of tissue [23]. Our aim was to apply the principles of gastric remodeling for weight loss to remodeling a megaesophagus or redundant neoesophagus in order to achieve the functional result of esophageal mucosectomy. Plication of the (neo)esophageal mucosa and submucosa should similarly narrow the organ, as shown in a simplified cartoon, Fig. 28.5. Rather than weight loss, the goal of these plications is to improve emptying and alleviate pain, regurgitation, and aspiration.

Device

The endoscopic suturing device, OverStitch™ (Apollo Endosurgery Inc. Austin, TX), uses a detachable head placed at the end of the endoscope and a handle placed close to the proximal opening of the accessory channels. The OverStitch™ requires a double channel endoscope (Olympus GIF-2TH180). A lever on the handle drives the needle driver on the detachable head. Suture is introduced through the larger accessory channel using a needle passing catheter. The OverStitch™ Tissue Helix (Apollo Endosurgery Inc. Austin, TX) is used through the smaller, second accessory channel to screw into and pull tissue up to the needle driving head. The components of the system are shown in Fig. 28.6. We place an

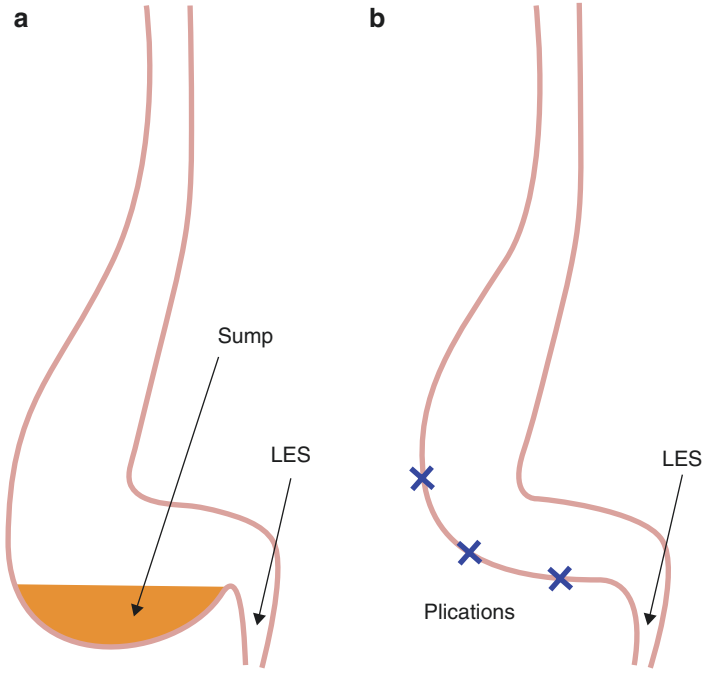


FIGURE 28.5 Simplified image demonstrating a sump in a dilated gastric conduit (**a**). Right panel demonstrating a straightened conduit after plications have been applied to the redundant portion (**b**)

OverTube™ (Apollo Endosurgery Inc. Austin, TX), to protect the oropharynx and upper esophagus from excessive abrasive trauma by the OverStitch™.

Procedure

POPE is performed under general anesthesia in the supine position. Anesthesia should be made aware of aspiration risk in these cases – due to anatomic emptying problems the (neo) esophagus likely contains undigested food and fluid despite patients remaining *nil* per os for 12 h or more. After confirming the patient and procedure in a standard time-out, the

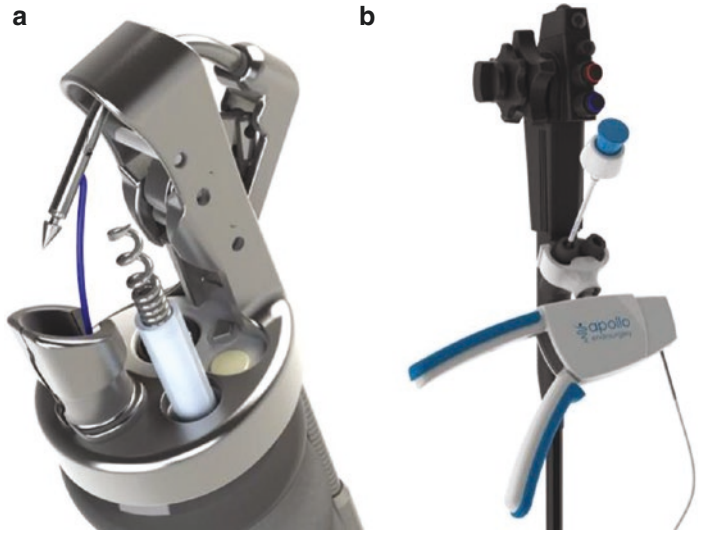


FIGURE 28.6 Apollo Overstitch™ device. Left panel (**a**) showing the endcap with needle driving apparatus and Tissue Helix. Right panel (**b**) showing the control devices—lever for driving the needle and needle passing catheter in the accessory channel. Images used with permission by Apollo Endosurgery

esophagus or neoesophagus is closely inspected with a high-resolution single-channel endoscope (Olympus GIF HQ190) for unexpected pathology. If appropriate, impedance planimetry to interrogate the esophagogastric junction (EGJ) or pylorus (EndoFLIP™, Medtronic Inc., Warsaw, IN) is performed to ensure the adequacy of prior myotomies. If indicated, per oral endoscopic myotomy (POEM) or per oral pyloromyotomy (POP) could be repeated at the time of POPE. We have previously published on expected planimetry values after complete myotomies of the EGJ and pylorus, which help guide intraoperative decision-making [22, 24, 25].

An OverTube™ is placed and the dual channel endoscope is fitted with the OverStitch™. A 2-0 polypropylene non-absorbable surgical suture is loaded and the device tested outside the body. The scope is introduced and advanced

to the most distal area of redundancy. Bites of tissue are taken from anterior to posterior along the surface of the redundancy, being sure to leave adequate lumen behind to avoid stricture. When the suture line is complete, the suture is cinched, anchored, and cut using the OverStitch™ Suture Cinch. The scope is withdrawn and the next plication proceeds as the prior. Plications are placed in a distal to proximal manner until the sump has been eliminated. The number of plications and the number of bites per plication is dependent upon the individual's anatomy. When plication is complete, the high-resolution scope is re-introduced to inspect for hemostasis and inadvertent injuries.

Technical Considerations

It is critical to maintain orientation while performing POPE and other endoscopic surgical procedures. Major landmarks identifiable during upper endoscopy with normal anatomy include the cricopharyngeus, aortic arch, left bronchus, left atrium, and EGJ. These are helpful to determine position along the length of the esophagus and should roughly correspond to expected "centimeters-at-teeth" noted on the endoscope. The aortic arch/left bronchus and left atrium are generally in the upper left field of view during endoscopy of a supine patient (with the operator standing to the patient's left), and can be used to help maintain anterior-posterior orientation. Anatomic landmarks may not be reliable in a megaesophagus or neoesophageal conduit. A useful maneuver is to drip some saline or water from the end of an injection needle—drips will fall down with gravity indicating the posterior direction for a supine patient. Once oriented, the position of vital structures surrounding the esophagus/conduit should be kept in mind as the procedure is carried out.

The OverStitch™ is capable of taking full-thickness bites of the GI tract. During ESG, full-thickness plications are desirable, theoretically improving durability of the revision. However, there are case reports of injury to surrounding

structures during ESG such as gallbladder perforation [26]. Presumably, the Tissue Helix can be driven beyond the gastric serosa and pull other tissues into the needle's path during a plication. While this is a rare event during ESG, injuries such as these in the mediastinum could be life-threatening. As demonstrated in the attached video, care is taken to avoid drilling too deeply with the Tissue Helix during POPE. Additionally, the endoscope remains a few centimeters from the mucosa, forcing the tissue to be tented away from surrounding structures as it is pulled into the needle's path.

Durability

ESG is a relatively new procedure lacking long-term data. A recent meta-analysis shows some weight loss parameters to be equivalent to laparoscopic sleeve gastrectomy at 12 months, and some series show persistent weight loss beyond 24 months [27]. This implies the plications are intact, continuing to promote weight loss at one year. It is unknown how long a plicated stomach will maintain its remodeled shape. Durability for POPE may be inferior to ESG, since the esophagus lacks a serosa and aggressive, full-thickness bites are unadvised. Durability will likely depend upon a variety of factors individual to each patient, such as extent of redundancy, number of plications, and number of bites per plication.

Case reports of re-do ESG for inadequate weight loss already exist [28]. These cases were completed without complication and patients had improved weight loss. It is reasonable to assume POPE could also be repeated if symptoms recur. For some patients, it may be possible to completely avoid a highly morbid esophagectomy or conduit revision using endoscopic remodeling as needed. It is possible that repeat plication would increase the technical difficulty and morbidity of a definitive surgical intervention, and it may be wise to turn to surgery early if symptoms cannot be controlled after a few endoscopic attempts.

POPE may also serve as a bridge to definitive esophagectomy or conduit revision. Patients with protracted regurgitation and/or aspiration pneumonia may be in poor condition for major surgery. If a sump is evident on imaging, POPE may be a reasonable strategy to decrease pulmonary infections and improve nutrition while considering definitive surgery. Given the chest discomfort reported by patients, there is likely some periesophageal/periconduit inflammation after POPE. It would be reasonable to delay definitive surgery for several weeks after POPE while pulmonary status/nutrition improves and inflammation from the procedure subsides. As of yet, there are no reports of esophagectomy or conduit revision after POPE.

Conclusion

The esophagus of end-stage achalasia and neoesophageal conduits are susceptible to developing redundancy and tortuosity, resulting in sump formation. This retained food and fluid can cause discomfort, regurgitation and aspiration pneumonia. Traditional treatment is esophagectomy or invasive conduit revision. POPE provides an opportunity to palliate challenging symptoms with a same-day, incisionless procedure. Given the large contrast in morbidity between POPE and alternative surgical therapies, with favorable long-term data POPE may become considered first-line therapy for appropriate patients. Patients must be selected carefully: sump should be evident on contrast imaging and other outlet obstruction ruled out prior to intervention.

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Chapter 29
Thoracic Applications: Endoscopic Approaches to Benign Esophagorespiratory Fistula Closure

Kyle L. Kleppe

Introduction

Esophagorespiratory fistula (ERF) is a rare condition with abnormal connection of the respiratory and digestive tracts. The most common presenting symptoms are postprandial cough, dysphagia, fever, and aspiration pneumonia. Depending on the site of communication, fistulas may be classified as either tracheoesophageal fistula (TEF) or bronchoesophageal fistula (BEF). Fistula can result from both benign and malignant conditions. Malignant fistula are five times more common and treatment is primarily focused on palliation [1].

Benign ERF can be congenital or acquired. Development of fistula may be the result of blunt or penetrating trauma, iatrogenic surgical injury, anastomotic complications after

K. L. Kleppe (✉)
The University of Tennessee Graduate School of Medicine, Knoxville, TN, USA
e-mail: klkleppe@utmck.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_29

esophageal surgery, immunodeficiency, indwelling stents, prolonged endotracheal intubation, caustic ingestion, or mediastinal lymph node involvement by infection or chronic inflammation [1]. Due to the higher expected survival in the benign ERF population, durable closure is desired.

Esophagorespiratory fistula have been traditionally managed through open surgical techniques such as esophagectomy, interposition flaps, or esophageal diversion. Efficacy for these open procedures is approximately 90%. However, surgical interventions have also been associated with a greater than 50% morbidity. [2]. Surgical therapies may not be advisable or possible due to a patient's medical status or prior thoracic surgery [3]. Endolumenal approaches have been increasingly employed in these scenarios as newer technologies and techniques have allowed for clinically successful closure in many patients with less associated morbidity.

While the main focus of this chapter is for application in the adult population, endoscopic approaches have been used in the pediatric population for both congenital TEF and recurrent TEF after surgical repair [4–6]. Some of the techniques described have been used with more frequency in that population but demonstrate effectiveness in the adult population as well.

Evaluation of Fistula

Diagnosis of ERF is confirmed through both radiographic and endoscopic evaluation. Individual modalities may have a low sensitivity for detection, therefore a high degree of clinical suspicion with use of both radiographic and endoscopic methods will result in detection. Esophagram is the most common radiographic study for evaluating fistula presence and location. Computed tomography is helpful for identifying the tract as well as associated pathologies including mass, lymphadenopathy, or abscess.

Endoscopic evaluation should be made to characterize the fistula as several factors are important in determining the

approach used and estimating success of closure. Location, number of orifices, size, degree of surrounding inflammation or fibrosis, and other concomitant esophageal pathology such as distal stricture can all be evaluated. Most cases will have a single orifice while up to 22.7% may have multiple [3]. A staging system has been described for fistula orifice size: Stage I—punctiform, described as less than the size of a closed biopsy forceps; Stage II—medium, larger but with no direct visualization of the respiratory tract; and Stage III—large, direct visualization of the respiratory tract possible from the esophageal lumen [3]. Endoscopic sampling of the fistula can be conducted at this stage via brushing or biopsy forceps to rule out malignancy.

Bronchoscopy aids in the thorough evaluation of the fistula. The characteristics enumerated above during endoscopy should be evaluated within the respiratory tree as well. Bronchial or tracheal stricture may also be present and can impact success of interventions. Simultaneous endoscopy and bronchoscopy has been reported to adequately assess the fistula tract as well as perform therapeutic interventions such as stent placement [7]. On occasion, fistula orifices may be difficult to locate or true connection may be in question. In this scenario simultaneous endoscopy may allow visualization of bubbles from the tract originating from the other lumen [8]. Other techniques include the use of methylene blue instilled through the gastroscope with visualization bronchoscopically or instillation of contrast under fluoroscopy [5, 7–9].

Therapeutic Approaches

Multiple different endoscopic modalities have been used in the successful treatment of benign ERF. Selecting an appropriate endoscopic intervention is influenced by patient factors identified during a thorough workup, operating room equipment and supply availability, as well as surgeon expertise in using the techniques described below.

Stenting

Endoscopic stent use in the esophagus is likely one of the more familiar techniques to endoscopists due to their use in malignant fistulas and other esophageal pathologies. Esophageal stents have therefore been applied to benign ERFs. Studies employing these techniques describe high rates of symptom improvement. Success is determined typicallyas occlusion of the fistula tract via radiographic methods, achieving the desired result in 70–90% of cases [7, 10]. However, this is contested in the literature with lower demonstrated closure rates after stent removal of only 45–54% [3, 10]. Some hypothesize that stents do not promote healing and only serve as a diversion of esophageal content from the respiratory tract [10].

Use of stents has been advocated for in cases of large fistulas and when concomitant stricture of the esophagus is present [3, 10]. Use in the acute postoperative setting following esophageal resection with anastomotic fistula has met with some success as well [11]. Commonly the choice for stent is an esophageal, fully covered, self-expanding metal stent which may or may not be fixated to the esophageal mucosa through clips or suture [10]. Stents are typically left in place for 4–6 weeks to avoid ingrowth and may require replacement if fistula is persistent [3].

Serious adverse events from stent placement in this population has been reported in up to 40% of patients including: gastrointestinal bleeding secondary to mucosal erosion, stent migration, thoracic spondylodiscitis, food impaction, stent mucosal impaction, and major chest pain [3, 10].

Dual therapy using both esophageal and airway stents may be required. This technique is listed in the American College of Chest Physicians guidelines of 2003 as a Grade C recommendation, providing the best overall results of symptom relief, although this is for palliation of lung cancer [12]. Specific circumstances which may warrant combined esophageal and airway stents include: when esophageal stenting may exacerbate an airway stenosis or when a large fistula is pres-

ent and the esophageal stent may migrate into the airway [8]. It has been recommended to place the airway stent first to avoid airway compression, as well as to place the esophageal stent with its upper margin higher than that of the airway stent to prevent distal migration of the esophageal stent which is a common complication [8]. In one study examining dual therapy they found a lower rate of fistula occlusion compared to esophageal stent monotherapy [10].

Mechanical Closure Techniques

Direct tissue apposition can help to restore mucosal continuity and promote fistula healing. Several endoscopic devices are available to achieve apposition and range in difficulty of use. Through-the-scope (TTS) clips are familiar to most endoscopists and have been used with mixed success [10].

Over-the-scope (OTS) clips have been utilized in fistula closure either alone or in combination with other therapies such as stent placement [3, 10]. Successful closure of fistulas originating from tuberculosis [13], post-tracheostomy [14, 15], and esophageal foreign body [16] have been described. OTS clips have been advocated for in cases with a recently developed fistula, a small orifice, and having smooth and non-fibrotic edges [3].

For larger fistula tracts, clips alone may not be able to reach both sides of the mucosa. Additional use of an endoloop with a dual channel endoscope can serve as a cinch. The endoloop is passed through one working channel and placed at the margins of the fistula circumferentially. TTS clips are then applied through the second channel securing the endoloop to the fistula margins in multiple locations. The endoloop is then tightened bring the mucosa in approximation [17].

Newer commercially available endoscopic suturing devices have been employed with demonstrated success in closure. Suturing the defect after cauterization with APC [18], and suturing the defect with subsequent stent placement [10] has also been described.

Occlusion of Tract

Chemical obliteration of the tract has been employed commonly in recurrent TEF in the pediatric population. Tissue adhesives such as cyanoacrylate and fibrin adhesive have been the most frequently employed with an overall success rate of 60%. Application has mostly been described from the bronchus side [6]. These chemicals induce an inflammatory response to promote granuloma formation and subsequent epithelialization [4]. Injection of material in the submucosa of the lateral walls of the fistula has also been described, thus occluding the lumen [19]. Use of tissue adhesive and combined sclerosing agent had the highest reported closure rate of 100% in the pediatric population [6].

Occlustion through the use of mesh placement also serves to create inflammation and obliteration of the tract. In a pediatric patient, an 8 ply, 0.5 cm piece of mesh made from small intestinal submucosa was placed from the tracheal side into the defect after electrocauterization of the tract resulting in successful closure [5]. In another pediatric two time recurrent fistula, epithelium was denuded with a brush from the bronchoscopic side then a small piece of 4 ply, 0.5 cm piece of the same type mesh was placed from the tracheal side with successful closure [20].

A serious complication with use of tissue adhesives, glue, or mesh placement can result from dislodgement of the substance into the airway, with aspiration into the distal airways [4].

Mucosal Disruption

The primary reason closure failure is the persistence of an epithelialized tract. Disruption of the epithelium through mechanical means can be performed with biopsy brushes, forceps, or suction. One of the simplest methods for destruction of the epithelium is electrocauterization. This can be applied through hot snares, biopsy forceps, advanced endoscopic knives, or argon plasma coagulator [4].

In a review of pediatric patients presenting with recurrent TEF, electrocauterization as sole therapy resulted in a closure rate of 67% [5]. Use of cauterization in combination with other therapies such as by suturing [18] or clip placement [15] is also described. Cauterization from the esophageal side may be inadequate to provide scarring. Additional cauterization has been applied from the respiratory side of the fistula in the pediatric population [5]. Electrocautery use on the respiratory side of the fistula does carry the risk of operative fire and resultant thermal damage; however, use of lower oxygen concentration can reduce this risk.

Chemical ablation of the mucosa can be accomplished with silver nitrate beads, 50% trichloroacetic acid or sclerosing agents such as submucosal injection of 30% NaCl or 0.5% polidocanol [4]. Topical application of trichloroacetic acid in pediatric patients with congenital and recurrent TEF was found to be 100% effective in long term closure in 14 pts [21].

Endoscopic Mucosal Resection

The most advanced treatment method involves endoscopic mucosal resection (EMR). This procedure provides the opportunity to remove at least a portion of the epithelialized tract with some of the surrounding mucosa and restore continuity of the esophageal mucosa. Techniques to accomplish this type of procedure are similar to other endoscopic surgical procedures such as per-oral endoscopic myotomy (POEM) and gastric EMR. Equipment includes a beveled dissection cap, injection needle, electrosurgical knife, and devices for closure such as through-the-scope clips, over-the-scope suturing devices, or stents [22, 23].

Resection of the epithelial tract is typically performed utilizing a saline lift of the mucosa and then incising with an endoscopic knife. Incising the distal aspect first preserves visualization for more proximal dissection. Additional saline lift with incision of the mucosa on either side followed by the proximal aspect allows for circumferential resection of the

mucosa. The mucosa can then be cleared off of the muscular layers and the tract identified and subsequently divided.

Providing adequate retraction of the fistula tract orifice to allow for a deeper division of the tract is important and the most technically challenging aspect of this procedure. Use of a dissection cap has limited force and directionality to apply traction on the dissected mucosa. Several techniques have been developed for providing optimal traction and are described below.

The "clip and line" technique uses a through-the-scope clip to provide retraction [24]. First the gastroscope is removed from the patient and a through the scope clip is advanced through the working channel. A long suture such as silk is then tied to one of the tines of the clip and left external to the scope. The clip is withdrawn back into the scope and the scope is reintroduced into the patient with the suture remaining outside of the mouth. The clip can then be deployed on the dissected tissue and the suture can be pulled externally to create traction on the tissue. Difficulties of this method include retraction limitations only in the cephalad direction, and unintentional clip dislodgement requiring repeat application of a new clip. Use of a dual channel therapeutic gastroscope can allow for retraction with a grasper while preserving a working channel for cautery but still has some limitations for direction of retraction.

A technique employed by the author is concomitant use of a bronchoscope in the esophageal lumen. Simultaneous evaluation of the respiratory side of the fistula with the bronchoscope allows for the presence of a separate endoscopic tower to be used during the case. The bronchoscope can be easily passed adjacent to the gastroscope within the esophagus. A grasper through the working channel of the bronchoscope can then be applied to the fistula tract for retraction. The bronchoscope can be independently manipulated providing retraction in all directions. Ability to release and regrasp the tissue is of major benefit over the clip and line technique.

Closure of the defect by reapproximation of the mucosa can be accomplished by use of TTS clips [22] or endoscopic suturing. TTS clips have been recommended to be anchored in the submucosa [22]. In some instances tissue fibrosis can preclude tissue reapproximation and a stent can be placed. One case report utilized an endoloop and clips to secure the stump of the tract but not to close mucosa over the fistula after EMR [23]. The muscular layers may also be approximated over the fistula tract providing a layered closure of the tract with mucosa being closed around deeper clips if used.

Clinical Success

Evaluation of true clinical success of these techniques is difficult based on the current literature. Many studies are limited by low case numbers, heterogeneous techniques, short term follow-up, or lack of objective studies demonstrating healing. The definition of "clinical success" in the literature is also variable including occlusion with a stent without healing, resolution of orifice via endoscopic evaluation, or resolution of symptoms such as pneumonia or postprandial coughing. Despite these limitations, there are several trends which are apparent that will be discussed below. Overall endoscopic treatment is safe, carries less risks than open surgical approaches, and has the potential to cure a large percentage of benign cases of ERF [4, 10].

There are several patient factors which likely play a role in fistula closure following endoscopic intervention. Presence of a tracheotomy was found to be associated with failure. There is a trend for punctiform and small sized fistula tracts to demonstrate the highest closure rates. Large fistula tracts have a lower healing rate as well as a higher risk of death, 71% in one study [3]. Proximal fistulas are more difficult to control and have decreased healing rates [10]. Radiation did not affect closure rates but did trend for prolonged healing

times [3]. These statistics were based on treatment including over-the-scope clips and stents, there are no large series using more advanced therapies.

An important factor to promote healing is disruption of the epithelial tract connecting the esophageal and respiratory lumens. In cases where fistula was the result of a recent antecedent surgery, and an epithelial lining is not well established, techniques utilizing clips and stents were more successful [11, 17]. If the process is chronic then addressing the epithelium should be required. Techniques can range from mechanical abrasion or cauterization to complete mucosal resection.

While there are cases demonstrating healing with use of a single modality, many of the studies utilized combined therapies at the same session. Use of simultaneous esophageal and airway stents demonstrating closure in 33–70% [7, 10]. Esophageal SEMS and OTC clips demonstrated 45.5–100% closure rate if used as the initial therapy [3, 10]. Occlusion with small intestinal submucosa mesh was reported after electrocauterization of the mucosa [5] or after abrasion of mucosa followed by fibrin glue application [20]. Some studies were able to compare combined modalities demonstrating higher levels of success. When electrocauterization was combined with tissue adhesive, closure was increased from 67–86% in pediatric patients with recurrent TEF [5].

The number of endoscopic treatments necessary to achieve closure has ranged from 1 to 19 with several studies demonstrating a mean number of treatment sessions between two and four [3, 5]. If multiple procedures were performed, some would elect to repeat the same procedure such as stent exchange [3, 10] or replacing mesh [20], while others proceeded with escalating therapies [24]. Escalating therapies may start out as clip application, followed by electrocauterization, then ESD [24] or stent, APC, and then ESD [22]. As mentioned before, esophageal stenting may not induce healing but may serve as a bridge to a more definitive therapy. Despite additional therapies, the absence of fistula closure after 6 months is associated with failure to close [3].

Fistula recurrence after surgical repair has been difficult to manage in both the adult and pediatric populations. Repeat thoracotomy has increased risks and endoscopic management has demonstrated success in this population [5, 6, 17, 20]. As mentioned previously, multiple endoscopic treatments may be required for fistula closure, and therefore repeat endoscopic options remain available if closure does not occur.

Conclusion

Increasingly, advanced endoscopic therapeutic modalities are allowing for closure of difficult esophagorespiratory fistulas in many patients. The reported therapies in the literature have shown ingenuity and documented success. Direct comparison of effectiveness between studies is difficult due to significant variances in techniques and heterogeneous patient populations. More advanced techniques such as EMR may offer increased healing rates in these patients. The specific choice of modality utilized will be highly individualized based on patient characteristics, equipment availability, and surgeon experience. Endoscopic therapies offer a chance for these patients to have closure of their fistula resulting in increased quality of life and life expectancy.

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Chapter 30
Endoscopic Ultrasound (EUS) Guided Biliary Drainage

Leonardo Sosa-Valencia and Lee Swanström

History and Background

People without the knowledge of their past history, origin, and culture are like a tree without roots. (Marcus Garvey).

Endoscopic ultrasound (EUS) is an endoscopic technique using dual imaging from a flexible endoscope, one in gray-scale for echosonographic images and the other one a standard color video image. EUS has evolved from diagnostic to therapeutic indications over the last two decades. Biliary interventions started as far back as 2001 at the Endoscopy Unit of the Paoli-Calmettes Institute in Marseilles; there French doctors developed an interest in EUS-guided interventions and started performing therapeutic EUS assisted biliary drainage. Marc Giovannini published a case of a

L. Sosa-Valencia (✉)
UNISTRA, Strasbourg, France
e-mail: leonardo.sosa-valencia@ihu-strasbourg.eu

L. Swanström
Institute of Image-Guided Surgery, IHU-Strasbourg, Strasbourg, France

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_30

56-year-old male patient in Endoscopy who had pancreatic cancer in the pancreatic head presenting with jaundice and who previously failed endoscopic retrograde cholangiopancreatography (ERCP) attempts to provide drainage. He was able to place a plastic stent utilizing EUS to guide a direct cutdown from the duodenum to the common duct with subsequent plastic stent placement using a standard duodenoscope [1]. Two years later, in 2003, two publications with more patients [2, 3] showed the use of EUS alone in an assisted biliary extrahepatic drainage. The first was from a German endoscopist who showed how an alternative EUS-guided cholangioduodenostomy (EUS-CDS—biliary drainage) was possible in four patients with pancreaticobiliary strictures due to malignancies which were unable to be drained by palliative ERCP. At that time, there were no specific instrumentation to perform EUS-CDS. All the tools have been repurposed from other endoscopic interventional procedures such as pancreatic pseudocyst drainage. Despite this, drainage was achieved in 3 of 4 patients (75%). The same year the experts in Marseille published their second manuscript focused on avoiding the use of percutaneous biliary drainage, as was common in the early 2000s. Percutaneous drainage had a known incidence of major complications (between 15% and 20%) including peritoneal bleeding. Again, as with the previous series, many of the methods used at the time are no longer used today (needle knife duct access, metal Sohendra dilators, plastic stents vs. today's lumen-apposing metal stents (LAMS) and naso-biliary drains for the first 48 h.

In 2004, Freeman and Mallory from the University of Minnesota-Minneapolis, published another technique called EUS-guided rendezvous drainage (EUS-RDV) for obstructed biliary and pancreatic ducts. They presented six patients with pancreatic cancer ($n = 5$) and anastomosis stricture ($n = 1$) where they successfully punctured the CBD or the main pancreatic duct (MPD) with EUS guidance and placed a guide wire across the papilla allowing an ERCP to be accomplished in 83% ($n = 5/6$) and a successful plastic stent placement in 3/6 (50%), thereby avoiding surgery or percutaneous transhe-

patic biliary drainage (PTBD) as a definite treatment [4]. During the video forum at DDW 2004 Professor Manuel Perez-Miranda from Spain presented his first EUS-guided biliary drainage (EUS-BD) performed at the end of 2003. Today his center performs more than 200 therapeutic EUS biliopancreatic and anastomotic digestive procedures a year and is a major teaching and training center for these different techniques [5] These early cases heralded a new era of biliary interventions which would lead to development of new instruments and techniques and an alternative approach to external radiological drainage for more patient-friendly treatments.

Over the subsequent two decades, more than 400 articles have been published in the literature regarding EUS directed BD. A recent meta-analysis and systematic review, published as an abstract, evaluated 19 articles with data from 480 patients who had EUS assisted gallbladder drainage (EUS-GBD) for cholecystitis in non-operable patients between 2000 and 2019. There was a technical success of 96% and a clinical success of 93%. Complications from all cases were 16.92% with almost half of them (7.03%) related to the stent (obstruction 4.23%, tissue overgrowth 4.65%, removal 9.21%, recurrent cholangitis/cholecystitis 3.75%). Among these groups, one out of three had perforations (4.77%). They described an overall mortality of between 9 and 31% (median of 18%) during different follow-ups. [6] The authors suggested that this procedure should still be reserved only for severely ill patients with acute cholangitis and terminal conditions such as biliopancreatic malignancy.

Training Issues

This new therapeutic tool is difficult to learn due to inherent technical and interpretational skills needed. Learning EUS-BD is complicated partly because most of the cases are concentrated in tertiary referral centers, meaning that the physician is required to spend several weeks at the teaching

hospital to gather experience, which is often only observational according to regulation policies that differ for each country. Simulators, ex vivo models and phantoms are often used to teach EUS but are not really adapted for EUS-BD. Many short courses, sometimes conducted by endoscopic societies at international congresses, train using porcine explant models. In 2011, the British Society of Gastroenterology (BSG) suggested that 250 cases were necessary for good quality training in diagnostic EUS, to include 80 endoluminal gastrointestinal cancers, 20 gastrointestinal submucosal tumors, and 150 pancreaticobiliary lesions recommended. Currently, 75 biopsies are recommended, including 45 for pancreatic malignancies. Today, the number of EUS-BD needed for proficiency has not been established. Trainees must master conventional endoscopy, image interpretation in ultrasound, CT, and MRI, and possess competency in interventional endoscopy such as ERCP.

It is also clear that standardized curricula and courses are needed to teach these interventional endoscopic biliary procedures. Teoh et al. in a multicenter review study of EUS-GBD suggested that 25 procedures were necessary to improve efficiency with shorter procedure times with similar success rates. He also recommended that learners start with simple procedures, such as drainage of pancreatic fluid collections [7].

Most university programs have incorporated training in EUS into their fellowship programs, usually in the form of an advanced endoscopy fellowship. Of course, physicians already working in hospitals and clinics do not have access to this type of university training programs. In Strasbourg, at the Institute of Image guided Surgery (IHU) we have focused on training using didactics and a new live animal simulated model (HiFiSAM) that allows doctors to perform a significant number of procedures in a very short time, always mentored by an expert. However, for EUS-BD specific training one requires a good grounding in basic EUS in order to progress in a new and complex technology and procedure. EUS-BD should be performed by qualified endoscopists and

in a center with appropriate surgical and interventional radiology support to help manage failed interventions and/or adverse acute or late events [8–10].

Indications

You don't have to see the whole staircase, just take the FIRST STEP. (Anonymous).

In general, indications for EUS-BD techniques include specific symptomatic and clinical features including fever, jaundice, abdominal pain, suspicion of cholangitis, and/or cholecystitis. The intention is to reduce intra biliary pressure and to restart biliary flow into the digestive tract. Typically, an obstructed biliary system is drained through the ampulla of Vater using a duodenoscope or percutaneously or with surgery. This is almost always successful, but in some cases (3–12%) an obstructing tumor of the duodenum or the ducts themselves may make an ERCP impossible even using a precut technique. Also, patients who have undergone gastrectomy with roux-en-y reconstructions have difficult access to the papilla. Many prospective and retrospective trials have demonstrated results that show a trend towards better outcomes with EUS-guided internal drainage for obstructing biliopancreatic malignancies, in cases of altered surgical anatomy, difficult to access papillas, and in some benign distal biliary stenosis [11].

In patients with jaundice, fever, and abdominal pain originating from a biliary malignant obstruction, the treatment is generally ERCP and sphincterotomy with stent drainage. Sometimes this procedure fails due to different conditions: (1) Difficult cannulation of the papilla related to anatomic variants in the biliopancreatic junction, (2) tumor infiltration of the papilla resulting in a distorted ampulla, and (3) duodenal diverticula containing the papilla. Access can be also altered by (4) tumor infiltrating or obstructing the duodenum and/or (5) duodenal stent obstruction. Other procedures like surgical biliary bypass (open or laparoscopic) and image

guided drainage (PTBD) could be performed when ERCP is not successful. However, surgery carries a higher mortality and morbidity in these often very ill patients with multiple comorbidities, old age, malignancies, complicated overall physical status or limited life expectancy. On the other hand, PTBD has clinical success rates between 56% and 100% depending on the volume of the center but may be associated with several complications, including bleeding, bile leaks, biliary peritonitis, pneumothorax, patient discomfort/inconvenience related to the external drain, and frequent need for catheter changes due to accidental catheter dislodgement or plugging [12].

In patients treated with percutaneous cholecystostomy for acute cholecystitis, recurrent cholecystitis can occur after the removal of the percutaneous catheter and ongoing patient surveillance is mandatory. In non-complicated and operable patients with acute cholecystitis, surgery is the gold standard. For patients that are poor operative candidates due to high-risk comorbidities including cirrhosis, ascites, coagulopathy, cancers, and cardiopulmonary conditions, EUS-GBD is emerging as a promising alternative.

Definitions

It always seems impossible until it's done. (Nelson Mandela)

EUS-BD with Emphasis on EUS-GBD

Since the first EUS-BD, many techniques have been described, and in the last 20 years instrumentation has also changed substantially. Although current tools are much better now, there are still needs to be solved in therapeutic EUS which means that further device and technique innovation should be pursued.

One can drain the intra hepatic biliary tree, either right or left, directly into the stomach or the duodenum and similarly

one can drain the extra hepatic biliary tree to either organ, either using the gallbladder or the common bile duct (CDB). This results in a cholecystogastrostomy (Fig. 30.1) or a hepaticoduodenostomy for internal liver drainage and a colecistogastrostomy for the gallbladder and coledocoduodenostomy (Fig. 30.2) for the CBD. Sometimes drainage of the right hepatic lobe into the stomach can be achieved using a communicating stent from the left placed across the biliary bifurcation. Access to the biliary tree through the liver can also be used to perform anterograde transpapillary drainage similar to interventional radiologists.

Inflammation of the gallbladder or acute cholecystitis can be a dangerous condition, especially in elderly patients with comorbidities contributing to a high surgical risk and poor prognosis. EUS-GBD is an option in this difficult cohort of patients who fail to respond to conservative treatment and antibiotics. A cholecystostomy tube (PTBD), first described in the 70s, or surgical cholecystectomy are options but both

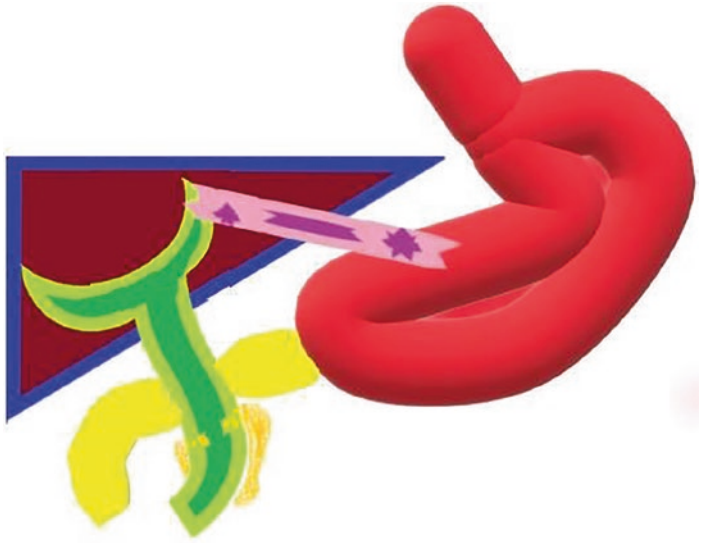

Figure 30.1 Hepaticogastrostomy

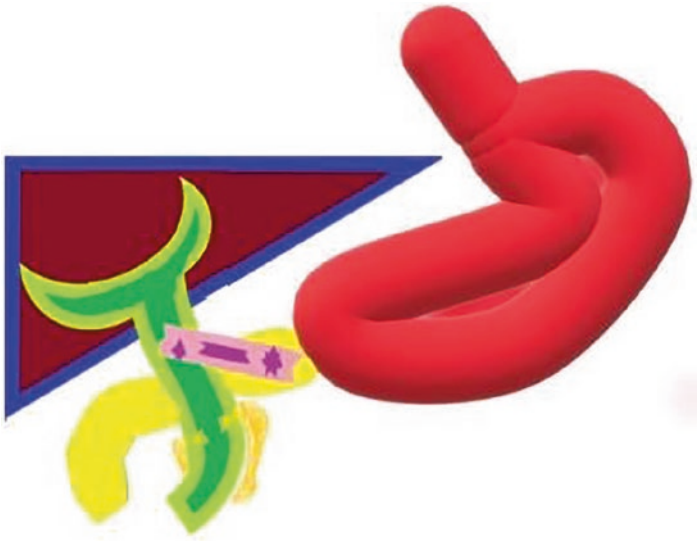

FIGURE 30.2 Choledocoduodenostomy

carry significant risk of complication. PTBD with risk of (1) hepatic or body wall tissue bleeding, (2) pneumothorax, (3) pneumoperitoneum, (4) bile leaks, (5) patient discomfort/inconvenience from the external drain, or (6) accidental catheter dislodgment due to patient movement after recovery. In addition, PTBD is an operator dependent technique as is EUS-BD. Percutaneous access has been used to place an endoscopic transpapillary drain through the cystic duct but may be technically challenging due to inflammatory strictures, tumor involvement, stones, or tortuosity of the cystic duct (cystic valves) and is therefore less commonly used as a technique for the acute inflammatory gallbladder.

The benefits of EUS-GBD in comparison to PTBD, is that the later requires multiple steps and is affected by the patient's weight—with higher BMI causing greater challenges and less effectiveness. The need for multiple device exchanges even over a wire can result in adverse events such

as gallbladder perforation, bleeding, and peritonitis. Today's EUS drainage systems are mostly one step devices which are quick and have better outcomes [13].

Procedure Outcomes

Education is not learning of facts, but the training of the mind to think. (Albert Einstein)

In 2012 a randomized trial in Gastroenterology compared EUS-GBD and PTBD in 59 consecutive patients. All patients had acute cholecystitis and contraindications for surgery and were randomly assigned. Technical feasibility, efficacy, and safety were similar after data analysis. However, post-procedural pain scores were lower in the EUS group. In this early experience no stents were used [14].

In 2012 Itoi and Binmoeller described their first five patients (median age 69.5 years) with acute cholecystitis that underwent four EUS cholecystoduodenostomies and one EUS cholecystogastostomy successfully using lumen-apposing metal stents (LAMS). Resolution of acute cholecystitis was observed immediately after stent implantation. No recurrence of symptoms was observed during a median follow-up of 9 months [15].

In 2014 a systematic review of EUS-guided treatments was published. EUS-BD was performed in 85 studies (91% level of evidence 3–4 systematic review of case-control studies, individual case-control study, case series and poor-quality cohort and case-control studies) with one (Ib) individual randomized controlled trial (with narrow confidence interval) and 7 (level IIb) individual cohort studies or low quality randomized controlled trials (e.g. <80% follow-up). A total of 1127 cases were evaluated with a mean technical success rate of 91% and a mean clinical success rate of 88%. However, overall complication rate was 26% with mortality of 0.4% (4/1127 patients). EUS-GBD in seven studies with more consistent data, one with level Ib, three with IIb and three with

III and IV evidence, showed in 97 cases a mean technical success of 98% and a clinical success of 98% with an overall mean complication rate of 16% [16].

In these case series, plastic stents were used for biliary and gallbladder drainage and therefore migration and leaks were seen during follow-up and reported as complications. After the arrival of LAMS and LEMS new data is available.

In 2020 a review analyzed 350 patients from 20 series and 13 case reports, specifically regarding the use of LAMS [17], all with non-operable acute cholecystitis and showing a mean technical success rate of 98.4% (100–84%) and a mean clinical success rates of 99% (100–92%) with a complications rate of 13% ($n = 45$), half of the rate seen with plastic stents. Half of the complications were considered minor, and only 22 complications were considered major adverse events. The most common complication was pneumoperitoneum ($n = 6$). Other complications included biliary peritonitis ($n = 6$), recurrent cholecystitis ($n = 6$), post-procedural fever ($n = 5$), sepsis ($n = 4$), stent migration ($n = 4$), late bleeding ($n = 3$), early bleeding ($n = 2$), bile leakage ($n = 2$), hematochezia or melena ($n = 2$), jaundice ($n = 1$), pneumonia ($n = 1$), pancreatic infection ($n = 1$), pain ($n = 1$), and Bouveret syndrome ($n = 1$). In these 33 reports only two reports accounted for 11 of the mayor adverse events: two early bleeding, one delayed bleeding, three sepsis, two stent migration, and three recurrent cholecystitis. In 4 of the reports, using the latest generation of LAMS, there were no adverse events reported at all. Teoh et al. published an International Registry of 409 patients with EUS-GBD with 62 adverse events (15.5%) and only 9% of reinterventions [7].

Since the original introduction of LAMS, many refinements of the technique have contributed to lower complication rates. These include: (1) identifying important vessels at the puncture site with Doppler capabilities, (2) avoiding gastric or duodenal sites too far from the gallbladder which can result in stent misplacement and dislodgment, (3) visualizing and avoiding vessels in the gallbladder wall that could cause bleeding, (4) overly small size of the LAMS (6 or 8 mm)

which could contribute to recurrent cholecystitis due to early obstruction, and finally (5) careful avoidance of spilling gallbladder contents into the peritoneal cavity which can cause sepsis. To further limit complication risks, newer LAMS have been developed, which aim to improve apposition of the gallbladder wall to the wall of the stomach or duodenum. EUS-GBD has been successfully described in cases where definitive therapy or a bridge to cholecystectomy is needed. These new systems all include the one step procedure with a hot tip, allowing access, guidewire placement, and LAMS deployment in an all-in-one procedure, shortening the procedure time, the X-ray exposure and multiple steps which might explain many of the complications.

Cholecystectomy remains the treatment of choice for acute cholecystitis according to most guidelines. When cholecystectomy is not possible, PTGBD and ERCP remain options, but EUS-GBD is becoming a new form of treatment for these patients due to its minimally invasive nature and low rate of adverse events, particularly as technology evolution has made it quicker and easier [10, 18].

Another advantage of the newer large caliber LAMS is that they allow not only gallbladder drainage, but also endoscopic evaluation and interventions in the gallbladder itself, using the durable fistula between the gallbladder lumen and the stomach or the duodenum. In fact, the term "bilio digestive anastomosis" has been coined when discussing LAMS procedures. These LAMS allow cholecystoscopy with clearance of the gallstones using Dormia baskets of different sizes and laser lithotripsy if needed and moreover permits endoscopic polypectomy opening a new era for gallbladder diagnostic and treatment including developments like confocal endomicroscopy, optical biopsies, and magnifying endoscopy. In one report an adenocarcinoma was diagnosed with a direct biopsy [19]. Gallbladder mucosa ablation and collapse has been described in animal models may be a future alternative to surgical gallbladder excision [20].

Long-term follow-up of EUS biliodigestive anastomosis have shown 1-year patency rates of more than 95% in patients

from two series [21, 22]. There is, however, a concern regarding the long-term consequence of permanent fistulization of the GB to the GI tract. The possible physiologic or oncologic consequences of digestive content going into the biliary system is incompletely understood. Despite the difference in pressure between the system and the fact that cholangitis after EUS-GBD is almost never reported, this undoubtedly calls for long-term evaluation. After a gallbladder drainage with LAMS, a second look is performed 2 or 3 weeks later to clear the gallbladder if cholelithiasis persists. At that time, most patients will have a double pigtail plastic stent exchange, particularly if: (1) they have cancer, (2) they are frail with multiple comorbidities, (3) they will have a LAMS for a prolonged period of time (including permanently). If at any point the bilio digestive anastomosis closes, biliary symptoms may recur.

Perez Miranda studied 22 patients with long-term EUS-GBD. The median follow-up was 24.4 months and no LAMS related adverse events were identified beyond the first year of the follow-up. During follow-up, 36 hospital admissions were required, but only one was related to gallstones related diseases. Therefore they suggested that EUS-GBD maybe a definitive treatment for acute cholecystitis in patient ineligible for cholecystectomy [23].

There is clearly a need for a multidisciplinary approach to biliary drainage with so many alternative approaches and intertwined algorithms. Miranda et al. recently published his retrospective experience with 2205 consecutive ERCP's over a 2-year period (2015–2017) with 7.7% (n = 170) of the ERCP's failing and going on to EUS assisted drainage. Only 0.1% were referred for PTHBD when both ERCP and EUS failed. EUS drainage alone was done in 116 patients and a combined ERCP/EUS approach was used in 54 patients [24].

Description of Techniques

Design is the silent ambassador of your brand. (Paul Rand).

All interventional procedures are performed with a therapeutic linear echoendoscope with a single operator channel 3.2 mm or greater. Several endoscopic accessories are needed: Partially covered metal stents (PCMS), 6 Fr cystotome, guide wires of 0.035," 0.025," 0.018," catheters, 19 Ga and 22 Ga EUS needles, balloon dilators, and plastic stents. A high-resolution fluoroscope with C-arm (2D) or a C-robot (3D) are recommended, although some experts do not use them. Lumen-apposing metal stents (LAMS) are a relatively new development, they are available in different sizes and "hot" (with cautery) and cold versions. LAMS are delivered using endosonographic, endoscopic, and fluoroscopic view (guidance) during the procedures. Several brands are available with minor differences in their size, shape and delivery mechanism. Hot LAMS of course require an electrosurgical generator, ideally one specifically designed for endoscopic use.

Common Bile Duct (CBD) Drainage

Common duct drainage by EUS is indicated if the duct is greater than 10 mm and after failed attempts at transpapillary drainage by ERCP. One should position the echoendoscope in the duodenal bulb as close as possible to the CBD. Care must be taken to avoid the gastroduodenal artery which is always adjacent to this site. Early techniques used a needle puncture of the CBD with a guide wire introduction sometimes using contrast media. The stent has a taper tip to dilate the tract as the stent is advanced. This technique has been replaced today by a direct access technique using a hot delivery system and smaller (6 or 8 mm) LAMS. A pure cut current is suggested (100 W) to avoid false routes. Once the tip of the system is within the CBD a pre-loaded guide wire (0.025″) is passed, at least during the learning curve of the endoscopist and in small CBD diameters (less than 12 mm) to avoid complications. The first part is performed under echographic guidance only, and radiological guidance if one

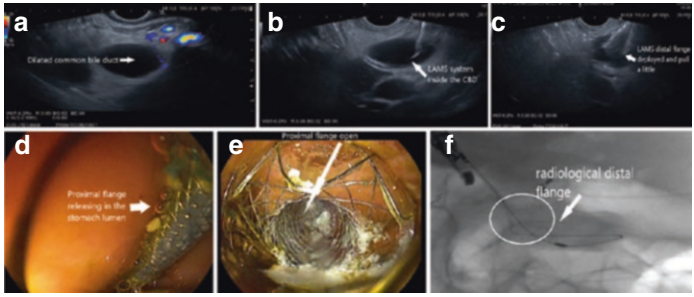

FIGURE 30.3 All the successive steps to place a hot system LAMS in the CBD (very similar for GBD). (**a**) Touching the anterior wall of the CBD with the system tip (no current yet). (**b**) Introduction within the CBD of the system with pure cut high current. (**c**) Passing a guide wide (optional). (**d**) Distal flange release. (**e**) Smooth system traction to release proximal flange within the scope. (**f**) Radiological 2D view of small LAMS in the CBD

needs to see the guide wire placement within the CBD (Fig. 30.3). It is important to start the current once the system tip touches the wall of the duodenum and then to push it toward the visualized CBD without allowing it to slide across the mucosal surface. Before starting, check the scope position with c-arm, as it is best to have the scope in a straight position. A curved position is possible but releasing the stent will be more challenging. Sometimes the distal flange takes a little time (a few seconds) to open and you will need to maintain pressure towards the CBD. If one releases pressure or withdraws the system or scope too early, the flange may come out of the CBD and unfold in the peritoneal cavity. If a guidewire was placed you will be able to salvage the situation by removing the first stent and placing a new one over the guidewire. Once the distal flange is completely opened, the endoscope is withdrawn and the proximal flange is released. Some endoscopists recommend releasing it within the operator channel and then pushing gently to endoscopically visualize the proximal flange open, while others prefer to open the proximal flange under endoscopic guidance. One should always see a black mark on the delivery catheter before releasing the

proximal flange. At the end one should see bile to know that a chodecoduodenostomy is achieved. If a cold delivery system is used, meaning that the tip of the delivery system does not have current for cutting, a needle, a guide wire, and a cystotome-dilator will be needed and it will demand more expertise, time and materials. Still, the LAMS will be preferred over a self-expanding covered metal stent [25].

In a study published in 2020, 70 consecutive patients from several centers who had EUS-CBD after ERCP failed were studied. Failure of ERCP was due to duodenal stenosis (44%) and to tumor infiltration of the papilla (22%). Time for each procedure was very short (5 ± 3 min). The technique described above was used in 98.5% of cases. The technical and clinical success rates were both 97.1% (69/70). Short-term adverse events (periprocedural and intrahospital) occurred in 1.6%. This experience Indicates the advantages of these drainage techniques [26].

EUS Gallbladder Drainage (EUS-GBD)

First described in 2007 in nine patients as rescue management for elderly and high-risk patients with acute cholecystitis who were determined to be unable to have surgery. In this report, all patients had successful drainage and there was only one report of pneumoperitoneum [27].

EUS-GBD is performed by transmural puncture of the gallbladder via the transgastric or transduodenal route. Endoscopists choose the site based on the best scope orientation, proximity to the target (gallbladder), and absence of vessels in the path as determined by doppler. The stomach is easier for targeting the gallbladder but food can on occasion occlude the stent and gastric peristalsis can result in early dislodgement. On the other hand, the duodenum is fixed and food is already processed but targeting can be harder. After selecting the best entry point and during deployment, it is crucial to keep the scope as stable as possible to avoid displacement of the guide wire or the system itself. This tech-

nique has changed over time and two approaches are currently described: the first one with a direct access with a hot LAMS system to join the gallbladder and the intestinal tract using the same described technique above for CBD access, or a second one which accesses the gallbladder with a direct puncture using a 19 g needle from the middle or lower part of the stomach, or sometimes from the duodenal bulb (less preferred). Contrast opacification is then performed under fluoroscopy following which, the needle is flushed with a little saline and a long guide wire is placed into the gallbladder lumen, again under radiological control (Fig. 30.4). Next a sufficiently sized tract should be made using a cystotome which will allow the LAMS to be placed over the wire and deployed as previously described. This lat-

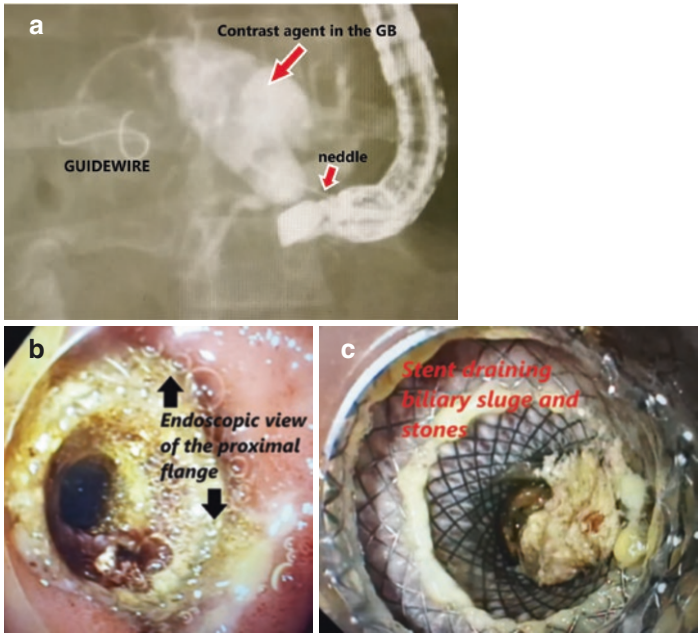

Figure 30.4 (**a**) Opacification of the gallbladder from the stomach puncture (optional). (**b** and **c**) Endoscopic view of the proximal flange of the LAMS with bile and biliary sludge

ter technique has been associated with more adverse events and has mostly been replaced with the single step "hot" system technique, especially in very inflamed and infected gallbladders where added manipulation is risky and difficult. The positioning of the stent can be confirmed endoscopically or fluoroscopically and by visualizing bile through the stent (Fig. 30.4a, b). It is, however, difficult to access leakage at this stage of the procedure.

Hepaticogastrostomy

EUS visualization of the left hepatic lobe is a prerequisite and is preferably done with doppler to look for interposed blood vessels. Measurement of the intrahepatic biliary duct in segments 2 or 3, should be made. If they are greater than 5 mm a transgastric puncture is possible. The procedure is even more feasible once the biliary system reaches 10 mm in diameter or more. The scope is positioned in the lesser curvature of the gastric body. Needle puncture of the biliary duct is achieved while avoiding interposing vessels is necessary to minimize chances of bleeding. Injection of contrast agent with a 1 to 1 dilution is done to radiologically confirm at a minimum, left biliary tree visualization. Two types of needles are possible: a 19 gauge "Menghini" tip or a 19-gauge access type. In the second needle type, the stylet is the cutting part. Some experts recommend withdrawal of the stylet before contrast injection to avoid air artifact in the biliary tract before the guide wire introduction. After puncture and contrast visualization (Fig. 30.5), the needle is flushed with 2–3 cm^3 of saline solution to minimize friction during introduction of a 0.035 rigid long guide wire placed deep in the right lobe or even antegrade into the duodenum if possible. The needle is then exchanged with a 6 French cystotome which is advanced through the gastric wall, the hepatic parenchyma and the biliary wall using a pure cutting current (electrosurgical setting varies among experts). Once the cystotome is advanced into the biliary tree cautery should no longer be

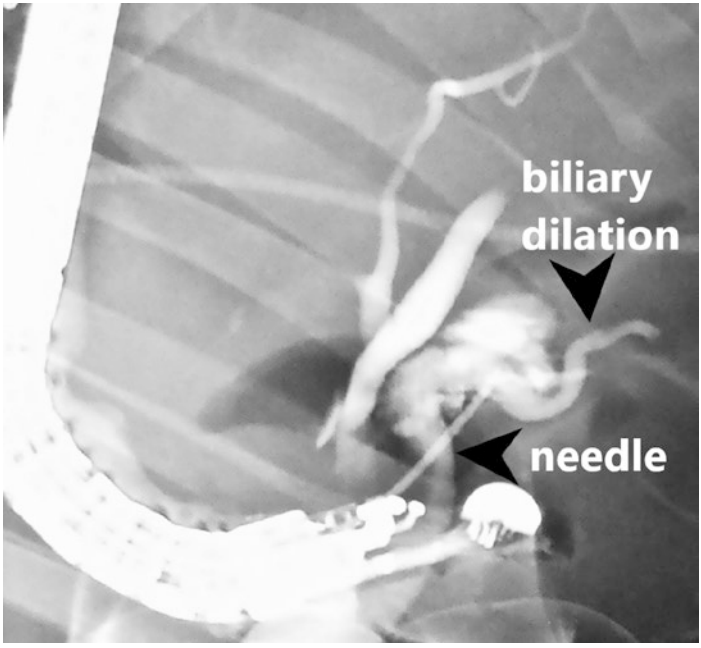

FIGURE 30.5 Intrahepatic biliary dilation visualization with opacification using contrast media

used and contrast agent is reinjected to verify correct position. After this, a new exchange is performed with the stent system. The position of the guide wire should always be confirmed with radiology using real time 2D video of high quality and moderate X-ray penetration (avoiding blocking by the inserted scope and instruments). The first part of deployment is radiological and echo graphic, and the second part is radiological with an endoscopic view. At the end, contrast agent can be gently injected through the stent to confirm its patency and detect early leaks. It is important to remember that the stent is not well attached yet, therefore it is very easy to dislodge it with aggressive scope movements. Direct con-

tact should be therefore avoided [9, 10]. Recently this procedure has been describing with a small modification. In this version, the scope is placed in the duodenum and the drainage is performed directly to the right hepatic lobe—either to segments 4, 5, or 6 [11]. During this procedure, stabilization of the scope is difficult and its position should be checked with fluoroscopy frequently during the procedure and extreme movements of the scope avoided. In general, a short scope position is better than a far one.

Rendez-vous Technique

This technique involves passing a wire into the intra- or extrahepatic bile duct, passing first through the papilla, and then being retrieved by duodenoscopy in order to allow controlled biliary interventions, as with an antegrade transpapillary stent placement. This procedure is rather challenging and therefore rarely used in the past. The availability of LAMS has changed rendezvous procedures to be increasingly used as a salvage procedure if other methods of draining the biliary tree fail during therapeutic EUS. An anterograde stenting of the CBD directly from the duodenal bulb has also been described but is also technically challenging.

Other techniques have been proposed such as advancing a stent through the papilla in an anterograde fashion using two methods: (1) the transduodenal approach to access the CBD and then the papilla duodenum space putting a stent in the same position as in ERCP or (2) using the transgastric approach through the intrahepatic biliary tree to access the papillary region and then placing a stent in the same ERCP fashion always (Figs. 30.6 and 30.7).

These two techniques have been proposed in situations where LAMS systems are not available, and instead self-expanding metal stents (SEMS) have been used. These can be less expensive but technically challenging to place.

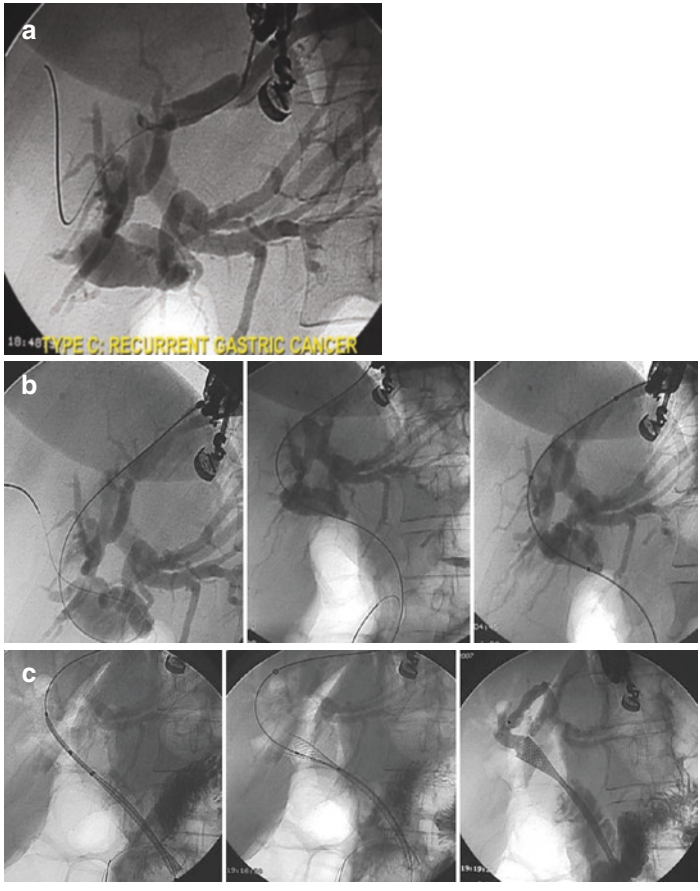

FIGURE 30.6 (**a** and **b**) Roux-en-Y gastrectomy patient with lymph node tumor recurrence causing a distal CBD stricture. (Courtesy of Professor Manuel Perez-Miranda MD, PhD, Associate Professor of Medicine, Valladolid University, Head of Gastroenterology, Hospital Universitario Rio Hortega, Valladolid, Spain)

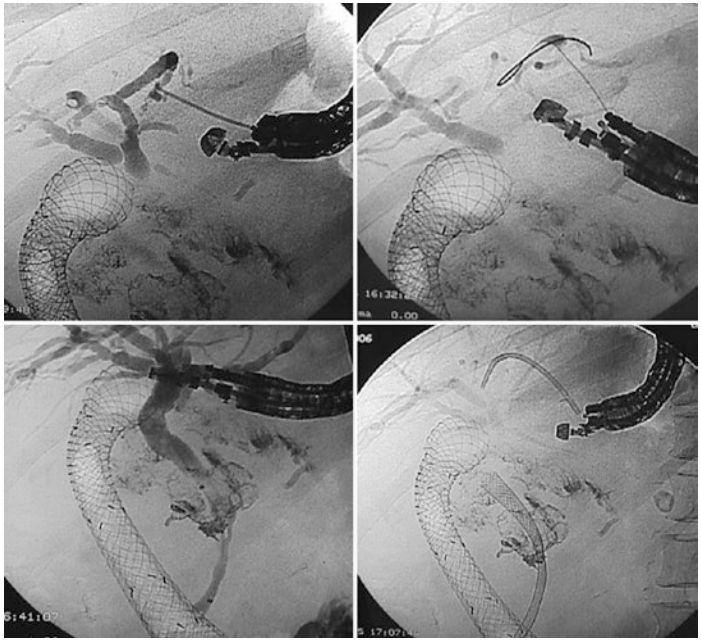

FIGURE 30.7 Needle puncture of left IHD for cholangiography and guidewire placement. Over the wire catheter insertion for puncture tract dilation and guidewire repositioning across the distal CBD stricture. Over the wire antegrade biliary SEMS insertion and deployment. Longstanding periampullary tumor with duodenal stricture treated with a duodenal SEMS developing biliary obstruction de novo. EUS-guided cholangiography following segment II puncture reveals a mildly dilated biliary tract above a distal CBD stricture. Two stents are sequentially placed, first a metal stent antegrade across the stricture and then a plastic hepatogastric stent for additional decompression and to facilitate future access. (Courtesy of Professor Manuel Perez-Miranda MD, PhD, Associate Professor of Medicine, Valladolid University, Head of Gastroenterology, Hospital Universitario Rio Hortega, Valladolid, Spain)

Conclusions

EUS-BD is a proven technique for decompression of the biliary tree. It is a viable alternative to surgery, PTHBD and perhaps even ERCP for some specific indications. Further advancements in instrumentation and techniques may make this minimally invasive endoscopic procedure the first option for therapeutic treatment for biliary obstruction. This represents a new era of biliary diagnostics and therapeutics.

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Chapter 31
EUS-Directed Transgastric ERCP (EDGE Procedure) for Management of Choledocholithiasis in Post-Gastric Bypass Anatomy

Yen-Yi Juo, Rebecca A. Burbridge, Jorge V. Obando, and Alfredo D. Guerron

Introduction

Obesity and rapid weight loss are risk factors for cholelithiasis development, likely due to mobilization of endogenous cholesterol during weight loss, decreased biliary motility secondary to reduced caloric intake and decreased cholecys-

Y.-Y. Juo · A. D. Guerron (✉)
Department of General Surgery, Duke University Health System, Durham, NC, USA
e-mail: yenyi.juo@duke.edu; alfredo.guerron-cruz@duke.edu

R. A. Burbridge · J. V. Obando
Division of Gastroenterology, Department of Medicine, Duke University Medical Center, Durham, NC, USA
e-mail: rebecca.burbridge@duke.edu; Jorge.obando@duke.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_31

tokinin secretion. Incidences of cholelithiasis development following bariatric surgery have been quoted to be between 32% and 42% [1]. While the majority of biliary complications after bariatric surgery consist of chronic or acute cholecystitis, approximately 12.2% develop biliary pancreatitis and 5.7% had choledocholithiasis [2].

The current management of biliary pancreatitis or choledocholithiasis consists of prompt decompression of the common bile duct either before, following, or concomitant with cholecystectomy. Due to its less invasive nature, the most commonly taken approach is endoscopic retrograde cholangiopancreatography (ERCP) rather than surgical common bile duct exploration. However, the Roux-en-Y gastric bypass anatomy, where the proximal stomach was transected and no longer in continuity with the duodenum, poses a specific challenge for endoscopists to reach the ampulla of Vater for biliary access.

Prior solutions to this particular problem involved the use of either laparoscopy-assisted ERCP, where the gastric remnant is accessed laparoscopically and the scope introduced through a surgical gastrostomy [3], or deep-enteroscopy-assisted ERCP, either with single-balloon-, double-balloon-, or spiral-assisted endoscopies [4]. The laparoscopy-assisted approach, while faster, may be associated with higher invasiveness and morbidity. A multi-center retrospective study has shown that laparoscopy-assisted ERCP in post-bypass patients has comparable success rates to that of ERCP in patients with normal anatomy [5]. The deep-enteroscopy-assisted approach is limited by forward-viewing optics and imperfect accessories, and therefore frequently associated with high technical failure rates.

In this chapter, we would like to describe a third approach where the gastric remnant is accessed under endoscopic ultrasound (EUS) guidance, directly from the gastric pouch, and review relevant literature regarding its technique and outcomes.

Technical Innovation

EUS-directed transgastric ERCP (EDGE) procedure describes the use of EUS guidance as a means of accessing the gastric remnant from either the gastric pouch or the Roux limb. The idea of accessing the gastric remnant with endoscopic ultrasound was first described in publication as early as in 2014, using a percutaneous access technique that is very different from the currently known EDGE procedure [6, 7].

Recently, a more prevalent form of EDGE procedure was described with the incorporation of a lumen-apposing metal stent (LAMS). LAMS, especially the AXIOS system (Boston Scientific, Marlborough, MA), has been increasingly used to create endoscopic anastomoses. The flanged ends allowed the creation of tissue apposition in the saddle of the stent. Besides draining fluid collections during transgastric cystogastrostomy or transduodenal choledochoduodenostomy, they are also used to traverse stenotic intestinal segments, such as gastro-gastrostomy in sleeve gastrectomies that have developed strictures at the incisura angularis. The covered stent provides tamponade after dilation of the anastomosis, reducing risks for bleeding and leakage. More importantly for the EDGE procedure, the relatively large diameter of the stent (20 mm) allows subsequent passage of a therapeutic endoscope (11.3–11.6 mm). Instead of inflating the gastric remnant and accessing it percutaneously, currently described EDGE procedures involves accessing the gastric remnant endoscopically with the creation of a gastrogastric or enterogastric (GG/EG) fistula with a LAMS, creating a pathway for the passage of a therapeutic duodenoscope for the ERCP.

Both iterations of the EDGE procedure could be described as a two-stage process: the first stage involved the creation of the GG/EG fistula under EUS guidance, and the second stage is the ERCP. Some institutions performed both stages under the same session, which is immediately therapeutic but risks perforation via LAMS dislodgement. Performing the two stages 10–14 days apart substantially

reduces the risk of perforation but allows the biliary disease process to fester during the interval as the GG/EG fistula matures. Some authors advocate for a shortened interval of 2–4 days between the two stages to get the most benefit out of both approaches [8].

Techniques and Pitfalls

The patient is placed supine in the endoscopy suite with fluoroscopy equipment available. The gastric pouch is reached with upper endoscopy. The gastric remnant or jejunum is located with a linear echoendoscope and accessed with a 19-gauge EUS needle (Fig. 31.1a). It is important to verify the needle position by injection of water-soluble contrast under real-time viewing with fluoroscopy, as sometimes the colon or adjacent jejunum blind-end can be mistaken for the gastric remnant [9]. Subsequently, the gastric remnant is distended with sterile fluid to allow visualization for EUS-guided needle access (Fig. 31.1b). A 0.035″ wire is then passed through the needle to maintain the GG/EG fistulous tract. Using a Seldinger technique, the needle was withdrawn and a 20-mm × 10-mm cautery-enhanced LAMS (AXIOS; Boston Scientific, Marlborough, MA) is advanced into the fistula over the guidewire. Under fluoroscopy and EUS guidance, the distal flange is deployed, followed by the proximal flange under both endoscopic and direct visualization (Fig. 31.2). Of note, there are reports of deploying LAMS both from the gastric pouch and from the proximal Roux limb. The lumen of the LAMS is then dilated with a balloon (CRE; Boston Scientific, Marlborough MA) to promote stent expansion. Case reports of bleeding at the gastrogastric fistula has been reported but usually subsides with balloon tamponade [10].

For fear of LAMS dislodgement, the ERCP is typically not performed for at least 3–4 days after creation of the GG/EG fistula. During ERCP, a duodenoscope (TGF-Q180V, Olympus, Central Valley, PA) is guided under direct visualiza-

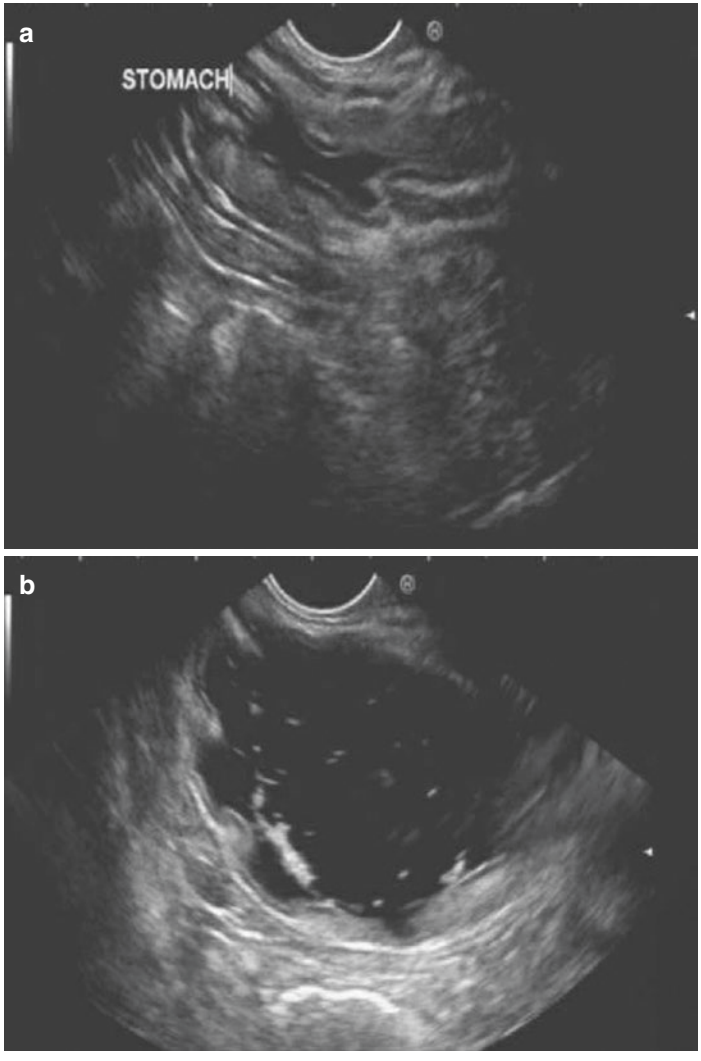

FIGURE 31.1 (**a**) Accessing the gastric remnant with a needle under endoscopic ultrasound guidance. (**b**) Distending the gastric remnant with sterile fluid

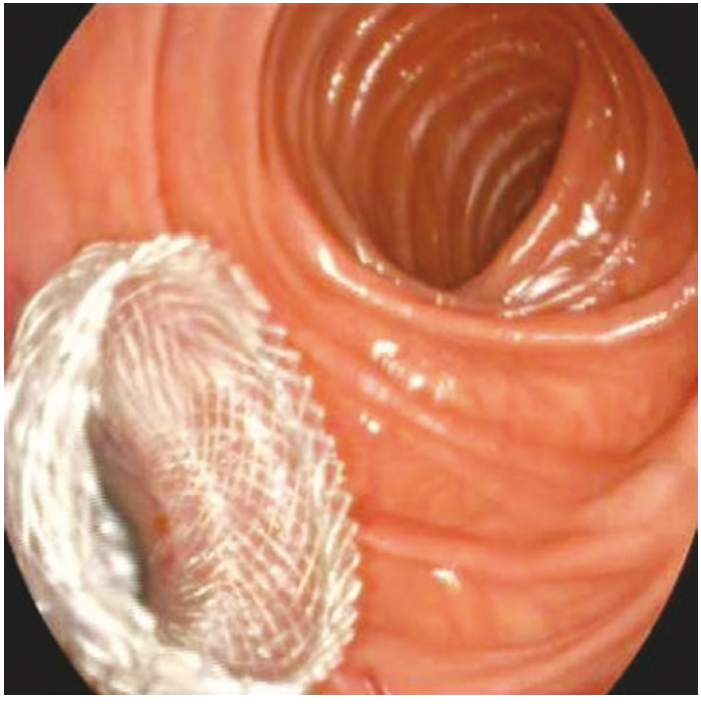

Figure 31.2 Deployment of the lumen-apposing metal stent (LAMS) across the artificially-created fistula between the Roux limb and the gastric remnant

tion and fluoroscopy through the LAMS into the second portion of the duodenum where the ampulla is visualized. The ERCP is then performed in the conventional antegrade fashion.

One of the major adverse events that could occur during the procedure is the dislodgement of the LAMS from within the gastric pouch, leading to large separations between the gastric pouch and the gastric remnant. This complication, when not addressed promptly, can be devastating due to the fresh iatrogenic gastric perforations. Several measures have been described to prevent or manage intraprocedural dis-

lodgement of LAMS, such as the use of an endoscopically placed suture [11] (Apollo OverStitch; Apollo Endosurgery, Austin, TX, USA) or over-the-scope clip (Stentfix OTSC System; Ovesco, Cary, NC, USA) to hold the proximal flange in place or introduction of a second LAMS [12] with a stent-in-stent technique to reappose the gastric remnant and gastric pouch.

Following completion of ERCP, the scope is withdrawn, taking care not to displace the LAMS. The time interval between ERCP and retrieval of the LAMS is typically 4–5 weeks, at the stent is removed. One of the major reasons for the relative reluctant adoption of the EDGE procedure among surgeons is the concern for the remaining GG/EG fistula and the potential for weight recidivism [13]. When the LAMS left in place for too long, there is the risk of tissue ingrowth into the stent and technical difficulty with removal and inadequate spontaneous closure of the fistulous tract, on the other hand, removing the LAMS too early may lead to free gastric perforation into the peritoneal cavity. Following removal of the LAMS, spontaneous tissue closure over the GG/EG fistula is expected, although some reports have described routine placement of over-the-scope clips or endoscopic sutures to close the fistula [14]. There is at least one report of persistent fistula to the excluded stomach after EDGE. The patient was a 72-year-old woman with a history of gastric bypass who presented with painless obstructive jaundice from pancreatic cancer. She received EDGE before Whipple procedure. However, the patient had persistent reflux and nausea/vomit after surgery. Cross-sectional imaging demonstrated preferential passage of food into a progressively dilated gastric remnant. This was managed with another gastrojejunostomy using LAMS under EUS guidance, resulting in rapid symptom resolution [10]. Other complications that have been described during the LAMS removal process included marginal ulcers at the gastric remnant and tissue embedment of the LAMS.

The major step summary of the procedure is illustrated in Fig. 31.3.

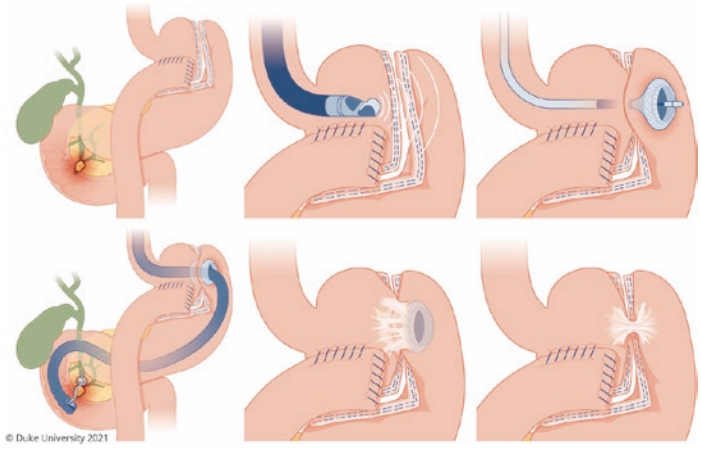

Figure 31.3 Procedure steps: (1) Schematic representation of post-gastric bypass anatomy (top left). (2) Localizing the gastric remnant with endoscopic ultrasound from the gastric pouch (top middle). (3) Accessing the gastric remnant and deployment of LAMS (top right). (4) Passage of endoscope into duodenum for ERCP (bottom left). (4) Completion of ERCP and withdrawal of endoscope (bottom middle). (6) Spontaneous closure of gastrogastrostomy following retrieval of LAMS (bottom right). (Illustrated by Megan Llewellyn, MSMI, CMI; copyright Duke University; with permission under a CC BY-ND 4.0 license)

Outcomes

Several single- and multi-institutional case series have been published with regard to short- and mid-term outcomes following the EDGE procedure (summarized in Table 31.1). In a recent single-center case series from University of North Carolina comprising 19 patients, clinical success rate was 100%. There were no adverse events although stent malposition occurred in 6 patients requiring rescue maneuvers. Stents were removed after an average of 182 days. Argon plasma coagulation was used for fistula closure in 12 patients and 1 patient developed a persistent fistula that required endoscopic closure [15]. Another single-center case series of

Table 31.1 Major case series in the literature and associated outcomes

Publications	Patient number	Technical success	Clinical success	Adverse events
James et al. 2019 [15]	19	100%	100%	Stent malposition ($n = 6$) requiring rescue maneuvers, persistent fistula requiring endoscopic closure ($n = 1$)
Wang et al. 2019 [18]	10	100%	100%	Stent malposition ($n = 2$) requiring rescue maneuvers
Kedia et al. 2019 [6]	43	96.5%	100%	Perforation ($n = 1$), pancreatitis ($n = 2$), stent dislodgement ($n = 3$), bleeding ($n = 1$)
Ngamruengphong et al. 2017 [22]	13	100%	100%	Stent malposition ($n = 2$), persistent fistula ($n = 1$)
Tyberg et al. 2017 [14]	16	100%	90%	Perforation ($n = 1$), stent dislodgement ($n = 3$)
Attam et al. 2015 [17]	10	90%	90%	No adverse events
De Benito Sanz et al. 2020 [23]	14	100%	100%	Stent dislodgement ($n = 4$)
Kochhar et al. 2020 [24]	26	100%	100%	Bleeding ($n = 2$), stent migration ($n = 1$)

19 patients reported 2 cases of bleeding and one jejunal perforation during duodenoscope insertion [16]. A separate multi-center case series with 14 patients also showed a 100% technical and clinical success rate with EDGE. Two incidents of LAMS maldeployment occurred that required rescue with a bridging stent. Similar conclusions were drawn by multiple independent case series with similar sample sizes [14, 17, 18], whereby high technical and clinical success rates were reported and the most common adverse event involved stent dislodgement. Some authors concluded that a total of 25 to 35 procedures may be required to reach learning a curve plateau [16].

In comparison with laparoscopy-assisted ERCP, the EDGE procedure was found to have similar technical success rate of gastrostomy creation (96.5 vs. 100%), ERCP completion (96.5 vs. 97.7%), ERCP needed to achieve clinical resolution (1.2 vs. 1.02), adverse event rate (24% vs. 19%) in a multi-center comparative study. In addition, EDGE was associated with shorter total procedure time (73 vs. 184 min) and length of hospital stay (0.8 vs. 2.65 days) [19]. A Monte Carlo simulation study assessing incremental cost-effectiveness ratios and net monetary benefit calculations showed that EDGE was the most cost-effective modality in post-RYGB patients for treatment of pancreaticobiliary diseases in comparison with deep endoscopy- or laparoscopy-assisted ERCP [20].

A systematic review and meta-analysis published in 2020 compiling twenty-four studies on 1268 patients concluded that the pooled rates of technical and clinical success with EDGE were 95.5% and 95.9%, respectively [21]. In contrast, pooled rates of technical and clinical success rate for laparoscopic-assisted ERCP were 95.3 and 92.9%, while those for deep enteroscopic ERCP were 71.4 and 58.7%. Pooled rates of all adverse events with EDGE were 21.9% for EDGE, 17.4% for laparoscopy-assisted, and 8.4% for deep enteroscopic ERCP, respectively. The most common adverse event associated with the EDGE procedure was stent migration (13.3%), followed by bleeding (6.6%).

Conclusions

The EDGE procedure represents a minimally invasive, effective, and feasible method to access the biliary tree in post-gastric bypass anatomy. The technique offers an appealing alternative treatment option besides laparoscopy- or deep-enteroscopy-assisted ERCP. While preliminary data has demonstrated excellent technical and clinical success rates, the concern for persistent GG/EG fistula remains. In addition, high operator endoscopy expertise and rescue options for the small chance of stent dislodgement during or after procedure must be readily available before embarking on the learning curve. It is paramount that a multidisciplinary approach involving both bariatric surgery and gastroenterology expertise be taken when making decisions to pursue an EDGE procedure.

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Chapter 32
Advanced EUS: Future Applications

Robert D. Fanelli and Luke K. Dombert

Introduction

Endoscopic ultrasound (EUS) was first pioneered by the Olympus Corporation in the 1970s. The initial focus for the development of EUS was to provide improved ultrasound imaging of the pancreaticobiliary system, which is commonly obscured by overlying bowel gas during transabdominal ultrasound approaches. Throughout the early 1980s, only a small number of institutions were outfitted to perform EUS, and the examination was limited to the use of radial-array instruments. By the end of the decade, the role of EUS was expanded to include the characterization and evaluation of many different lesions of the gastrointestinal tract beyond

R.D. Fanelli (✉)
Department of Surgery, The Guthrie Clinic, Sayre, PA, USA

Minimally Invasive Surgery, Surgical Endoscopy, Geisinger Commonwealth School of Medicine, Scranton, PA, USA

L. K. Dombert
Robert Packer Hospital Guthrie Clinic Residency Program in General Surgery, Sayre, PA, USA

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_32

pancreaticobiliary disorders [1]. Nonsurgical evaluation of subepithelial lesions of the approachable portions of the gastrointestinal (GI) tract became possible, expanding the indications and utility of EUS further. By the late 1980s, the use of EUS for staging foregut malignancies had become well established, and the quest for expanding its indications and offerings was launched.

The early 1990s brought massive transformation to the utility of Endoscopic ultrasound (EUS). Pentax Corporation and the Hitachi Corporation collaborated, and together, developed the first linear array EUS system. While commonly used today, linear array echoendoscopes allow for real-time tracking of a needle across the field of view. The value of EUS increased when therapeutic capability was established, beginning with fine needle aspiration (FNA) for tissue diagnosis of GI neoplasia. This created an expanding need for EUS [1].

Wilson-Cook Endoscopy, now Cook Incorporated, refined FNA needles during this period, enabling accurate sampling of GI tract lesions and the tissues of adjacent organs. Although FNA needles for EUS use are commonplace items produced by many equipment manufacturers, continued advancements in needle configuration have allowed for enhanced utility and the expansion of procedures offered. These changes in the bevel design of the needle affect the quantity and quality of the sample per pass.

Reverse core needles designed for liver biopsy have allowed EUS-guided hepatic sampling to become more mainstream. Development of forked-tip needles, including the Franseen needle tip, have been associated with improved diagnostic yields that bridge the gap between FNA and what is now referred to commonly as fine needle biopsy [2, 3].

Just as the miniaturization of all endoscopes has benefitted advancements in the field of GI endoscopy, miniaturizing components of the echoendoscopes used for EUS enabled the inclusion of larger diameter working channels. This has permitted the development of larger instruments, stents, and

devices that have continually pushed the boundaries for EUS toward its future state [1]. It is these advances, some in use now and others envisioned for the future, that will be discussed in this chapter.

Diagnostic EUS

The foundational purpose of EUS was to provide enhanced visualization of intra-abdominal organs and structures at a time when transabdominal ultrasound was a low-resolution modality with limited capabilities, and computed tomography (CT) and magnetic resonance imaging (MRI) had both limited resolution and availability. The enhanced capabilities of EUS were recognized immediately, fueling its growth and refinement. Miniaturized ultrasound crystals have improved diagnostic imaging capabilities, and the concomitant improvements in computer processing power over recent decades have produced sharp images that can be manipulated and enhanced in many ways. Modern EUS processors have presets that improve penetration for analyzing deeper lesions and others that enhance the distinction between layers of the GI tract, especially useful in evaluating esophageal and gastric lesions. Auto-sensing processors have brought plug and play connectivity to EUS as well. Processors now recognize the echoendoscope once attached and automatically select settings and profiles optimized for that particular endoscope while still preserving the user's ability to customize the imaging approach.

Elastography is a newer technique that evaluates the stiffness of tissues targeted within the field of view during EUS. By evaluating the effects of shear forces on tissues, elastography provides another tool to the endosonographer evaluating patients with suspected malignancy. Its use does not replace the need for FNA tissue sampling but increases diagnostic capabilities for lesions seen during EUS, especially when other characteristics are difficult to evaluate qualitatively [4]. In our practice, we have found elastography to be

of particular utility in selecting the specific region of a tumor that is likely to be of the highest diagnostic yield during FNA. While we sample as much of the tumor as possible for broad representative analysis, elastography helps us identify the region to be targeted for the first and second pass of the needle so that we are assured that optimal diagnostic opportunity has been realized early on in the procedure. This, combined with real-time cytologic analysis performed by the pathologist present during the procedure, improves diagnostic yield.

Lymph node analysis is a mainstay of EUS during staging evaluation for malignancy. Adenopathy identified on cross-sectional imaging, and positron emission tomography (PET) will often require tissue analysis in order to finalize treatment decisions. Using EUS with FNA to sample lymph nodes identified on PET and other imaging studies has long been a standard in evaluating a patient with malignancy undergoing endoscopic ultrasound (EUS). Elastography may be useful in evaluating individual or collections of nodes and selecting those where FNA is most likely to be helpful in the staging of patients and in contributing to informed treatment decisions [4].

Another addition to the diagnostic EUS armamentarium is the use of contrast-enhanced EUS (CE-EUS). CE-EUS utilizes contrast agents with particle sizes smaller than erythrocytes that emphasize venules and small vessels to aid in distinguishing pathologic entities. This allows improved assessment of pancreatic masses, particularly enhancing the endosonographer's ability to distinguish neoplasia from organized inflammatory collections. CE-EUS is useful in the identification and evaluation of lymph nodes most concerning for malignancy as well. Imaging during CE-EUS demonstrates vascular filling defects in malignant nodes, allowing the endosonographer to focus on those nodes with an abnormal appearance, improving FNA yields and lessening procedure and anesthetic times. Initially, CE-EUS was used in the evaluation of peri-pancreatic nodes, but its role now has expanded to include the evaluation of peri-esophageal and peri-aortic

lymph nodes as well [5]. It is likely that CE-EUS will be utilized increasingly going forward as additional agents and techniques are developed.

Confocal laser endomicroscopy (CLE) is a newer imaging modality that enables evaluation of the mucosal surfaces encountered during endoscopy at the subcellular level of resolution, permitting virtual biopsy of the tissues through the recognition of key cellular features [6]. The use of CLE for the evaluation of pancreatic cyst walls has introduced another tool for use by the endosonographer in evaluating the benign versus the malignant potential of pancreatic cystic and other lesions. A 19-gauge needle is directly placed within the cyst or other structure, and real-time images of the epithelial surface are interpreted by the endosonographer. EUS-guided through-the-needle biopsy forceps recently have been developed to obtain histological samples, both independently and as an adjunct to CLE. The through-the-needle biopsy forceps are introduced through a 19-gauge FNA needle, either directly after needle puncture or following CLE, to capture a histologic sample. Success rates for obtaining a useful tissue sample have been reported to be 95.6%, and 74.6% of these samples are adequate for definitive histologic diagnosis [7]. This technique expands the diagnostic algorithm available during EUS to include imaging appearance, elastography, fluid aspiration for analysis, FNA, fine needle biopsy, CLE, and direct sampling of cyst walls with forceps that provide a histologic sample. Each development cements the utility of EUS in the diagnosis and treatment of GI tract lesions, enhancing its value as our field moves forward.

One of the most exciting advances coming to diagnostic EUS that will serve as a foundational element for a new phase of interventional EUS is combined modality imaging or image-guided endoscopy. Many scientists, engineers, and clinicians are working toward multimodality guidance for EUS by combining and linking CT, PET, and MRI images to a system that will permit placement of the echoendoscope in such a location as to guide the evaluation of a lesion seen on cross-sectional imaging. Presently, endosonographers use

their refined skills in the interpretation of cross-sectional imaging and other radiologic techniques to identify the target lesion and then utilize their knowledge of gross and sonographic anatomy to align with the lesion and accomplish tissue sampling. This requires tremendous experience, and the learning curve for EUS has been cited as one reason that this service has been limited in some geographic locations and why training opportunities remain limited [8]. It is proposed, however, that if cross-sectional imaging from familiar modalities like CT could be combined with EUS imaging systems, experienced endoscopists earlier along their EUS learning curve would be enabled to locate even small or difficult to identify lesions for diagnostic and therapeutic intent. Fused images allow the endoscopist to track the advancement of the echoendoscope through the GI tract and to visualize its proximity to the target lesion while maintaining a sonographic view of the tissues. Combined modality imaging is one of the most exciting developments coming and one that we predict will impact the regional availability of EUS globally.

Therapeutic EUS

One recent advance in the realm of diagnostic EUS takes advantage of the close proximity of the stomach to the liver. Cook Incorporated has produced the EchoTip Insight™ Portosystemic Pressure Gradient Measurement System. This system utilizes an FNA needle for transgastric access to the portal venous system, allowing the endosonographer to obtain direct measurements of portal pressure. The needle then is redirected into the hepatic venous system to obtain direct measurements of systemic venous pressure, allowing the calculation of the portosystemic pressure gradient in the analysis of portal hypertension [9–11]. This represents one of the first alternatives to the decades-old techniques used by interventional radiologists to measure this gradient. This approach is likely to lead to a resurgence of interest in the treatment of portal hypertension, and we predict that there

will be novel techniques forthcoming that leverage this approach and enable placement of a portosystemic shunt for elective and emergent mitigation of the untoward effects of elevated portal pressures [12].

One of the most significant recent additions to the EUS tool set was the development of lumen apposing metallic stents (LAMS). The Axios™ Stent family, now produced by Boston Scientific Corporation, allows for EUS-guided placement of a self-expanding covered metal stent that bridges from one lumen to another, holding the structures in close approximation until a tract is established by its unique dual-flange design [13]. Largely used for drainage of benign pancreatic fluid collections like pseudocysts and walled-off pancreatic necrosis, this system has revolutionized the care of patients with inflammatory pancreatic fluid collections [14]. The newest addition to the Axios™ family has a 20-mm diameter, which will facilitate pancreatic necrosectomy going forward. The availability of LAMS with longer traversing lengths and wider luminal diameters, presently under development, will allow for more creative uses, many of which are likely to represent off-label indications, that will enhance options for patients requiring internal decompression of malignant biliary obstructions, malignant gastric outlet obstructions, and other conditions that now require external drainage or surgical intervention [15]. The drainage of non-pancreatic abscesses and other fluid collections approachable through the GI tract is likely to expand, enhancing the future role of EUS in the algorithm for endoscopic management of surgical complications [16–18]. Using LAMS to create GI tract anastomoses, like gastrojejunostomy as one example, will soon blur the lines between EUS and minimally invasive GI tract surgery even further [16].

Cholecystoenterostomy for acute cholecystitis in the infirm patient at high risk for abdominal surgery has been under investigation throughout the past several years and likely will grow in utility as the technique continues to evolve. Cholecystectomy can be treacherous in this setting, whether performed laparoscopically or via laparotomy, and the risk of

common bile duct injury is elevated significantly in the acute setting. Cholecystostomy tube placement has become a mainstay of care for such patients in some centers, but these external drains become plugged or dislodged, and symptoms are likely to recur after their removal as they are ineffective in clearing stones from the gallbladder. Patient acceptance is poor, and external drains and tubing limit patient activity levels and reduce the quality of life perceptions. Applying EUS in this ill patient population allows for evaluation of the gallbladder wall, seeking to identify those with gangrenous changes or gallbladder necrosis who will benefit from surgery rather than drainage despite the risks, and provides an avenue for placement of LAMS to decompress the gallbladder in those in whom gallbladder necrosis does not mandate a surgical approach. This acute intervention reduces the luminal pressure within the gallbladder immediately, while the subsequent endoscopic interventions permit clearance of gallstones from the gallbladder [15, 19, 20]. If there is any one indication for EUS that should prompt the interest of all surgical endoscopists, this is it. This set of biliary interventions has the potential to impact the role surgeons play in the treatment of biliary stone disease forever. Developing a combined skill set that includes surgical and endoscopic approaches to the needs of all patients will be increasingly more valuable as the future evolves.

Postsurgical anatomy poses new challenges to transoral endoscopic procedures, like EUS and endoscopic retrograde cholangiopancreatography (ERCP). Specifically, Roux-en-Y gastric bypass procedures for weight loss and other indications have limited our ability to access the remnant stomach, duodenum, and ampulla for inspection and evaluation, due to reconstruction using gastrojejunal anastomoses. Although laparoscopic assisted access to the gastric remnant is an effective tool for providing access when urgent ERCP and EUS are needed in patients with surgically altered anatomy, dense adhesions, and other issues may increase the risk of enterotomy or lead to laparotomy in some patients, increasing the invasiveness of treatment. Regardless of whether laparotomy

or laparoscopy is successful, most patients will be required to maintain a gastrostomy tube for some time in order to preserve a route of access for future intervention, and patients generally poorly tolerate these.

The use of EUS-Directed Transgastric ERCP (EDGE) is an alternative that many patients and endoscopists find superior to traditional approaches. The EDGE procedure is initiated by performing EUS to identify a pathway from the gastric pouch, or more commonly the alimentary limb, to the remnant stomach. Needle puncture, fluid distension of the targeted portion of the remnant stomach, and placement of LAMS result in a temporary connection that restores transoral access to the remnant stomach and downstream components of the GI tract. After a healing period of two weeks, EUS or ERCP can be performed through this established tract, and when all therapeutic maneuvers have been completed, the LAMS is removed endoscopically, and the defect closed using clips or sutures. The EDGE procedure is emerging as the least invasive method of performing ERCP in patients with surgically altered anatomy [21]. This same approach is used in patients with surgically altered anatomy who require other interventions such as drainage of abscesses and pancreatic fluid collections or assessment of pancreatic neoplasia. These interventions are collectively known as EUS-Directed-Transgastric Interventions or EDGI and represent the cutting edge of therapeutic EUS at present [22].

Weight loss and the control of obesity-associated comorbidities have been a central focus for surgeons and endoscopists for some time, as we seek the least invasive alternatives that will benefit the multisystem needs of our patients. Balloons and space-occupying devices, endoscopic gastric partitioning, and other sutured plication-based approaches have been employed for some time, and these continue to be refined as variable success and durability rates have been noted. EUS has been utilized for the delivery of weight loss therapy as well. EUS-guided injections of Botulinum Toxin A within the gastric wall have been shown to reduce gastric capacity and to delay gastric emptying, producing a sensation

of early satiety and weight loss [23]. EUS-guided injection of hyaluronic acid within the lower esophageal sphincter region has been utilized in concert with gastric balloons, enhancing their weight loss efficacy [23]. We anticipate that as other pharmaceutical adjuncts are developed and trialed for weight loss, the precision injection patterns possible with EUS will keep this approach at the fore of many future developments.

Another development that surely will impact the future care of patients with obesity and other GI tract challenges that require reconstruction through the formation of surgical anastomoses is the use of magnetic compression anastomotic devices. The common theme to these procedures, whether intended for weight loss or to address GI tract pathology that does not require resection, is the endoscopic placement of self-forming magnetic rings on either side of the proposed anastomotic union. Once deployed and formed, the magnets are attracted to each other, resulting in pressure necrosis and fusion of the adjacent tissues, resulting in a patent anastomosis. The devices are spontaneously passed, leaving an intact anastomosis in their place [24–26]. One study evaluated the creation of jejunoileal anastomoses with the self-forming magnetic rings delivered endoscopically by simultaneously advancing two endoscopes, one transorally, and the other transrectally. Initial procedures were performed under laparoscopic surveillance, but feasibility has been shown for the totally endoscopic placement of these devices. The anastomoses remained patent at twelve months and yielded weight loss as predicted, secondary to rapid intestinal transit and shortened mucosal contact time [27]. We anticipate that continued success with these and other devices will lead to EUS-based applications that will further supplant surgical practice, providing yet another exciting reason for surgeon endoscopists to add EUS to their skill set.

Therapeutic approaches to malignant diseases will continue to require robust EUS skills in the future. Screening for malignancy, securing the diagnosis through a variety of EUS-guided techniques, and alleviating obstructions and complications of malignant lesions are already the mainstays of EUS

practice. Newer approaches, like the direct delivery of chemotherapeutic agents or radiation spheres for brachytherapy, will continue to evolve as new agents become available [28–30]. As techniques for endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and submucosal tunneled endoscopic resection (STER) continue to evolve, and equipment supporting safe, rapid, and reliable endoscopic resection is developed, the role of EUS will evolve too [31–33]. EUS will become even more important in identifying which patients will be able to be treated using endoluminal surgery and which will require more traditional approaches like standard minimally invasive surgical approaches to resection. EUS images may have looked like weather maps in the past, but in our estimation, they are a map to the future.

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Chapter 33
Cholangioscopy

Richard Johnson and Benjamin K. Poulose

Cholangioscopy

Cholangioscopy has been around for several decades. It has evolved from the sole realm of the surgeon performing direct cholangioscopy in the operating room to something that can be done in the operating room, endoscopy suite, or interventional radiology lab. The first cholangioscopes were designed with the endoscopist looking into an eyepiece connected to the device's handle for direct viewing within the lumen of the biliary system. After gaining entry, some surgeons used these to explore the biliary tree by incising the cystic or common

R. Johnson
Division of Trauma, Critical Care, and Burn Surgery, The Ohio State Wexner Medical Center, Columbus, OH, USA
e-mail: Richard.johnson@osumc.edu

B. K. Poulose (✉)
Division of General and Gastrointestinal Surgery, The Ohio State Wexner Medical Center, Columbus, OH, USA
e-mail: Benjamin.poulose@osumc.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_33

bile duct. Until the advent of laparoscopy, this operation required an open incision whereby the surgeon was already looking directly at the biliary tree and able to palpate it, so the endolumenal evaluation may not have added much to the operation. When laparoscopy came about, the cholangioscope could be passed through a laparoscopic port into the biliary tree through a dilated cystic duct allowing for endolumenal evaluation of the biliary tree. One difference of cholangioscopy compared to upper endoscopy, ERCP, colonoscopy, or even bronchoscopy is that it requires continuous irrigation through the scope into the biliary lumen. This can be done with sterile normal saline or sterile water. If one performed electrohydraulic lithotripsy, normal saline is recommended to facilitate stone fracture.

As endoscopy continued to improve, the idea of passing the small caliber cholangioscope orally and down to the ampulla of Vater was pursued. There are multiple described ways of direct visualization of the biliary tree [1–3]. One of the main issues was the location and difficulty in getting the cholangioscope to the biliary system. To allow for the passage of the scope into the biliary tree, cholangioscopes are of very small caliber with delicate fiber optics and not as much tip deflection as available in modern endoscopes. To overcome this, side viewing duodenoscopes used for endoscopic retrograde cholangiopancreatograms (ERCP) were used as a conduit of the cholangioscope. Duodenoscopes have a working channel diameter of 2.0–4.8 mm. With a small enough cholangioscope, one can pass the cholangioscope through that working channel and then into the biliary tree. This has come to be known as the mother-baby or mother-daughter technique. One drawback of this technique is that it would require two endoscopists. One endoscopist is controlling the duodenoscope, and one is controlling the cholangioscope. This drawback limited the more widespread use of early cholangioscopy via a mother-daughter design (Fig. 33.1). As technology

FIGURE 33.1 Courtesy of Boston Scientific showing early mother-daughter design. [With permission from Boston Scientific Corporation].

advanced, the cholangioscopes and duodenoscopes were developed with video chips that allowed the procedure to be done by just one endoscopist. With this design, the images from both cholangioscope and the duodenoscope can even be placed on the same monitor in a picture in picture design instead of requiring one to directly view through the handle of the scope.

In 2007 Boston Scientific developed a disposable cholangioscope that can accomplish the mother-daughter design called the Spyglass. This has undergone further evolution so that the current model has its working channel to allow for the passage of instruments and wires. The procedure steps are very similar to a traditional ERCP with cannulation of the biliary tree, and a sphincterotomy is performed. Then one can leave a wire deeply cannulated within the biliary tree and pass the SpyScope over this wire through the working channel of the duodenoscope into the common bile duct (Figures 33.2, 33.3, 33.4, 33.5, and 33.6). The SpyScope has a

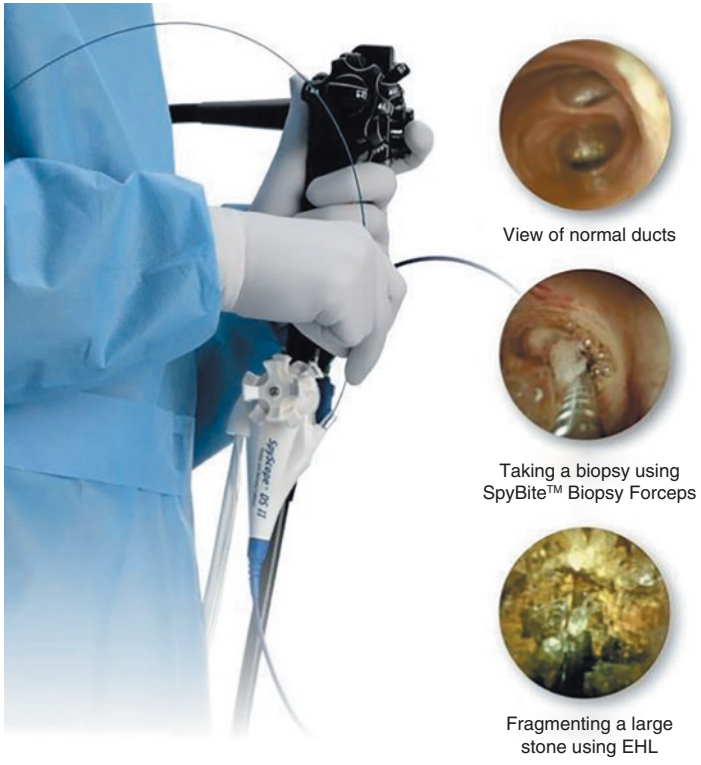

Figure 33.2 Courtesy of Boston Scientific. SpyScope system. [With permission from Boston Scientific Corporation]

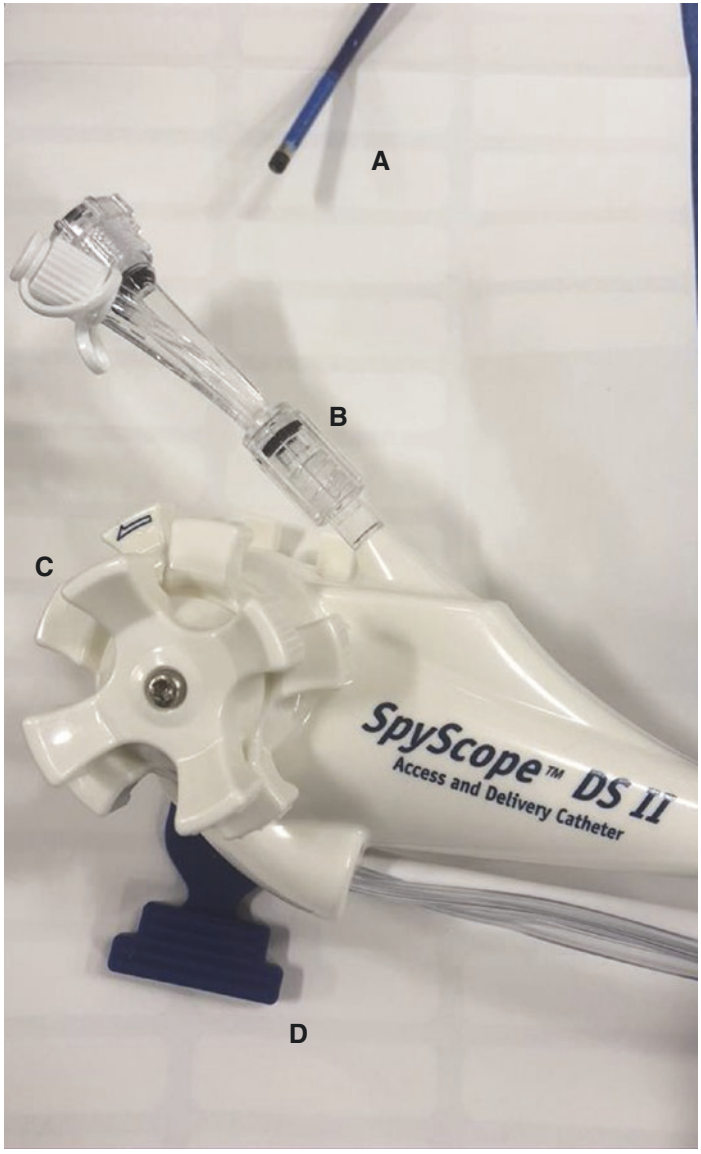

FIGURE 33.3 (A) Distal end of the cholangioscope. (B) Working channel port. (C) Control knob dials. (D) Attachment strap used to secure cholangioscope to endoscope

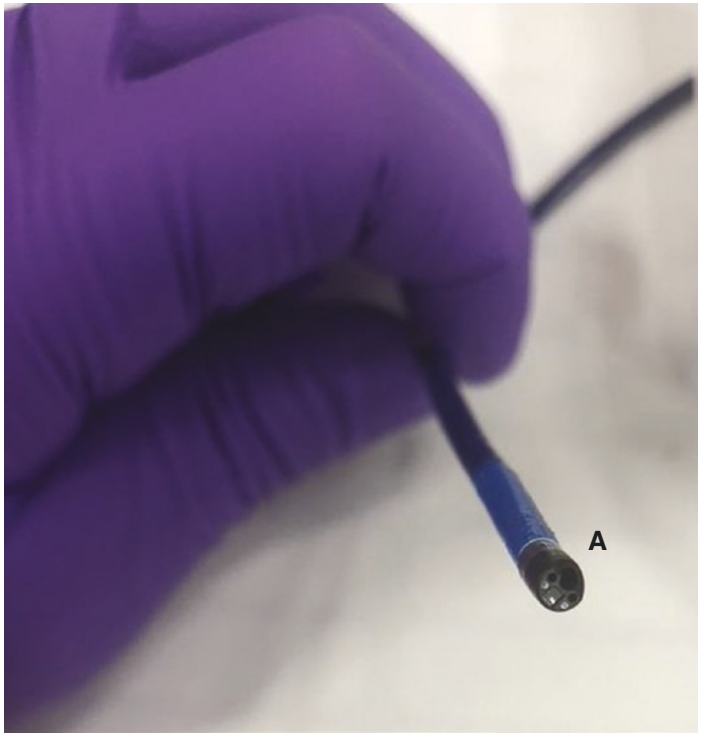

FIGURE 33.4 Distal end of cholangioscope (**A**) showing working channel, light, irrigation, and suction ports

control handle that attaches to the standard duodenoscope and then is inserted through the working channel of the duodenoscope. The SpyScope handle has three ports and two control wheels to allow for tip deflection in four directions. The accessory channel is 1.2 mm in size and allows for the passage of various tools such as guidewires, biopsy forceps, and lithotripsy catheters [4].

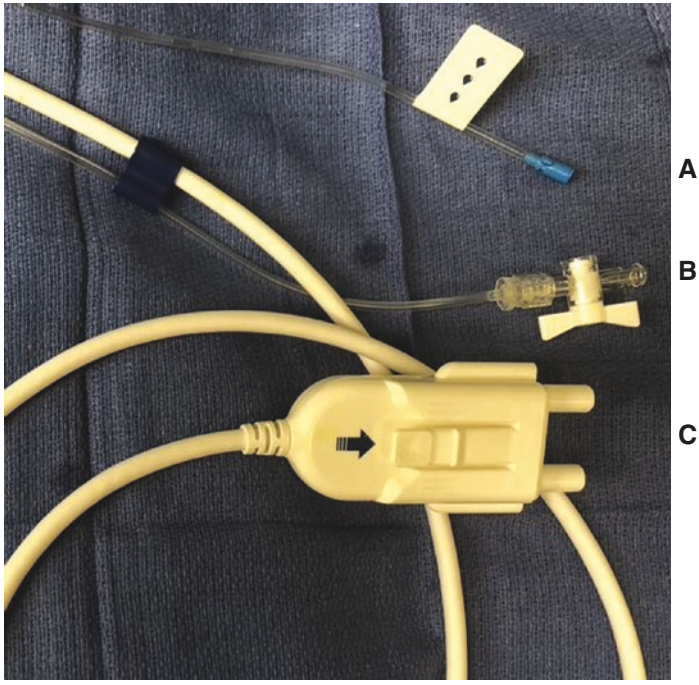

FIGURE 33.5 (A) Irrigation port. (B) Is aspiration port. (C) Is a catheter cable that connects to Digital Controller

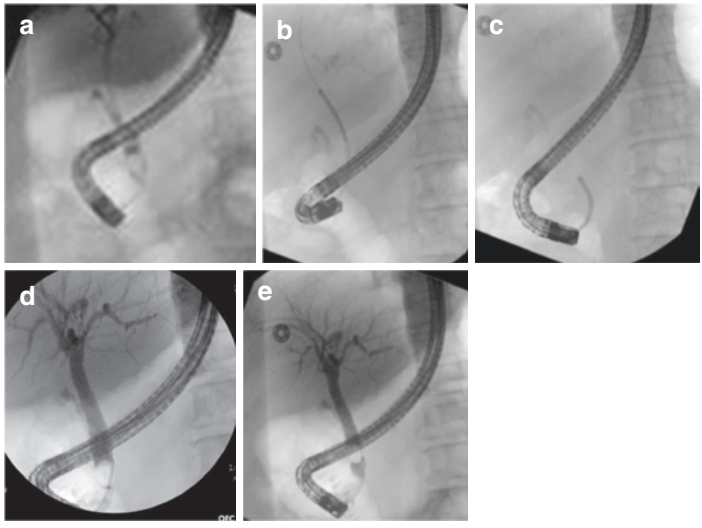

FIGURE 33.6 (**a**) An Initial cholangiogram with CBD stone. (**b**) Cholangiogram with Cholangioscope passed into the CBD over a wire. (**c**) Cholangioscope against stone prior to lithotripsy. (**d** and **e**) Completion cholangiogram showing a clear biliary tree. *CBD common bile duct*

Transhepatic Cholangioscopy

Another avenue of approach for cholangioscopy is to use percutaneous transhepatic biliary access. In the scenario where one is unable to cannulate the biliary tree endoscopically, an endoscopist can gain access from above with a percutaneous transhepatic cholangiogram catheter. Once this tract is mature, it can be dilated up to a 12 French sheath that will then allow for direct passage of the SpyScope or similarly sized cholangioscope. In the authors' experience, this can be very helpful in the post liver transplant patient who has a stricture at the biliary anastomosis precluding passage of the cholangioscope from below. These patients will often develop proximal choledocholithiasis and, with a cholangioscope from above on, is able to perform lithotripsy. This is a conve-

nient option to remember when dealing with the very difficult to endoscopically cannulate biliary tree. Also, the stricture is able to be directly biopsied as the SpyScope does allow for the passage of an endoscopic biopsy forceps through its working channel. This has been shown in some case series to improve the sensitivity of diagnosis of an indeterminate biliary stricture as compared to endoscopic retrograde cholangiogram with brushings [5, 6].

Peroral Cholangioscopy

Another option is direct peroral cholangioscopy. These devices are being developed and are primarily in experimental and trial usage. The concept is to allow for direct cholangioscopy without a duodenoscope like is done in the mother-daughter design. These rely on either a balloon near the distal end to provide leverage or two sections of the scope that bend. They can have a learning curve like any new device but come with the possible benefit of using one scope that can be reusable instead of one reusable duodenoscope and a single-use cholangioscope.

Electrohydraulic Lithotripsy

Electrohydraulic lithotripsy (EHL) deserves a brief description given its utility in managing complex calculous disease of the biliary tract and its close relationship to cholangioscopy. This technology was originally invented for use in the mining industry, where it is used to fragment stones without the need for traditional explosives or mechanical mining equipment. A typical EHL catheter is a 1.9 French nitinol device that contains two coaxially insulated electrodes that are open at the distal tip of the catheter. During cholangioscopy, the irrigation channel is used with a constant flow of normal saline that aids with the EHL catheter use. A generator creates a series of high voltage electrical impulses when the endoscopist

steps on a foot pedal. These impulses can be set at 1 to 20 per second with various power settings. These will create sparks between the two electrodes at the distal tip of the catheter that will then cause high amplitude hydraulic pressure waves. These waves will then fragment the stones to facilitate removal.

Conclusion

For decades, interventional proceduralists have relied on fluoroscopic imaging to guide access and intervention in the biliary tree. This has been done percutaneously, directly in the operating room, or endoscopically. However, even with improvements in these technologies, an endoscopist has still been looking at two-dimensional shadows of a three-dimensional structure. Thanks to improvements in endoscopic devices including mother-daughter scopes, transhepatic devices, and emerging per oral biliary scopes along with electrohydraulic lithotripsy, cholangioscopic interventions previously viewed as impossible are becoming increasingly achievable with minimal sequelae.

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Chapter 34
Role of Endoscopic Bariatric Therapies in a Comprehensive Multidisciplinary Metabolic and Bariatric Program

Alexander Abdurakhmanov and Abdelrahman Nimeri

Introduction

Endoscopy is an important component of a metabolic and bariatric surgery program. From pre-operative screening endoscopy, to endoscopic primary therapy, to post-operative management of complications, this chapter will outline the various roles of endoscopy in metabolic and bariatric surgery (MBS).

A. Abdurakhmanov · A. Nimeri (✉)
Atrium Health Weight Management, Carolinas Medical Center, Charlotte, NC, USA
e-mail: alexander.abdurakhmanov@atriumhealth.org; abelrahman.nimeri@atriumhealth.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_34

Pre-operative Endoscopy

There is some debate whether every bariatric patient should undergo routine upper endoscopy prior to MBS [1]. Alteration in the gastrointestinal anatomy precluding endoscopic access to the remnant stomach and duodenum occurs in some of the most effective MBS such as the Roux en-Y gastric bypass (RYGB), one anastomosis gastric bypass (OAGB), and the biliopancreatic diversion with duodenal switch (BPD-DS). For this reason, some centers perform routine upper endoscopic evaluation prior to primary MBS in all cases. However, surgical planning is rarely influenced by pre-operative upper endoscopy findings in asymptomatic patients. Therefore, most surgeons support the use of pre-operative upper endoscopy only selectively as the most common findings are esophagitis, gastritis and a hiatal hernia [2, 3]. A 2021 American Society for Metabolic and Bariatric Surgery (ASMBS) position statement on the use pre-operative and post-operative upper gastrointestinal endoscopy states that though there may be attrition of patients by requiring pre-operative upper endoscopy, even in the asymptomatic patient, the evidence suggests an esophagogastroduodenoscopy (EGD) may guide treatment of "modifiable conditions" (such as duodenal ulcers, H. pylori, etc.) prior to bariatric surgery and also identify anatomical abnormalities or even a decision to abort surgical intervention [4].

Pre-MBS endoscopy for evaluation is commonly performed selectively in symptomatic patients or patients with signs of foregut pathology [5]. These include hiatal hernia, gastroesophageal reflux disease (GERD), Helicobacter pylori infection, gastric/duodenal ulcers, suspected upper gastrointestinal bleeding, or unexplained iron deficiency anemia. Although the finding may not necessarily affect operative planning, it can alter care and lead to optimal outcomes. If a significant hiatal hernia is encountered, the surgeon may counsel the patient regarding simultaneous repair during MBS or consider RYGB rather than sleeve gastrectomy (SG). If Helicobacter pylori infection is detected on mucosal biopsy, the patient could be treated with triple therapy for

eradication, as the organism is possibly associated with marginal ulcers after RYGB [6, 7]. If esophageal changes from GERD are encountered, such as severe esophagitis or Barrett's esophagus, then surgical planning will steer away from procedures such as sleeve gastrectomy.

In revisional bariatric surgery, pre-operative endoscopy is performed more routinely and is used for diagnosis and treatment planning [8]. The most common diagnoses requiring revisional bariatric surgery are marginal ulcers, anastomotic stricture, gastrogastric fistula, evidence of reflux changes, band erosion or slippage with gastric bands, and kinking/stenosis with SG, or weight regain after SG or RYGB.

Pre-operative endoscopy is typically performed in an ambulatory setting with the patient under conscious sedation, in the left lateral decubitus position, to help protect the airway and allow the surgeon access to the oropharynx and esophagus. The risk of airway complications is higher in patients with obesity considering MBS compared to the general population that undergoes upper endoscopy due to the higher incidence of sleep apnea and apneic events during the procedure [9]. In addition, pre-operative screening prior to MBS is not an approved indication by insurance carriers. Thus, the surgeon must weigh the risks and benefits, along with cost and logistics of pre-operative screening upper endoscopy in every case to optimize pre-operative care and surgical planning.

Intra-Operative Endoscopy

Upper endoscopy is widely utilized intra-operatively during primary and revisional MBS. In primary SG, the endoscope can be used as a bougie to gauge the sleeve size and endoscopically evaluate the incisura to potentially decrease the rate of stenosis [10, 11], as well as to perform a leak test with air insufflation under water, and to make sure there is no luminal bleeding from the staple line. Similarly, in RYGB, upper endoscopy is used to evaluate the gastrojejunostomy

for patency and bleeding, as well as to perform a leak test with air insufflation under water. Like in SG and RYGB, when performing BPD-DS, upper endoscopy is used intra-operatively to evaluate the sleeve and the duodenojejunostomy for bleeding, leak or stenosis. Additionally, intra-operative endoscopy is an important adjunct to laparoscopy in revisional MBS to assess the position of the gastroesophageal junction, confirm the presence of a hiatal hernia, determine whether the patient has a gastrogastric fistula in RYGB, as well as evaluate the new anatomy for bleeding, leak or stenosis [12]. If there is a positive leak test or intra-luminal bleeding encountered on endoscopy, then additional techniques can be utilized to fix these problems before leaving the operating room and help prevent future complications.

Endoscopy to Manage Post-operative Complications

Patients with persistent gastrointestinal symptoms following MBS may benefit from upper endoscopy as a diagnostic and therapeutic tool compared to a radiographic exam if one suspects stenosis after RYGB or SG. Symptoms such as persistent nausea, vomiting, abdominal pain, reflux, dysphagia, suspected upper gastrointestinal bleeding, and weight regain, could be evaluated with upper endoscopy. Findings such as marginal ulcers, stricture, and leaks can be managed with medical and endoscopic therapies with less morbidity than operative interventions.

Endoscopy and Dilation for Stricture After RYGB and SG

A stricture after RYGB and SG may present with the patient experiencing nausea, vomiting, and dysphagia several weeks after MBS when they are advanced to regular diet. Upper

endoscopy may reveal a tight gastrojejunostomy after RYGB, sometimes as small as a pinhole (Fig. 34.1). Endoscopic balloon dilation has been shown to be a very effective treatment for stricture, usually requiring serial balloon dilations from 12 to 15 mm for 60-s intervals, with a success rate approaching 95%, based on timing from the initial operation [13, 14]. The incidence of stricture varies based on the technique of gastrojejunostomy creation, with circular stapled having the highest rate. Strictures after RYGB are amenable to endoscopic dilatation in the first 3–6 months after surgery and usually require operative revision if the stricture does not resolve. If there is an associated marginal ulcer, then medical therapy is warranted as well.

Stenosis after SG may be due to angulation at the incisura, or a twist in the SG. It is less common than stricture after RYGB, but is treated similarly with balloon dilation and endoscopic stenting [15]. However, it is less successful than stenosis after RYGB and many patients may require operative intervention to treat stenosis after SG [16]. Perforation and stent migration are potential risks for endoscopic interventions, however, success rates remain high with less morbidity compared to operative interventions.

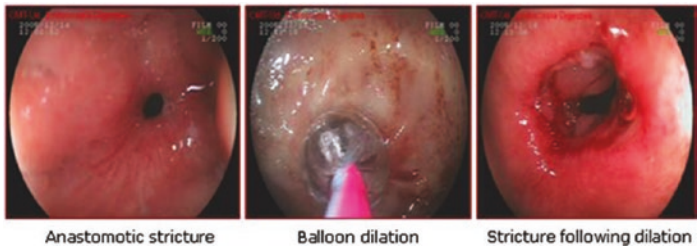


Figure 34.1 Endoscopic balloon dilation. ((With permission from Springer Nature). Da Costa, M., Mata, A., Espinós, J. et al. Endoscopic Dilation of Gastrojejunal Anastomotic Strictures After Laparoscopic Gastric Bypass. Predictors of Initial Failure. *OBES SURG* 21, 36–41 (2011))

Endoscopy for Upper GI Bleeding After RYGB

Intra-luminal bleeding from the staple line remains a rare complication after MBS, and endoscopic management is a mainstay of therapy [17]. Bleeding after a RYGB is estimated to be in the range of 0.8% to 4.4% and typically occurtomy, gastric pouch, or remnant stomach [18]. at the gastrojejunostomy, gastric pouch, or remnant stomach [18]. Bleeding in the immediate post-operative period after MBS can present as hematemesis, dark stools, tachycardia, melena or anemia. Care must be taken if the patient presents acutely with hematemesis to avoid performing endoscopy in the usual setting under sedation in the endoscopy suite. This is particularly important in patients presenting immediately after MBS. These patients are at a high risk for airway complications and should have the endoscopy performed under general endotracheal anesthesia in the operating room in case operative intervention is needed.

Endoscopy may reveal bleeding from the gastrojejunostomy or staple line, and clots may be present over the site of bleeding which should be completely removed with irrigation prior to any endoscopic intervention. Endoscopic management options include through-the-scope-clips, over-the-scope-clips, coagulation, epinephrine injection [18] and also hemostatic sprays. In the long-term, marginal ulceration is a common cause of upper GI bleeding after RYGB, and medical management with proton pump inhibitors and mucosal coating agents are the mainstay of therapy [18–20]

Endoscopy for Treatment of Leaks

Leaks are a rare complication after MBS that need prompt recognition, drainage, and source control, along with distal enteral feeding access as the mainstay of therapy. All leaks after MBS are not the same, and management depends on the

type of procedure performed. Leaks after SG usually occur at the most proximal portion of the staple line near the gastroesophageal junction, making operative repair in this region very difficult [21]. Due to the inflamed friable tissue as well as risk of causing stenosis, operative repair is often not feasible [22]. Recently, several endoscopic options are available to manage leaks after SG including endoscopic esophageal stents. In addition, double pigtail stents are used for internal drainage of the gastric leaks after SG with good results [23]. Endoscopic techniques can be utilized to plug or close the leak in certain situations with clips, sutures, or fibrin glue. The endoscopic VAC sponge has had good outcomes in helping bridge a leak to a future definitive safe repair [24].

Similarly, leaks after RYGB and BPD-DS are difficult to repair in the early post-operative period and management consists of wide drainage and enteral feeding. Recently, the emergence of endoscopic covered and partially covered stents has helped to divert enteral flow downstream and provide continued source control [25].

Primary Endoscopic Therapy for Obesity

MBS has proven to be superior to medical therapy and lifestyle modification alone when it comes to long-term durable weight loss and resolution of comorbidities [26]. However, MBS is not indicated for patients with class I or II obesity and MBS is not without risks, causing patients to seek safer alternative options. As endoluminal techniques have advanced, primary endoscopic weight loss procedures have emerged [27, 28]. These procedures are generally characterized into space occupying gastric devices, endoscopic suturing devices, aspiration therapy, and endoscopic small bowel intestinal bypass devices.

Although there are no broadly accepted criteria or recommendations for when to implement endoscopic weight loss options, there are certain groups of patients that can benefit

from these procedures. This includes patients with BMI between 30 and 40, or high-risk patients, who wish to forego the surgical risks that come along with MBS [29]. The intragastric balloon has been used in the super obese to help facilitate weight loss prior to metabolic surgery, as well as a definitive procedure in those with lower BMI. As endoscopy advances, along with technical ability of proceduralists, the role of endoscopy in metabolic therapy will continue to grow.

Space Occupying Devices

Space occupying devices include intragastric balloons (Fig. 34.2), transpyloric shuttle, and Plenity. Intragastric balloons (IGBs) work by decreasing gastric volume and altering gastric motility [30]. In addition, IGBs lead to a change in

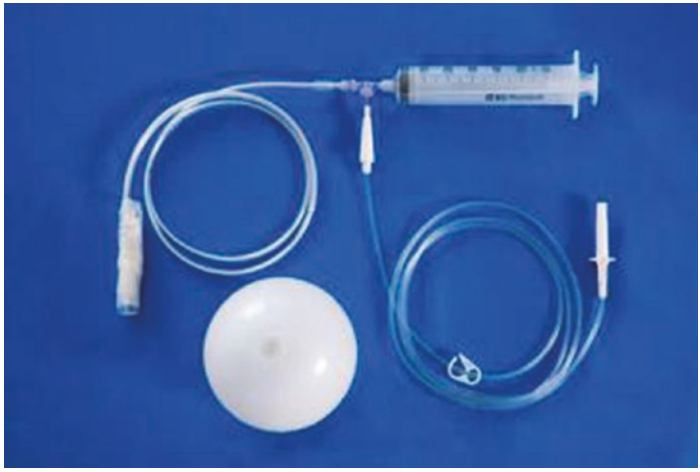


FIGURE 34.2 Intragastric balloon device, tubing, and inflated balloon. ((With permission from Springer Nature). Keren, D., Rainis, T. Intragastric Balloons for Overweight Populations—1 Year Post Removal. *OBES SURG* 28, 2368–2373 (2018))

gastrointestinal hormone levels such as leptin and ghrelin, which also appear to play a role in weight loss [31]. Currently, there are three Food and Drug Administration (FDA) approved space occupying devices for patients with BMIs between 30 and 40: the Obalon, Orbera, and ReShape Duo. Mean total body weight loss (%TBWL) after IGBs is 10% in a recent review [32], while also improving comorbidities such as diabetes, cholesterol, and hypertension. These devices are placed endoscopically with endoscopic inflation of the balloon. IGBs can only remain in situ for 6–12 months due to spontaneous deflation, a potential drawback that can lead to complications if the IGB passes beyond the pylorus. IGBs are safe, yet rarely serious adverse events were reported in approximately 10% of cases, and included injury to the esophagus, gastric outlet obstruction, gastric perforation, gastric ulcers, and aspiration pneumonitis. In addition to the three FDA approved IGBs in the US, the Elipse balloon, approved in Europe and currently under FDA evaluation, is swallowed and then externally filled [33]. It has the advantage of self-emptying after four months and passing through the GI tract, avoiding the need for endoscopy altogether. IGBs represent a temporary solution to a chronic disease.

The transpyloric shuttle (TPS) is a device designed to sit across the pylorus and cause delayed gastric emptying. A successful pilot study and recent randomized trial reported approximately 10% TBWL and 30% EWL with TPS [34, 35]. The catalog of adverse events were similar to IGBs but were less frequent at 2.8%. Another benefit of TPS is that unlike the IGB, it does not need to be removed after a certain period of time.

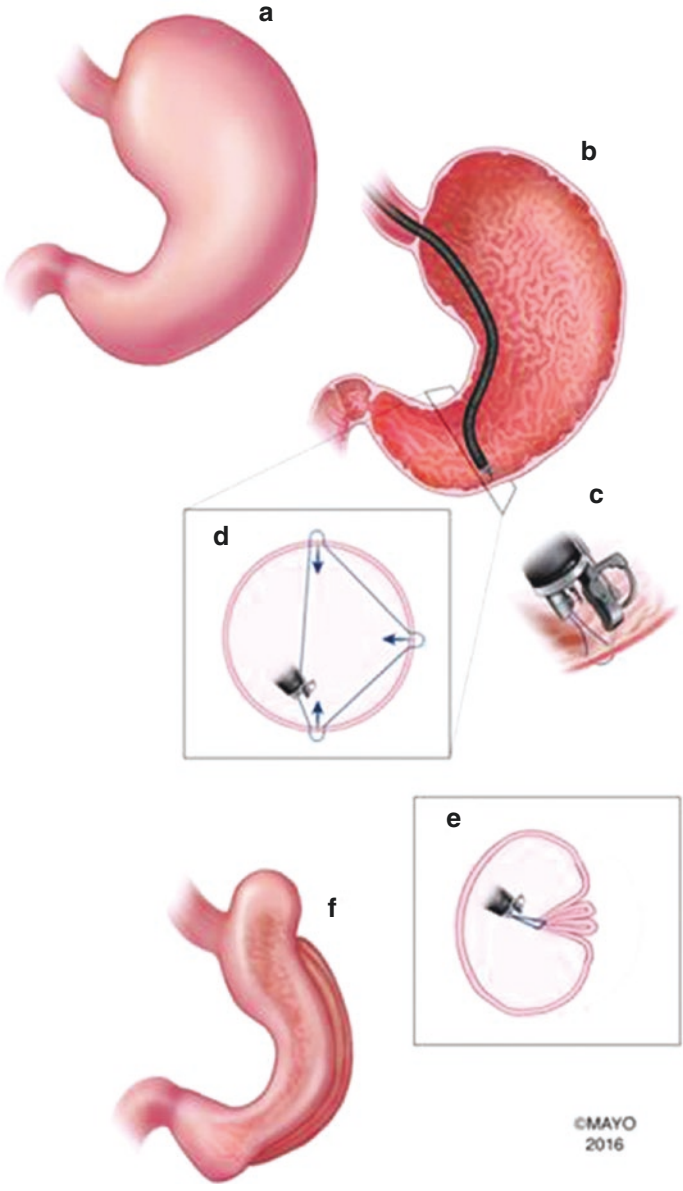
Plenity is a capsulated device containing hydrogel particles that is orally administered twice daily. These particles expand when mixed with water, and lead to early satiety, delayed gastric emptying, and delayed glucose absorption. It is FDA approved in patients with a BMI of 25–40, and has shown a 6.4% TBWL over 6 months [36]. No serious adverse effects were reported.

Endoscopic Suturing/Stapling Devices

Endoscopic suturing devices (Fig. 34.3) include the Appollo OverStitch and Primary Surgery Endoluminal (POSE). The Apollo OverStitch Suturing System is a full thickness endoscopic suturing device, which allows for the creation of endoscopic sleeve gastroplasty (ESG), a procedure that mimics sleeve gastrectomy. ESG restricts the stomach to a sleeve configuration, while also reducing ghrelin production [37]. There have been several groups who have had success with ESG, and a recent meta-analysis showed an average %EWL of 57.7% and %TBWL of 15.1% at six months [38]. With a serious adverse events rate of only 2.2%, the ESG has shown to be effective and safe. The same technology is also used to endoscopically revise the gastric pouch or tighten the gastrojejunostomy after RYGB.

Primary surgery endoluminal (POSE) uses an incisionless operating platform to perform full thickness tissue plication of the fundus and distal gastric body. This delays gastric emptying and provides a feeling of satiety, and also improves leptin levels [39]. A recent systematic review and meta-analysis compared weight loss outcomes of ESG to POSE, and found that %EWL at one year to be 53% with ESG and 45% with POSE [40]. Although ESG has proven to be superior for weight loss, it appears to carry a slightly higher risk of complications when compared to POSE. Both procedures have shown to be effective and safe and provide an endoscopic alternative to weight loss.

Figure 34.3 Schematic of endoscopic sleeve gastroplasty using over the scope suturing technology. (**a**) External stomach. (**b**) Starting position of ESG. (**c**) Detail of suture passage. (**d**) Suture pattern for gastroplasty. (**e**) Luminal view of plication. (**f**) External view post-procedure. ((With permission from Springer Nature). Lopez-Nava, G., Sharaiha, R.Z., Vargas, E.J. et al. Endoscopic Sleeve Gastroplasty for Obesity: a Multicenter Study of 248 Patients with 24 Months Follow-Up. *OBES SURG* 27, 2649–2655 (2017))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Aspiration Therapy

Another FDA approved endoscopic device for obesity is the AspireAssist (AA), which is a percutaneous gastrostomy tube coupled with a skin port and aspiration tube. The AspireAssist functions by the patient partially draining ingested food. A 4-year follow-up study since FDA approval of the device, reported %TBWL of 18% and %EWL of 50% [41]. AA also showed improvement in comorbidities, lowering HbA1C, cholesterol, and blood pressure, while having a low rate of serious adverse events. Patients accept the obvious esthetic drawback of the AA for the benefits it provides with weight loss. Patients were not more likely to develop eating disorders or malnutrition with this device.

Endoscopic Small Intestine Bypass Technology

The gastroduodenojejunal bypass sleeve (GJBS) is a 120 cm endobarrier placed endoscopically from the GE junction down to the jejunum, mimicking gastric bypass effects. A small sample of patients who had the device positioned correctly over 12 months experienced a %EWL of 54% without any adverse events [42]. The drawback remains in the difficulty of keeping the endobarrier in correct position, and additional research is being undertaken to improve this aspect. A recent trial in the United States was halted by the FDA for a high incidence of liver abscesses in the endobarrier group [43].

The incisionless magnetic anastomosis system (IMAS), also currently undergoing FDA evaluation, uses magnets placed endoscopically at the proximal jejunum and terminal ileum. These magnets will self-assemble and create a controlled fistula/anastomosis over time, creating an enteral distal diversion. Pilot studies showed a %TBWL and %EWL of 14.6% and 40.2% respectively, with no adverse events in the small sample of patients [44]. The magnets are eliminated

through the GI tract naturally. Although none of these devices are currently FDA approved, human trials have been promising.

Conclusions

Endoscopy is an integral component of the diagnosis and management of patients with obesity and is an important adjunct to any comprehensive metabolic and bariatric surgery program. Endoscopy is part of the pre-operative evaluation, intra-operative evaluation and post-operative management of complications after MBS. In addition, endoscopy is an option for patients with obesity who are high risk for MBS, who do not qualify for MBS, or patients with obesity who are not considering MBS.

Disclosures The authors have no conflicts of interest to disclose.

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Chapter 35
Endoscopic Anatomy of the Bariatric Patient

Mohanad R. Youssef, Ashraf S. Farhoud, Meredith Freeman, Rachel Moore, and Carlos Galvani

Introduction

Obesity is a significant risk factor for gastrointestinal pathology, including gastroesophageal reflux disease (GERD), erosive esophagitis, hiatal hernia (HH), and Barrett's esophagus. These diseases are 2–3 times more common in patients with obesity [1, 2]. Many of these conditions are clinically relevant and significantly impact patients undergoing bariatric surgery. There is evidence that the chosen procedure

M. R. Youssef · C. Galvani (✉)
Division of Minimally Invasive and Bariatric Surgery, Department of Surgery, Tulane University, School of Medicine, New Orleans, LA, USA
e-mail: myoussef1@tulane.edu; cgalvani@tulane.edu

A. S. Farhoud · M. Freeman
Tulane University, School of Medicine, New Orleans, LA, USA
e-mail: afarhoud@tulane.edu; mfreema5@tulane.edu

R. Moore
Moore Metabolomics, New Orleans, LA, USA
e-mail: rachel.moore@mooremetabolics.com

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_35

might be changed if specific pathological upper GI findings, such as a large HH or Barrett's esophagus, are detected preoperatively [3].

The routine use of endoscopy before surgery has been debated [4]. Surgical and gastrointestinal communities have contradictory recommendations on preoperative endoscopy before bariatric surgeries with the absence of leading evidence to date (Table 35.1). While some surgeons perform routine preoperative endoscopy, others recommend preoperative endoscopy only in the presence of clinical symptoms or when the stomach or duodenum will be excluded, after laparoscopic Roux-en-Y gastric bypass (LRYGB) or duodenal switch/biliopancreatic diversion.

Systematic review and meta-analyses have reached different conclusions. Bennett et al. in 2016 analyzed 12,261 patients from 48 studies undergoing EGD before primary bariatric surgery. They found that only 7.8% of EGDs

Table 35.1 Different societies recommendations for pre-operative EGD in bariatric patients

Society	Recommendation summary for pre-operative EGD in bariatric surgery patients
European association for endoscopic surgery	Included in preoperative evaluation in all patients
American Society for Gastrointestinal Endoscopy [5]	Recommended for patients with GERD symptoms[a]
American Society for Metabolic and Bariatric Surgery [6]	Reserved for symptomatic patients[a]
Society of American Gastrointestinal and Endoscopic Surgery [7]	Does not include EGD in preoperative workup/evaluation

[a], e.g., heartburn, regurgitation, dysphagia, or any postprandial symptoms that suggest a foregut pathology and/or who chronically use antisecretory medications"

resulted in a change in surgical management. When excluding H. pylori infection (which can be tested for noninvasively), only 2.5% of procedures resulted in a change in medical management. They concluded that in patients at average risk for upper GI pathology, EGD should be considered optional [8]. Parikh et al. conducted a larger study (6166 patients) and reached a similar conclusion: only 7.6% of EGDs altered management, and routine screening was not recommended [9]. Other studies support routine use, especially in Europe [10]. The balance may shift towards routine EGD as the incidence of both sleeve gastrectomy and of GERD are rising [11].

For the purpose of this chapter, we will focus our attention on preoperative endoscopic evaluation and long-term (>30 days) postoperative evaluation.

Pre-operative Endoscopic Evaluation

Esophagogastroduodenoscopy (EGD) plays an integral role in the pre-and postoperative management of patients undergoing bariatric surgery. It is frequently used by surgeons in the preoperative evaluation of bariatric patients to assess for any preexisting anatomical variations or upper GI pathology. Although controversial, EGD can also help the surgeon to determine the most appropriate procedure for the patient. The procedure and findings are usually documented with pictures or a video system. Biopsy specimens can be obtained by passing forceps and taking small mucosal samples for histology studies.

The majority of findings include hiatal hernias (Figs. 35.1 and 35.2), gastritis (Fig. 35.3), esophagitis (Figs. 35.4 and 35.5), gastric or esophageal ulceration (Fig. 35.6), and Barrett's esophagus (Fig. 35.7). In addition, gastric findings such as gastric polyps (Fig. 35.8), Helicobacter pylori infection, peptic ulcer disease, and food bezoars (Figs. 35.9 and 35.10) are not uncommon in this patient population.

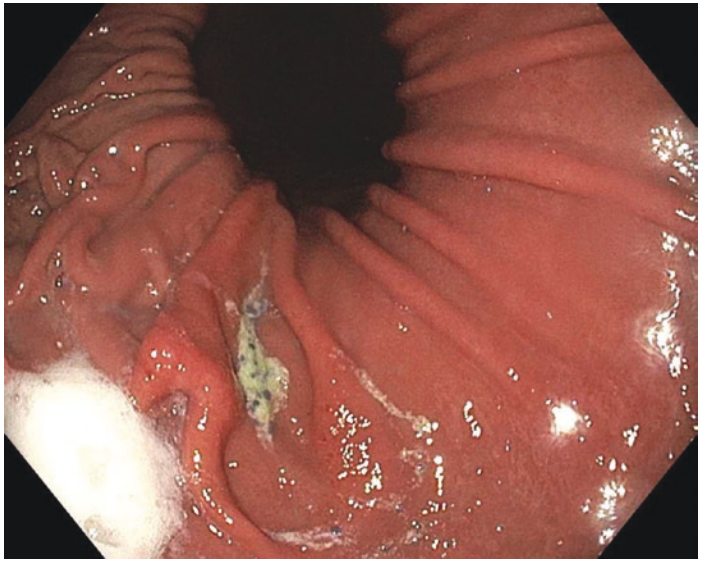

Figure 35.1 Large hiatal hernia in an asymptomatic patient

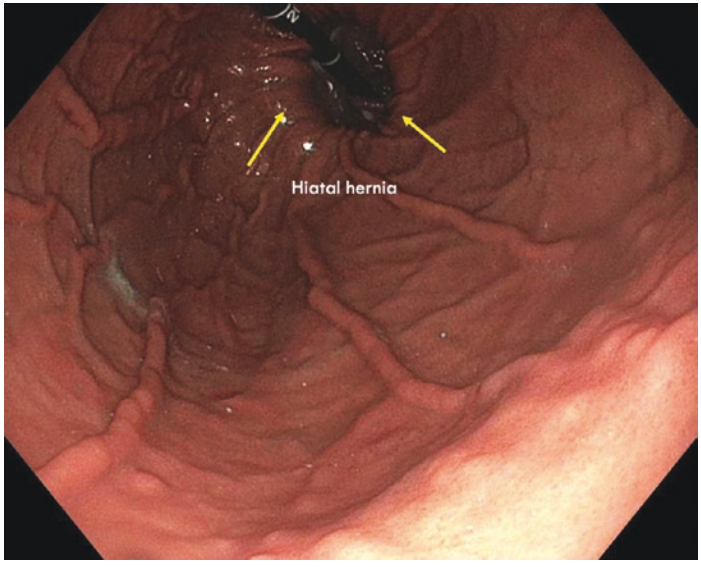

Figure 35.2 Large hiatal hernia (retroflexed view)

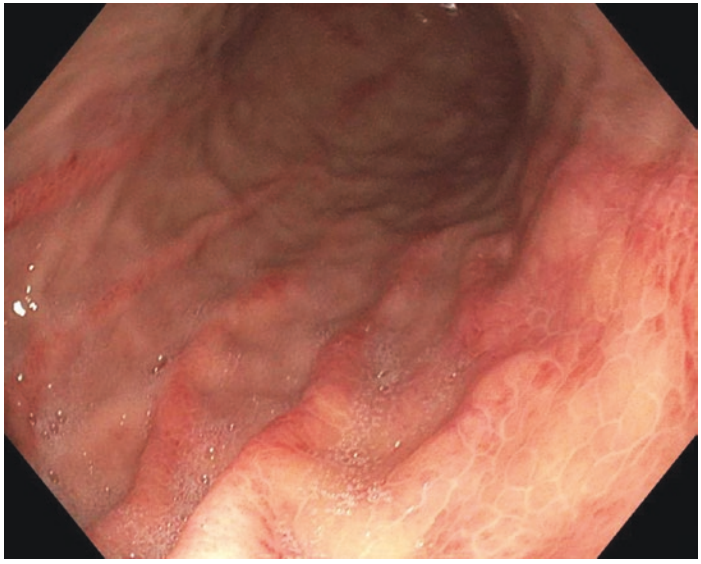

FIGURE 35.3 Erosive Gastritis

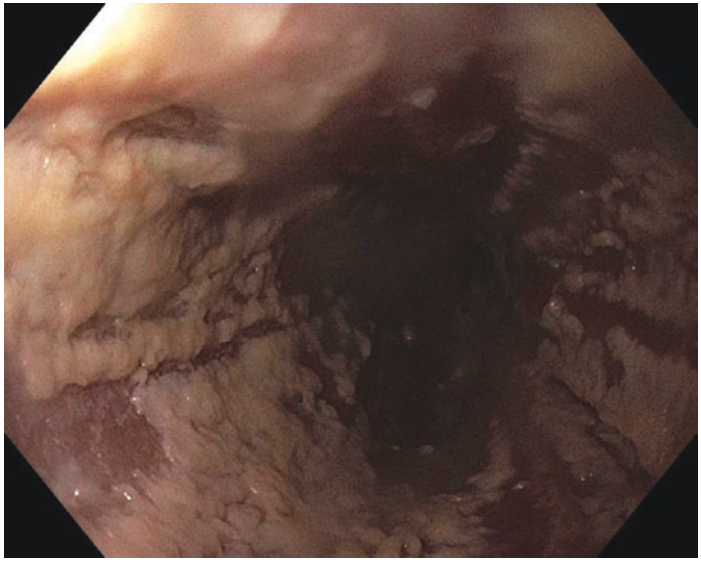

FIGURE 35.4 Candida esophagitis

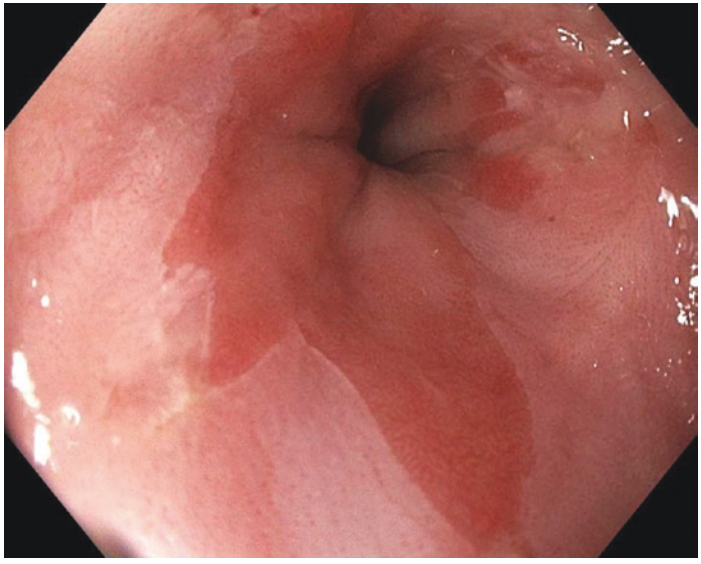

Figure 35.5 LA Grade C Esophagitis

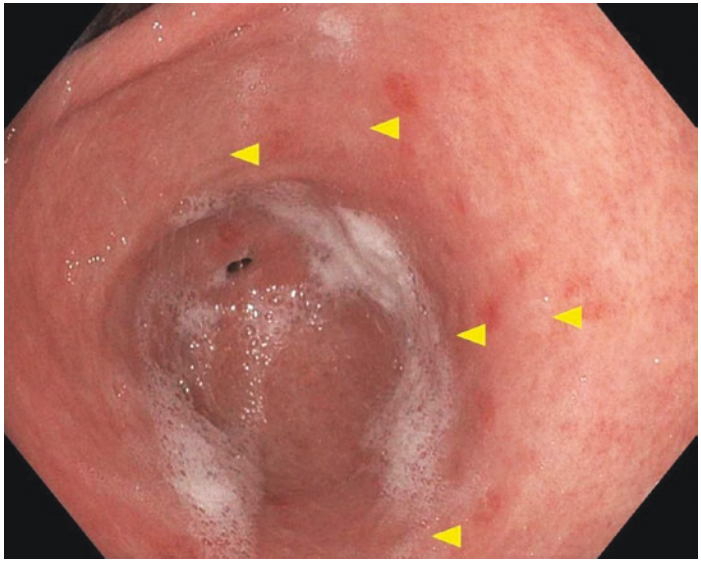

Figure 35.6 Prepyloric ulcers

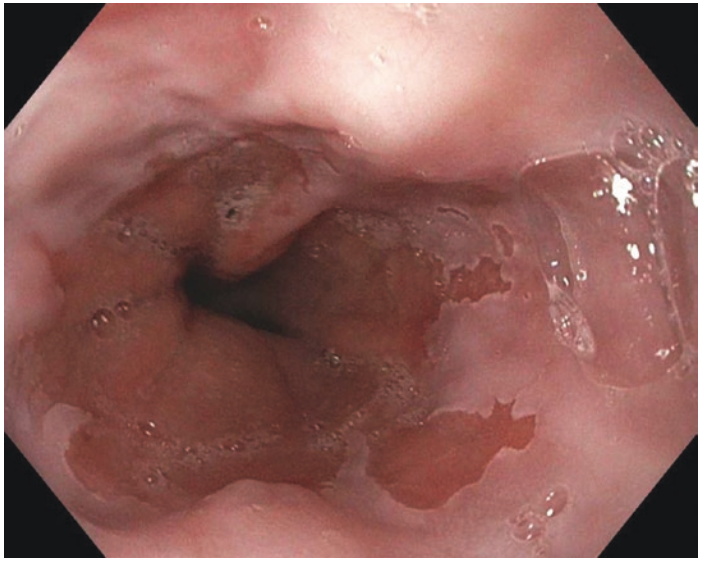

FIGURE 35.7 Barrett's esophagus

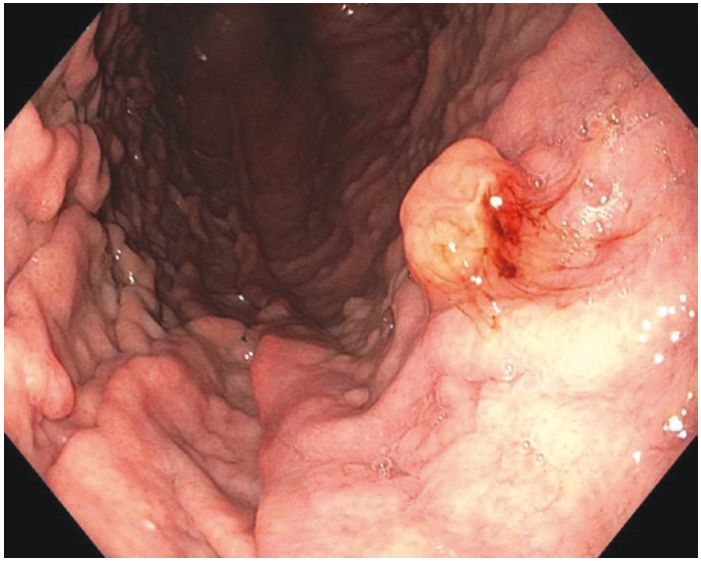

FIGURE 35.8 Multiple Gastric polyps

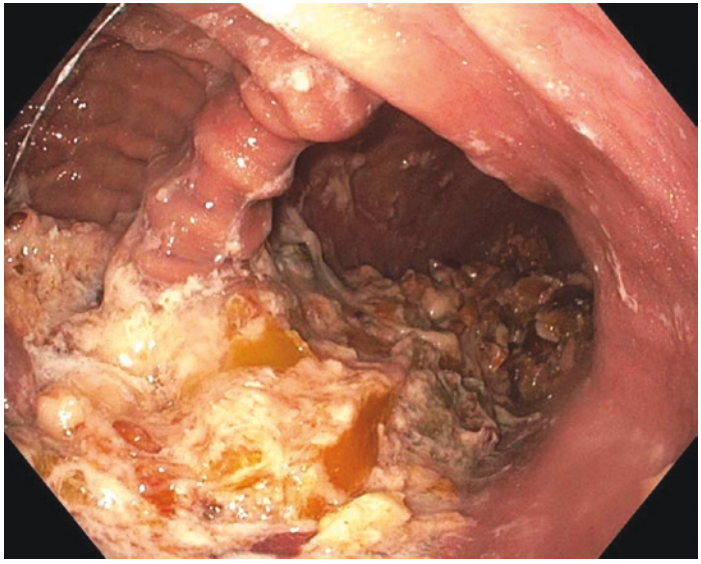

Figure 35.9 Large food bezoar in a patient with a large hiatal hernia

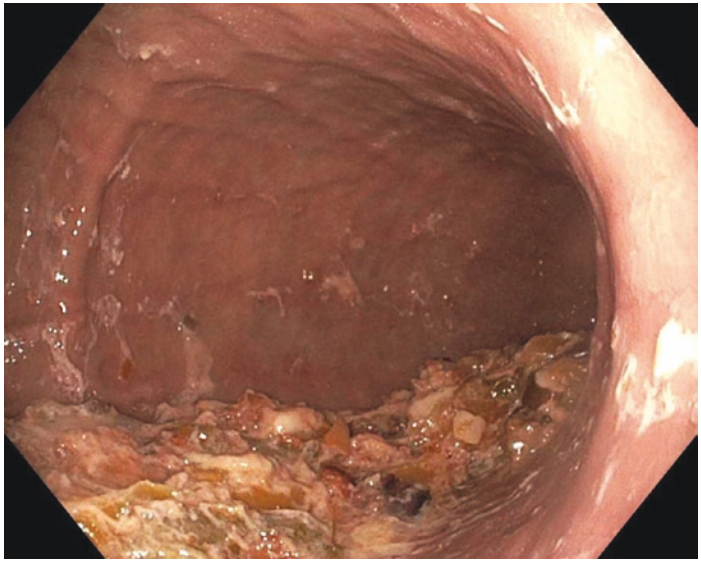

Figure 35.10 Large food Bezoar in the antrum and body of the stomach. Patient with no known history of gastroparesis

Postoperative Endoscopic Evaluation

It is recommended that EGD should be performed in bariatric patients that are potential candidates for preoperative surgery to detect abnormalities that may influence the choice of surgery or the development of postoperative symptoms and complications and to evaluate symptoms [3, 8].

Postoperative endoscopy is indicated for two main reasons: obesity persistence and/or complications of the index bariatric procedure.

Upper endoscopy provides useful information about the underlying anatomy and should ideally be performed by either a bariatric surgeon or an experienced gastroenterologist with extensive knowledge of bariatric surgery anatomy. In many instances, anatomic abnormalities or complications will determine if the patient is a candidate for a conversion, corrective, or reversal procedure [12]. The initial evaluation should focus on the review of previous imaging studies and operative records if available. The use of carbon dioxide insufflation may be useful due to its rapid absorption to prevent long-lasting distension of the GI tract.

The potential abnormalities/complications of bariatric surgery vary by procedure.

Sleeve Gastrectomy

Normal Findings

Endoscopy should reveal a normal non-dilated esophagus and gastroesophageal junction (GEJ) with no evidence of hiatal hernia. Upon entering the gastric sleeve, the endoscopist should first see a small or no neofundus (proximal dilation of the stomach) and a gastric tube of approximately under 2 cm wide (36–40 F). If retroflexion is possible, that indicates too much fundus was left at the time of the original operation and /or there is dilation of the sleeve (Fig. 35.11). The mucosal ridge from the healed staple line should be

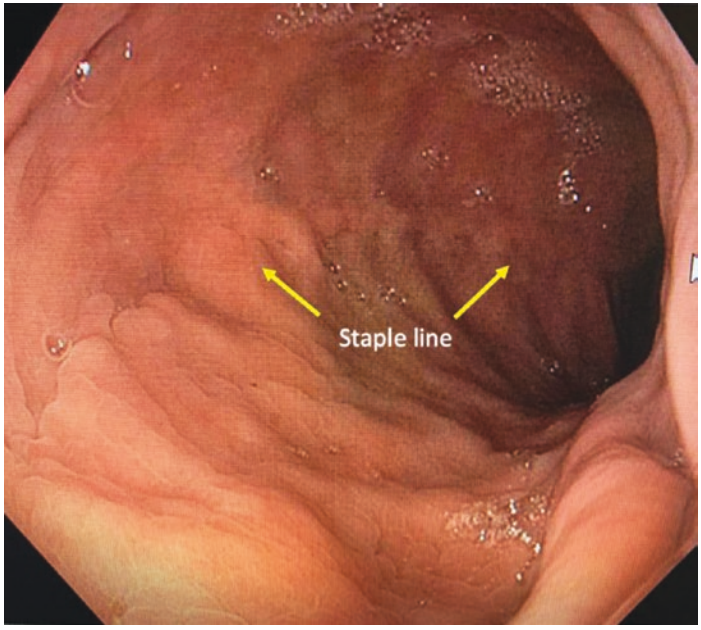

Figure 35.11 Normal endoscopic view of sleeve gastrectomy demonstrating healed staple line along the body of the stomach

straight with no twisting, and the endoscope should pass through the sleeve and into the antrum [13]. The pre-pyloric area is of variable size depending on the surgeon's preference (2–6 cm). If a duodenal switch is performed with the sleeve gastrectomy, a post-pyloric duodenal, ileal anastomosis should be visible distal to the pylorus [14].

Abnormal Findings

Severe GERD is the most common cause for revisional surgery after sleeve gastrectomy. Similarly, weight regain is another common reason for consultation. Patients can also suffer from sleeve dilation and strictures.

- Large neofundus/retained fundus: Large proximal dilation of the sleeve along with distal narrowing can frequently explain GERD symptoms as well as weight regain [13]. In this case, a large gastric pouch can be observed distal to the GEJ, extending to the left of the patient. Because of the proximal dilation, a pseudo-stoma/narrowing can be observed distal to the pouch. The gastroscope may be able to be retroflexed within the sleeve. (Fig. 35.12) The presence of a hiatal hernia is also not uncommon. (Fig. 35.13).
- Dilation of the gastric tube or stomach: Commonly an anatomic reason for weight regain due to the large gastric volume [13] (Fig. 35.14).

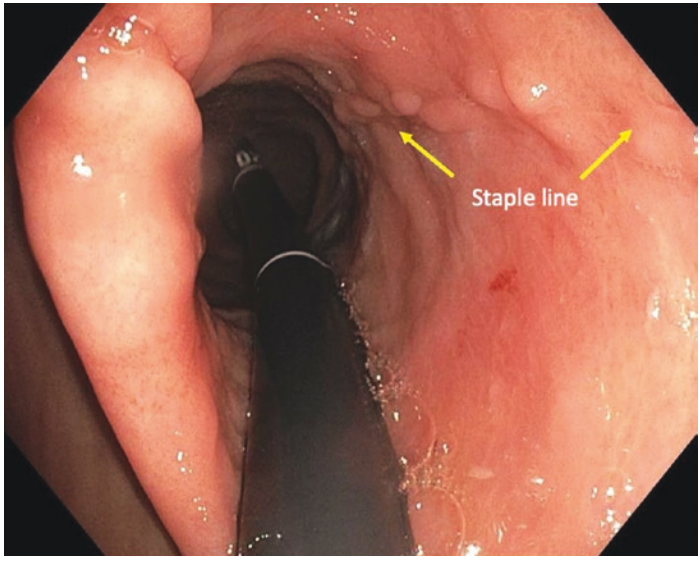

Figure 35.12 Dilated sleeve gastrectomy with neofundus, dilated gastric tube, and normal staple line (Retroflex view)

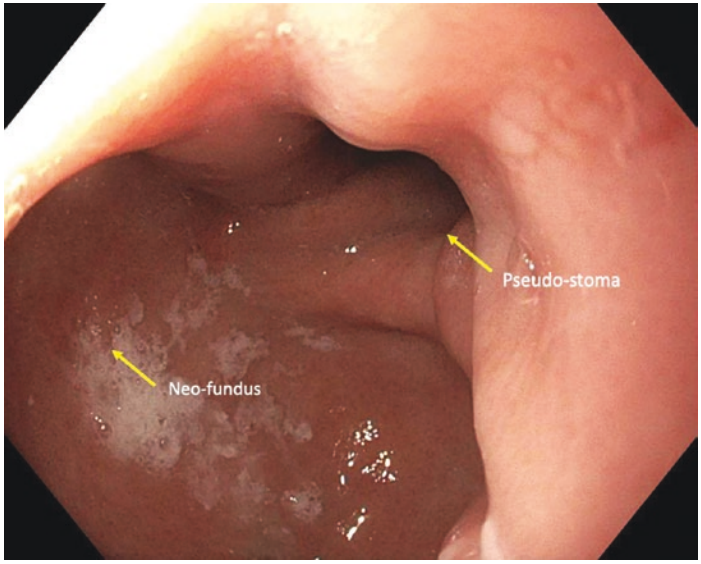

Figure 35.13 Abnormal endoscopic view of sleeve gastrectomy in a patient with severe GERD revealing a large neofundus and pseudo-stoma into the rest of the stomach

- Twisting of staple line/strictures: Patient presentation is similar to a gastric outlet obstruction with food intolerance, nausea, and vomiting. During the endoscopy, kinking or twisting of the distal portion of the sleeve can be observed. The most common site stricture is the incisura angularis [15]. (Figs. 35.15 and 35.16).

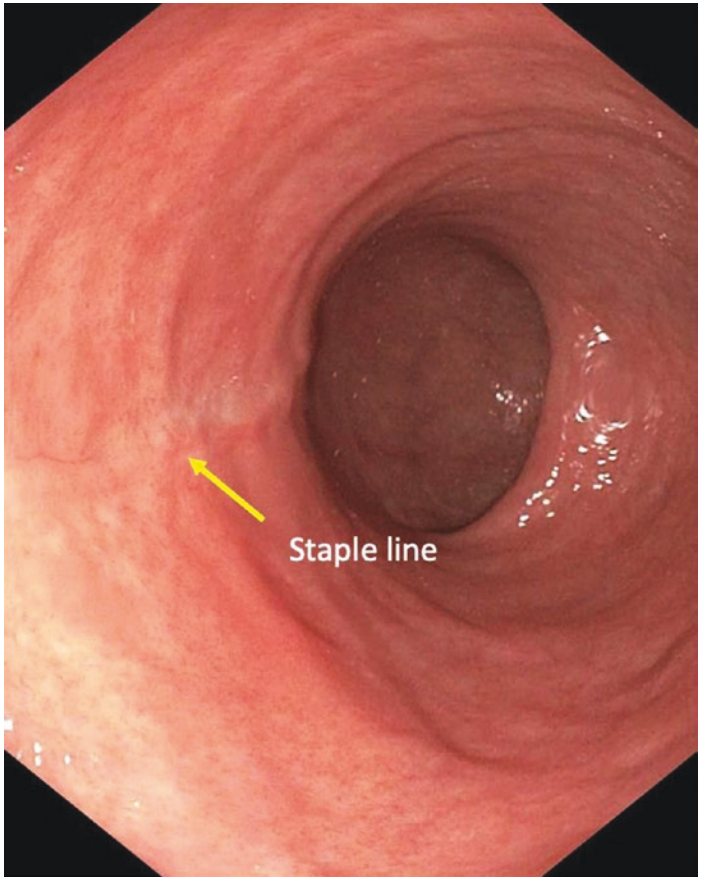

FIGURE 35.14 Endoscopic view of the dilated body of the stomach in sleeve gastrectomy patient with weight regain

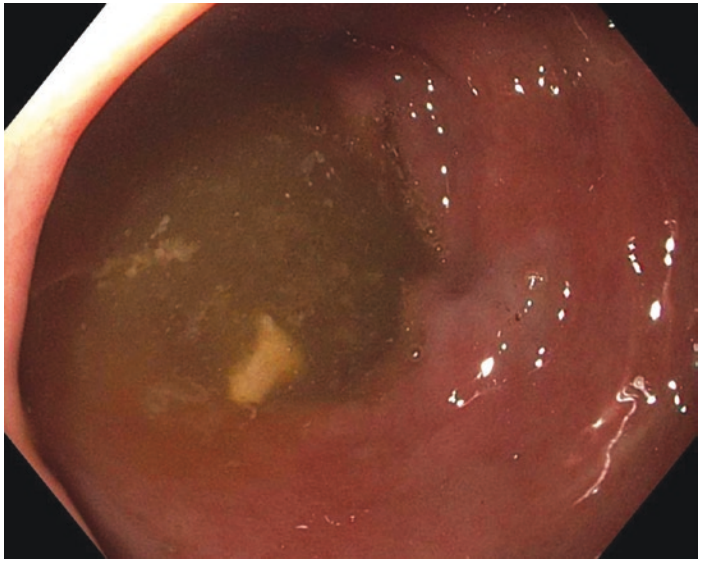

Figure 35.15 Endoscopic view of distal stricture in sleeve gastrectomy patient complaining of nausea and vomiting

Chronic Sleeve Fistula

A gastric leak after LSG can be considered chronic after 12 weeks. Chronic gastric fistula can progress to complex anatomical situations, such as esophagogastrobronchial and/or esophagogastro-pleural fistulas (GBPF), as well as gastro-cutaneous (GCF) or gastro-colic fistulas [16]. (Figs. 35.17 and 35.18).

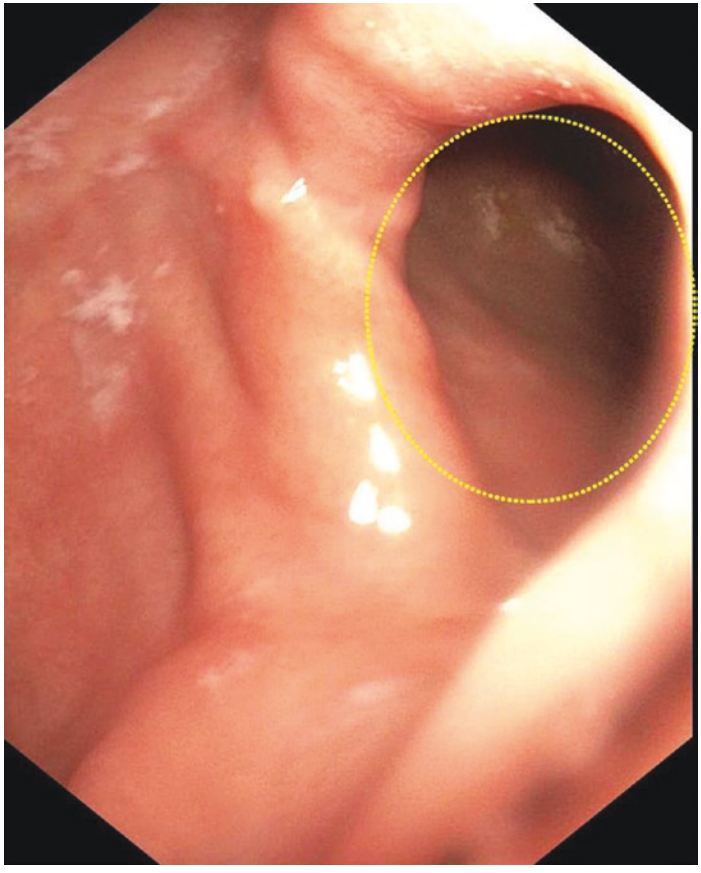

FIGURE 35.16 Endoscopic view of a distal stricture in sleeve gastrectomy patient

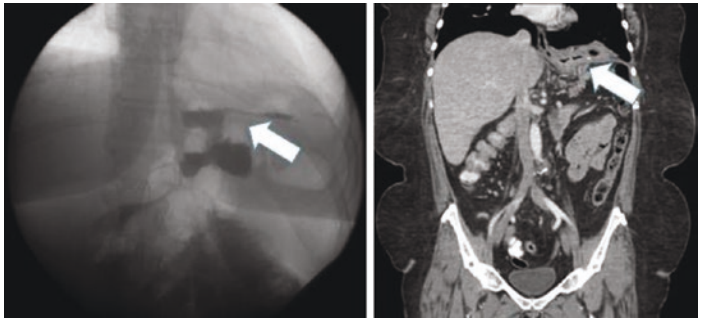

FIGURE 35.17 Barium swallow and CT scan (coronal view) demonstrating the presence of a gastro-pleural fistula 2 years post-sleeve gastrectomy

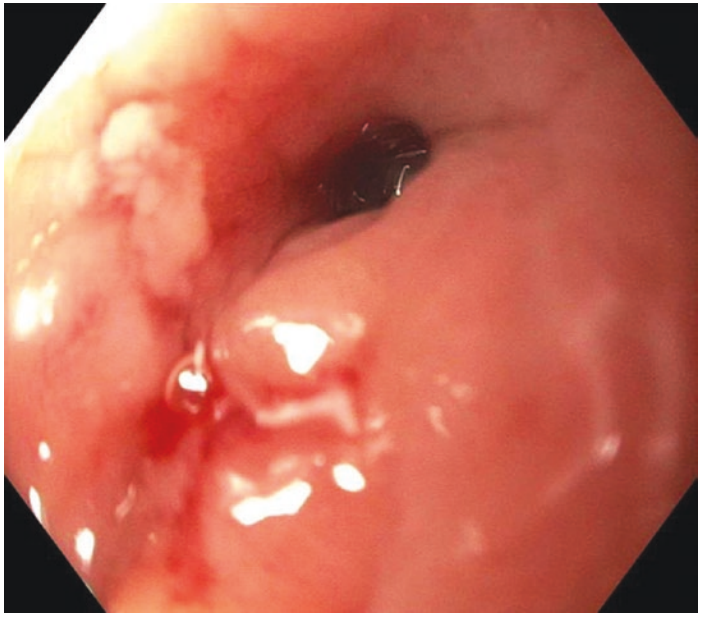

FIGURE 35.18 Endoscopic view of chronic fistula at the level of the angle of His, two years after sleeve gastrectomy. EGD demonstrates the presence of staples at the fistula orifice

Roux-en Y Gastric Bypass

Normal Findings

The endoscopy should first reveal the newly constructed gastric pouch with a healed staple line that appears as a mucosal ridge. The gastric pouch is typically about 3–5 cm in length. The gastrojejunal anastomosis should measure less than 20 mm in diameter and, once passed, should reveal a double-barrel view of the alimentary limb (Roux limb) and blind limb [13, 17] (Figs. 35.19 and 35.20). The relative positions of the limbs are dependent on the operating surgeon's preference. The endoscopist should assess the size (length/width) of the blind limb. The alimentary limb is of variable length (75–150 cm) with normal-appearing jejunal mucosa [13–17]. There may be bile present when approaching the jejunojejunal

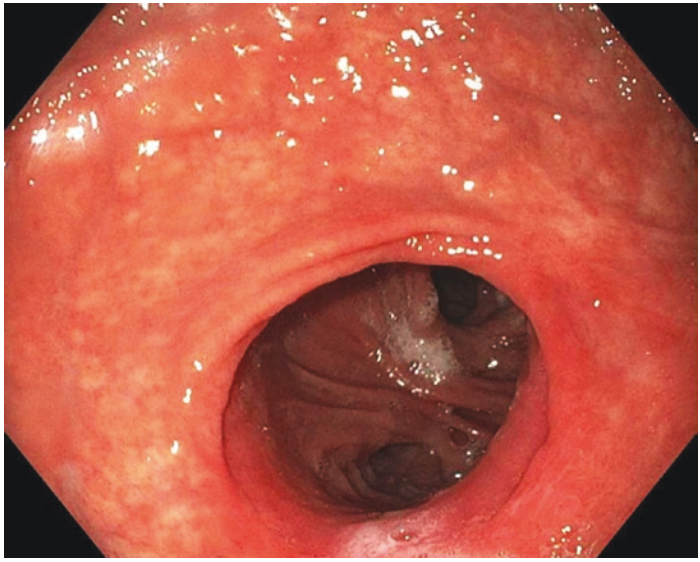

FIGURE 35.19 Normal endoscopic view of double-barrel anatomy in Roux-En-Y gastric bypass (this is not a normal view, this is a dilated gastro-jejunal anastomosis)

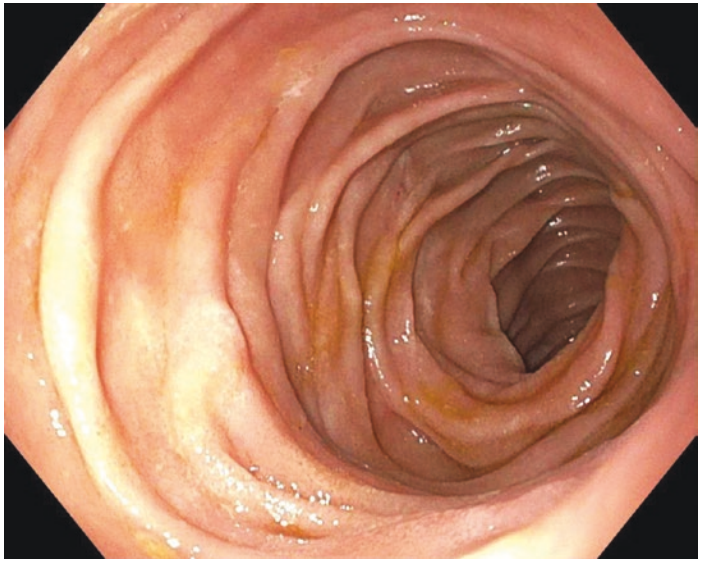

FIGURE 35.20 Normal endoscopic view of small bowel bypass with bile tinge

anastomosis. Standard gastroscope may not permit proper visualization of the jejunojejunal anastomosis and in this situation, an endoscopy or balloon enteroscopy may be required [13, 14]. These expected findings are dependent upon procedural variation and surgeon preference. As such, it is necessary for the endoscopist to collaborate with the bariatric surgeon and thoroughly review the operative notes.

Abnormal Findings

Marginal ulcer, bleeding, anastomotic stricture, dilated gastric pouch, and gastro-gastric fistula are some of the common complications seen after RYGB. In addition, patients may experience weight regain due to anatomic abnormalities.

- Dilation of the gastric pouch and/or gastro-jejunal anastomosis (GJA): Retroflexion within the pouch is an indicator

of the presence of a gastric pouch that is too long or too wide, or both (Figs. 35.21 and 35.22). A widened GJA is confirmed when its diameter exceeds 2 cm on the upper endoscopy [13] (Figs. 35.23, 35.24, 35.25, and 35.26).

- Gastro-gastric fistula (GGF): Gastro-gastric fistula between the gastric pouch and the remnant is a cause for weight regain and GERD. GGF can either happen due to technical error resulting from the incomplete division of the stomach during the creation of the pouch or chronic marginal ulcer perforation into the remnant stomach. Endoscopic identification of the fistula involves careful examination of the gastric pouch (including retroflection) and staple line. If not direct visualization, endoscopic examination under fluoroscopy may be needed or fluoroscopic exam alone [13] (Fig. 35.27).
- Marginal Ulcer: Patients usually present with epigastric pain, nausea, vomiting, dysphagia, and sometimes perforations [16]. Endoscopy is the procedure of choice for diag-

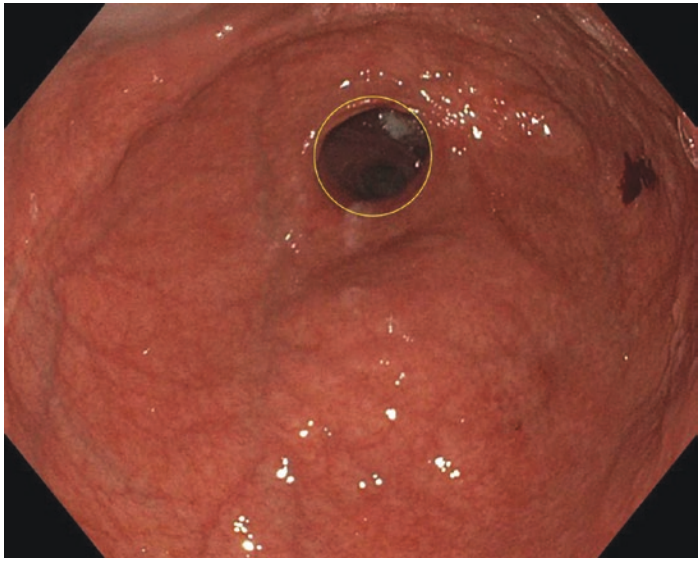

Figure 35.21 Dilation of the gastric pouch

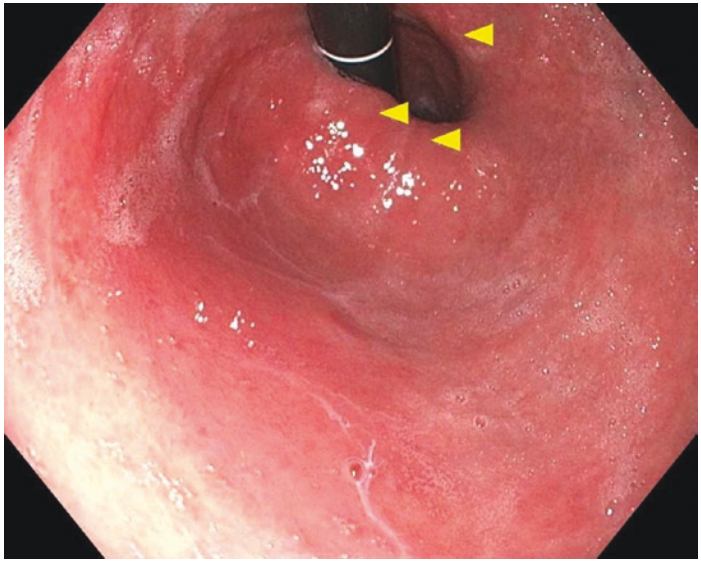

Figure 35.22 Dilation of the gastric pouch with hiatal hernia (retroflex view)

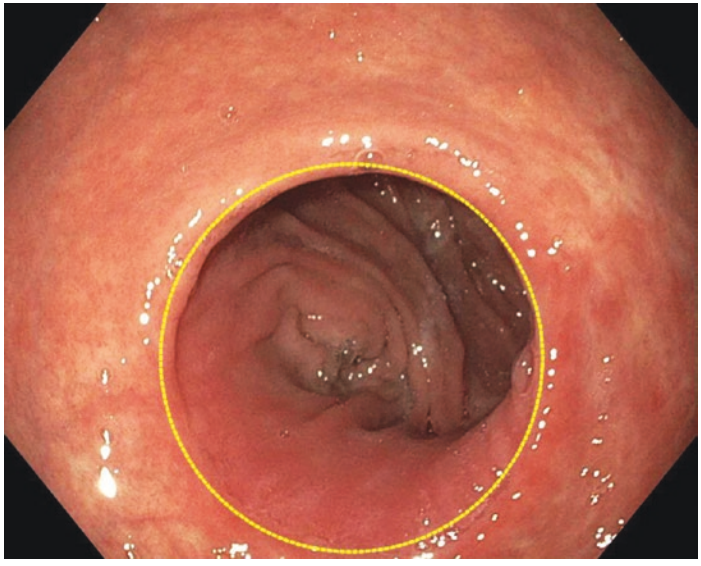

Figure 35.23 Dilated GJA

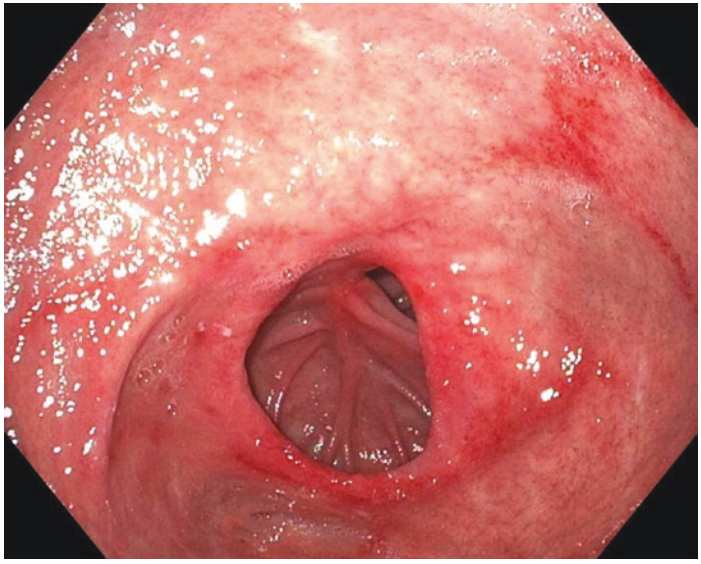

Figure 35.24 Dilated GJA

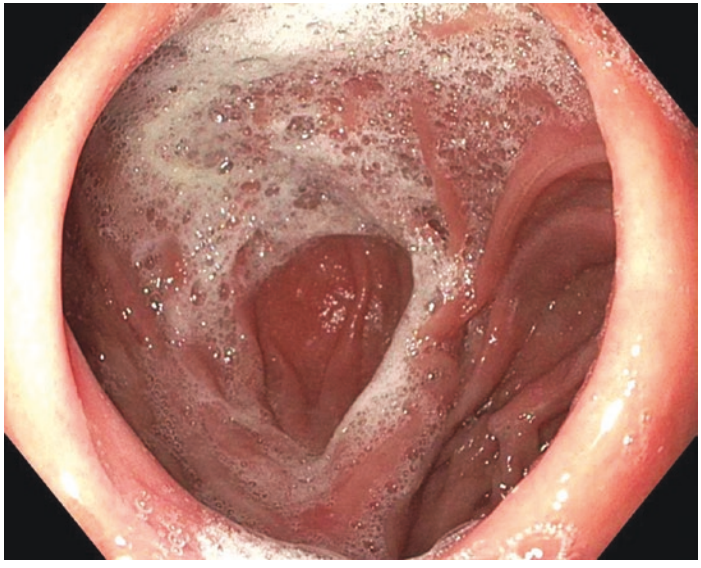

Figure 35.25 Dilated GJA with staples

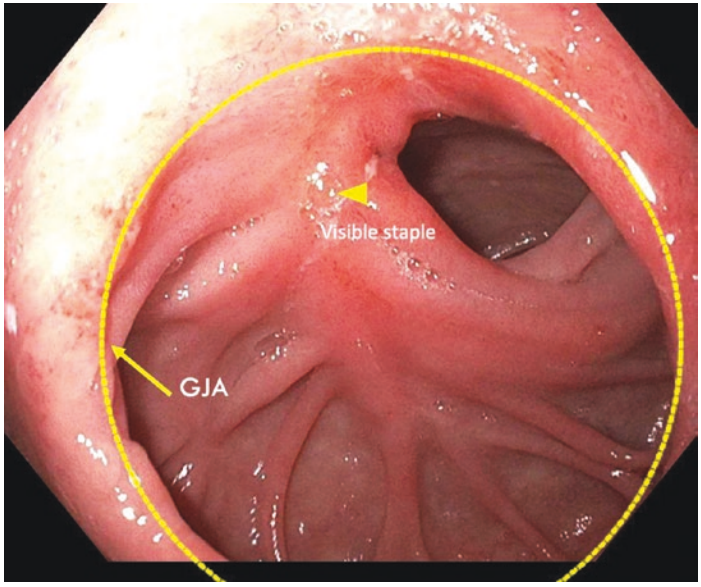

Figure 35.26 Dilated GJA with staples and double barrel anatomy

nosis. Typical endoscopic findings are mucosal erosions at the gastrojejunal anastomosis, typically on the jejunal side. During the endoscopy, biopsies should be taken to rule out H pylori [18]. Also, whenever possible, any foreign materials such as staples and non-absorbable sutures should be removed [19, 20] (Fig. 35.28).

- Anastomotic strictures: defined as the inability to pass a standard gastroscope through the GJA, suggesting a lumenal size of <10 mm (Figs. 35.29 and 35.30). The most common presenting symptom is dysphagia [17, 21]. Endoscopy is not only the mainstay for diagnosis but, in many cases, the main therapeutic alternative [22–27]. GJA strictures can be graded endoscopically and classified into four groups [28]: (Figs. 35.31 and 35.32).
  - Grade I: Mild stenosis, which will allow a 10.5-mm endoscope to pass;

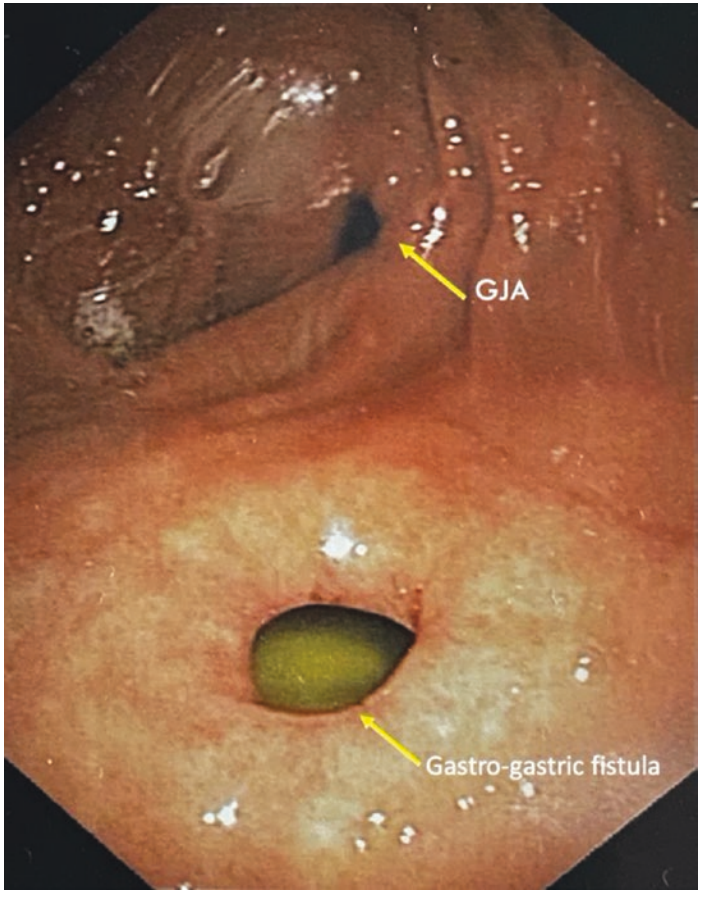

FIGURE 35.27 EGD showing gastro-gastric fistula

- Grade II: Moderate stenosis, which will accommodate an 8.5 mm pediatric endoscope;
- Grade III: Severe stenosis, through which a guide-wire can be passed;
- Grade IV: Complete/near-complete obstruction, which is non traversable.

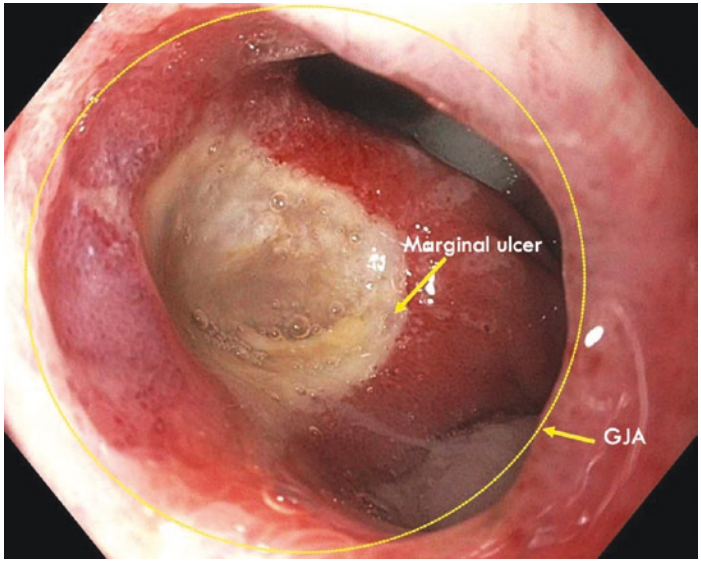

Figure 35.28 Marginal ulcer in gastric bypass patient

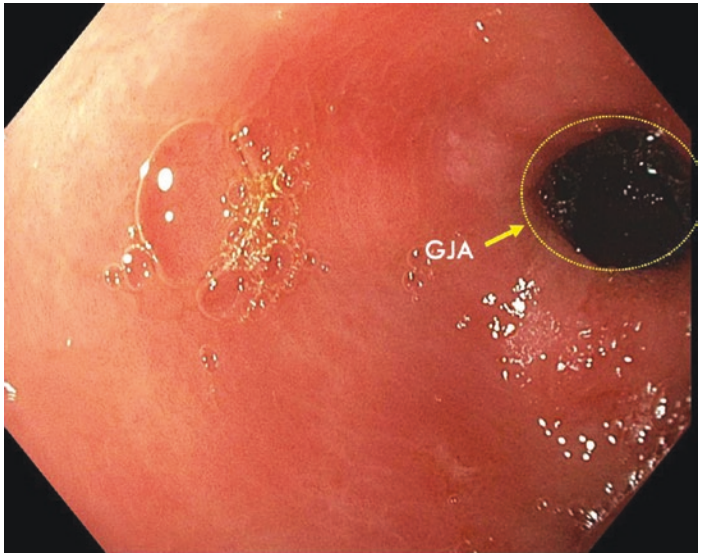

Figure 35.29 GJA stricture in gastric bypass patient

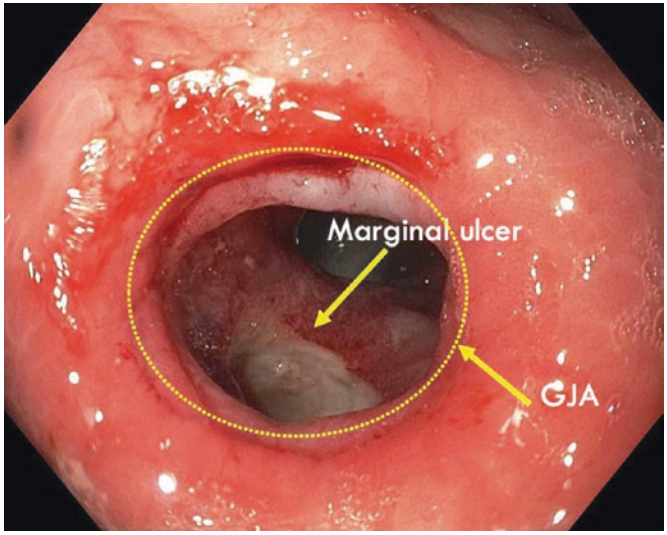

FIGURE 35.30 GJA stricture with a marginal ulcer in gastric bypass patient

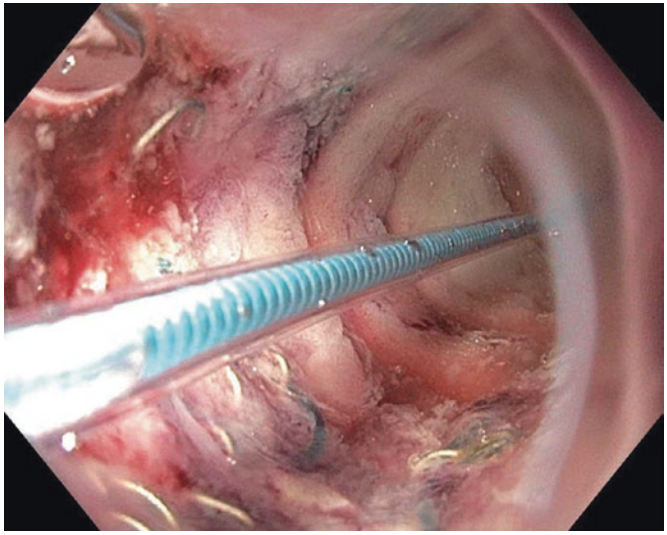

FIGURE 35.31 Endoscopic dilation of GJA stricture using a TTS balloon

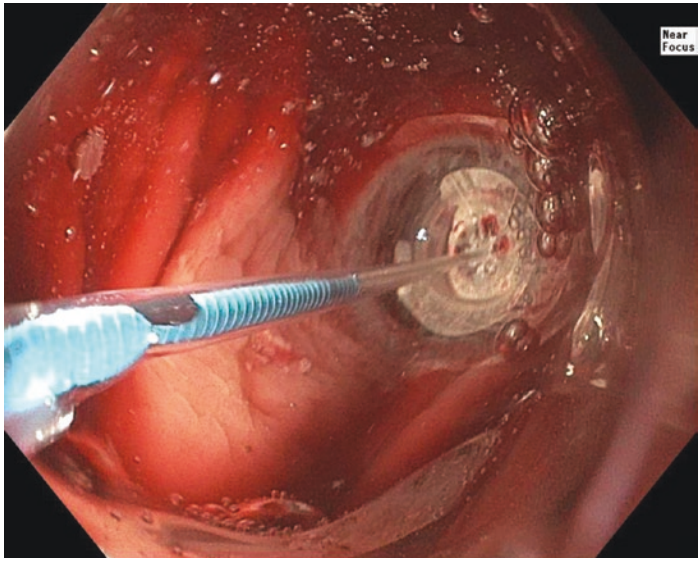

Figure 35.32 Endoscopic dilation of GJA stricture using a TTS balloon

A Laparoscopic Adjustable Gastric Band (LAGB)

Normal Findings

Endoscopy of postoperative adjustable gastric band patients should reveal a normal esophagus and gastroesophageal junction and not hiatal hernia. The gastric pouch should be approximately 2 cm in length and demonstrate a variable amount of circumferential compression based on the inflation status of the gastric band [13–15]. Whenever possible is recommended to deflate the band in preparation for upper endoscopy. After the gastric band is traversed, a retroflexed view can further assess the position of the band and any other abnormalities such as erosions. The rest of the upper GI tract should unaltered.

Abnormal Findings

Postoperative complications after LAGB are band slippage, pouch enlargement, erosion, stenosis, band intolerance, esophageal dilation, and severe GERD. It is worth mentioning that many of these complications can be diagnosed and treated with fluoroscopy.

- Band slippage/prolapse: involves migration of the band from its original position, causing prolapse of the stomach above the band. It is usually diagnosed with contrast fluoroscopy. Endoscopy should be performed after deflation of the band. On endoscopy, a large gastric pouch is visualized above the band, sometimes with significant erythema and edema [29] (Fig. 35.33).

Band Erosion

This is an uncommon but serious complication of LAGB. Port site infection, loss of restriction, and weight regain are the

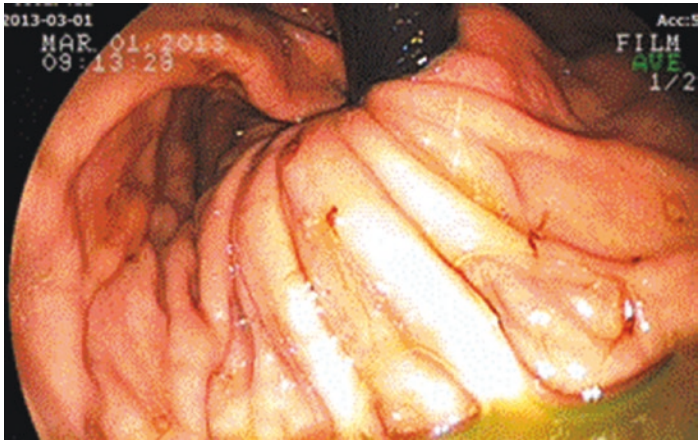

FIGURE 35.33 Gastric band prolapse ©2016 Kang SH (Kang SH, Yoo JS (2016) Gastric plication for repeated gastric band prolapse after endoscopic treatment: A case report. Glob Surg, Volume 2(4): DOI: https://doi.org/10.15761/GOS.1000143)

most common symptoms. Endoscopic evaluation of patients that present with symptoms is warranted [18]. An upper endoscopy can be diagnostic and therapeutic. Deflation of the band is recommended. Most frequently, band erosion is diagnosed on retroflex view after traversing the band. In selected patients' endoscopic removal is possible [21]. The greater the degree of erosion that is present, the more likely the success of endoscopic removal (Fig. 35.34).

- Esophageal dilation: Patients usually present with GERD and dysphagia. A barium swallow is commonly diagnostic.

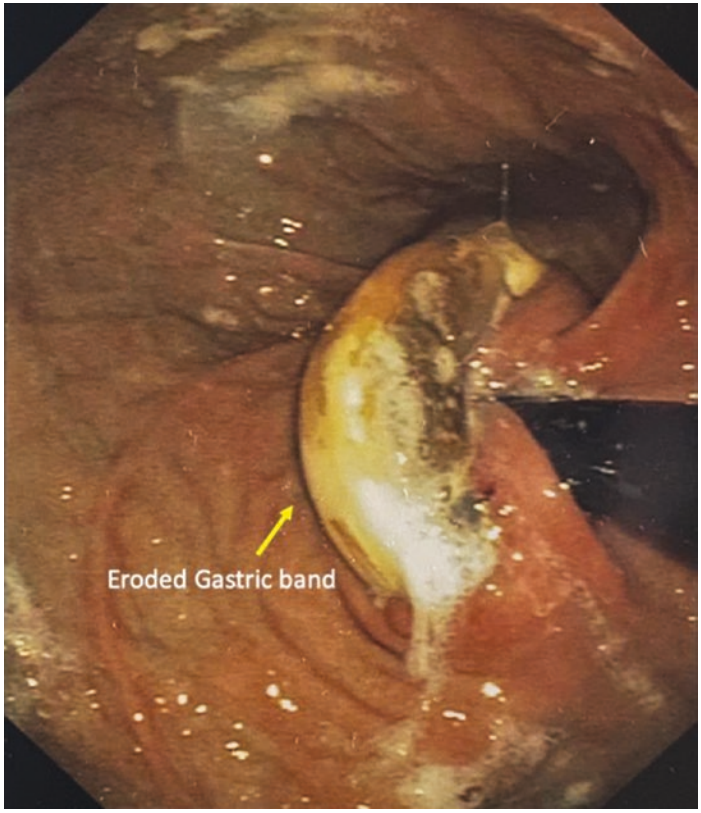

FIGURE 35.34 Retroflexed view of the stomach showing band erosion. Approximately 50% of the circumference of the band is exposed

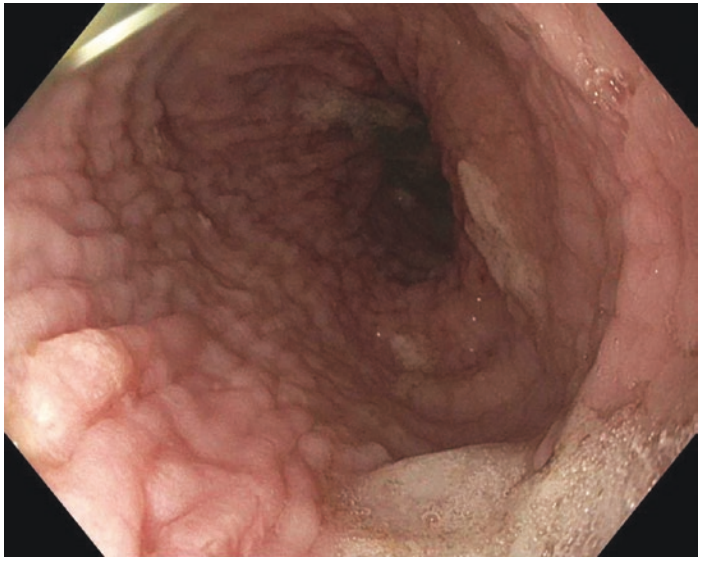

FIGURE 35.35 Endoscopic view of dilated distal esophagus/pseudo-achalasia post-LAGB

However, endoscopic evaluation is required to rule out the presence of severe esophagitis, slippage, erosions, etc. Usually, upper endoscopy demonstrates the presence of a dilated proximal and distal esophagus depending on the duration of the condition with pooling of secretions. It is not uncommon to find severe esophagitis from food stasis (Fig. 35.35).

Biliopancreatic Diversion with Duodenal Switch (Single Vs. Two Anastomosis)

Normal Findings

This operation entails a gastric sleeve that is usually performed over a larger size bougie 40 Fr or larger and the creation of a duodeno-ileostomy (DI) just distal to the pylorus with or without Roux-en Y reconstruction (Single anastomo-

sis duodeno-ileal bypass with sleeve gastrectomy) [13]. Similar to a primary sleeve, endoscopy reveals a narrow gastric tube with a preserved pylorus and either an end-to-side DI or a loop anastomosis. A double-barrel configuration can also be observed, similar to gastric bypass.

Abnormal Findings

Late complications (>30 days) are similar to sleeve gastrectomy, such as large neofundus/retained fundus, dilation of the gastric tube or stomach anastomotic leak, and twisting of staple line/strictures and were already described. Other complications could involve commonly involve small bowel obstruction and malnutrition. Gastrointestinal side effects include flatulence, malodorous stools, and steatorrhea, as well as dumping syndrome, bacterial overgrowth, malnutrition, iron deficiency, protein-calorie malnutrition, hypocalcemia, and deficiency of fat-soluble vitamins, vitamin B1, vitamin B12, and folate.

Endoscopic examination is limited to the sleeved stomach, the first portion of the duodenum, and the ileum. The mucosal ridge from the staple line of the sleeved stomach can be examined during the endoscopic examination. Once the pylorus is passed, careful inspection of the DI anastomosis can reveal abnormalities such as strictures. The mucosa of the ileum can also be examined as well as the blind loop.

Vertical Banded Gastroplasty

Normal Findings

In this procedure, the upper stomach near the esophagus is stapled vertically to create a small pouch along the lesser curvature of the stomach. The outlet from the pouch to the rest of the stomach is restricted by a non-adjustable band.

Postoperative endoscopy of a vertical banded gastroplasty patient should first reveal a normal gastroesophageal junction. There is 10–12 mm diameter banded stoma at the distal end of the vertically oriented pouch along the lesser curvature of the stomach, approximately 70–80 mm from the gastroesophageal junction. Under normal conditions, the gastric pouch should have a left lateral staple line and single lumen, which may have restricted access due to swelling. Once the lumen is traversed, the unaltered distal stomach and duodenum can be assessed. Endoscopic retroflection should reveal the gastric partition with a normal fundus of the stomach, greater curvature, and antrum (Figs. 35.36 and 35.37).

Abnormal Findings

The vertical banded gastroplasty (VBG) procedure is no longer performed in the US. However, thousands of procedures were performed, and the need for revisional surgery following VBG has ranged from 21% to 56%, with approximately 46% of pre-operative diagnoses being food intolerance. Complications that are associated with VBG include stomal stenosis, staple line disruption, pouch dilation, erosion of the band, and gastroesophageal reflux.

- Stomal stenosis/Pouch dilation: stomal stenosis is usually secondary to a tight ring or mesh. During EGD, a large, dilated pouch with an intact lateral staple line was seen, which correlated with the patient's frequent vomiting and severe GERD symptoms (Fig. 35.38). Inability to pass a standard gastroscope through the outlet/stoma is greatly diminished in these patients. The area of the lateral vertical staple line is typically intact in these patients. If the gastroscope is able to transverse the stoma, the remaining of the upper GI tract is unchanged. Endoscopic dilation of stomal stenosis via through-the-scope balloon (TTS) or wire-

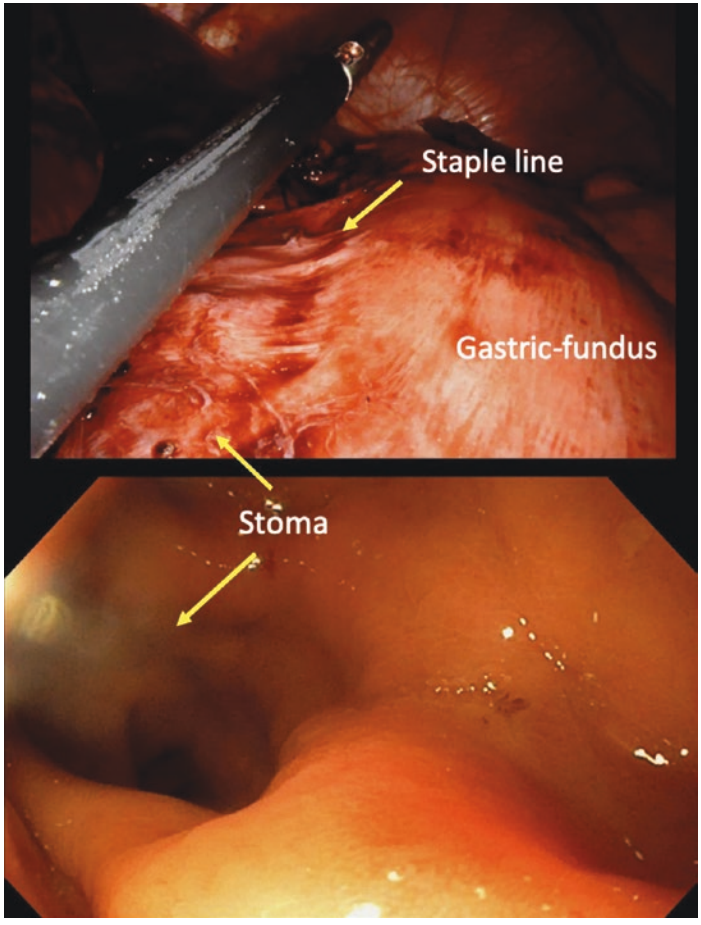

Figure 35.36 Normal vertical banded gastroplasty VBG anatomy (Intraoperative and endoscopic view)

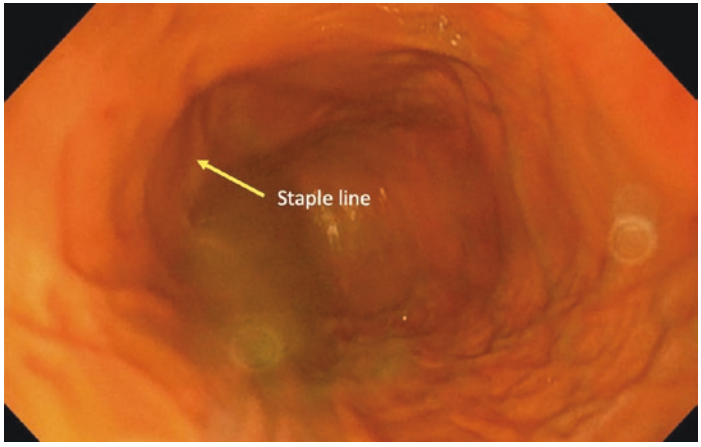

FIGURE 35.37 Gastric fundus following vertical banded gastroplasty

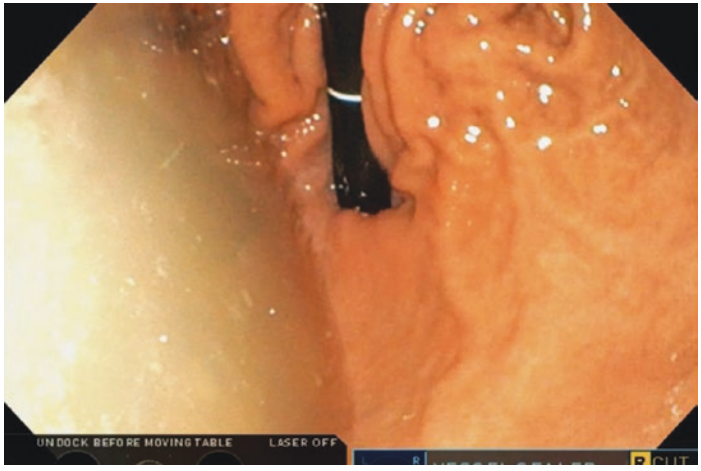

FIGURE 35.38 Dilated gastric pouch following vertical banded gastroplasty with partial obstruction of the stoma (retroflex view)

guided bougie dilation is usually not effective due to the presence of a silastic ring or mesh, which represents an extrinsic compression.

- Staple line disruption: A change of eating habits causing weight to regain could indicate staple line disruption. Typically, upper endoscopy performed in these patients could reveal the presence of fistula/s between the gastric pouch and the gastric fundus along lateral vertical staple line with a normal size pouch (Fig. 35.39).
- Band Erosion: Usually presents with nausea/vomiting, regurgitation, epigastric pain, and dysphagia. However, it could also present with weight regain due to lack of restriction. Band erosion is best diagnosed endoscopically. Upper endoscopy demonstrated the foreign body inside the stomach. Eroded gastric bands can potentially be removed endoscopically (Fig. 35.40).

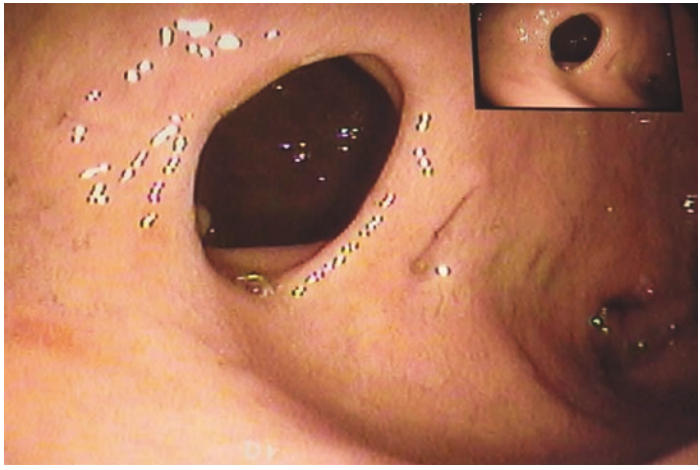

FIGURE 35.39 Endoscopic view of the gastro-gastric fistula on the staple line of 15 mm and 20 mm with normal pouch. © 2012 Fedoua Rouibaa, M. Surace, Marc Barthet et al

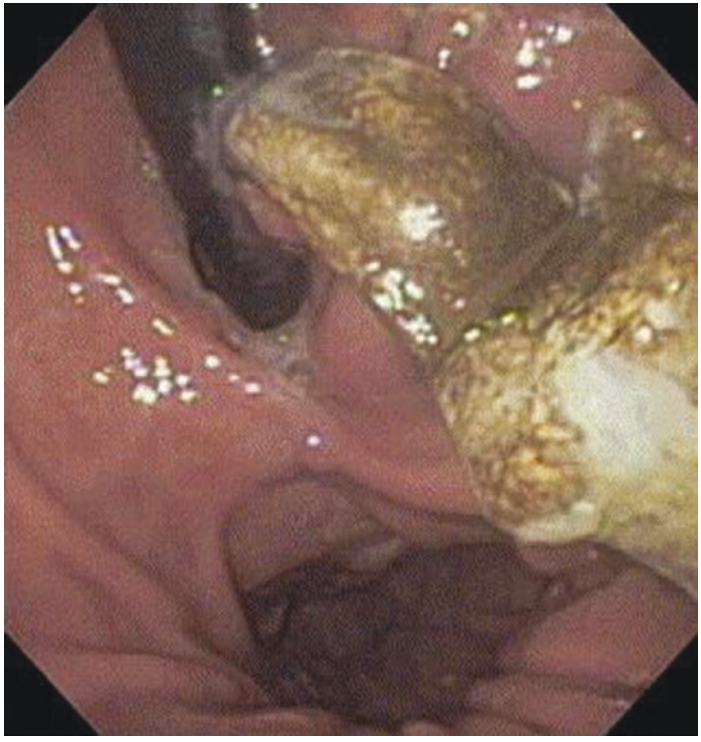

FIGURE 35.40 Eroded band is best visualized in a retroflexed view

Conclusions

The value of a screening endoscopy before bariatric surgery in asymptomatic patients remains a topic of debate. Frequent indications for upper endoscopy in the postoperative bariatric patient (>30 days) include the evaluation of symptoms, the management of complications, and the evaluation of weight regain.

Nonetheless, upper endoscopy plays a critical role in the diagnosis and sometimes treatment of post-bariatric surgery patients. For that reason, endoscopists and surgeons should

be accustomed to the normal surgical anatomy and its potential alterations. Importantly, upper endoscopy can help the surgeon to determine the most appropriate procedure for the patient.

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Chapter 36
Intragastric Balloon Therapy

Marina Kurian and Loic Tchokouani

Obesity has been recognized as an increasing worldwide pandemic with numerous health consequences if gone untreated. It has been linked with cardiovascular disease, neoplasms, pulmonary disease, and even infertility. Thus, multiple weight loss modalities have been explored, including lifestyle modification, medical treatment, surgical options, and, more recently, endoscopic options. Many patients categorized as obese (BMI >30) do not qualify for the proven and sustained weight loss provided by surgical therapy, although weight loss in these patients confers a health benefit. Even of those who do qualify, only 1–2% of these patients go through surgical therapy due to the perception that surgery is too risky [1]. Also, there is a subset of patients undergoing surgical therapy, which carries an overwhelming risk of perioperative events. These patients are still in need of weight loss. Herein lies an opportunity for other modalities of weight loss interventions, including space-occupying intragastric balloons (IGBs). IGBs

M. Kurian (✉) · L. Tchokouani
NYU Langone Grossman School of Medicine, New York, NY, USA
e-mail: Marina.kurian@nyulangone.org; Loic.Tchokouani@nyulangone.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_36

can be adjuncts to lifestyle modification for those that do not qualify for surgical intervention, alternatives to those who do qualify or do not prefer surgery, or be a bridge to reduce the risk for eventual weight loss surgery.

The concept of a space-occupying intragastric balloon therapy for obesity originated in 1982 after recognizing the natural weight loss effects of bezoars by Nieben [2]. In 1985, the United States Food and Drug Administration (FDA) approved the Garren-Edwards Gastric Bubble to treat obesity. The balloon was placed in the stomach, filled with 220 cm^3 of air, left in the stomach for 3–4 months, and then removed. Subsequent randomized control trials did not show significant weight loss compared to diet and lifestyle modification. Also, complications including migrations, erosions, and bowel obstructions were encountered, and the device was taken off the market in 1992. Concurrently in Europe, two additional IGBs were developed in the 1980s (The Taylor Balloon and Ballobes Bubble) with subsequent models in the following decades (see Fig. 36.1 bazerbachi) [3] for all available world market IGBs that became popularized worldwide.

There are currently four intragastric balloons approved by the USA (FDA) for adults with body mass index (BMI) from 30 to 35 kg/m^2 and one or more obesity-associated comorbid conditions. To qualify for IGB therapy, these patients must have failed weight loss through lifestyle or pharmacologic interventions. In Europe, however, IGB use is more broadly approved for patients with BMI $\geq$ 27 kg/m^2. These indications allow for treatment for patients who may not otherwise be eligible for bariatric surgery but still benefit from early intervention. These currently approved balloons include the Orbera Balloon, Reshape Duo Balloon, the Obalon balloon, and the Transpyloric Shuttle. The Reshape Duo device was acquired by Apollo Endosurgery—manufacturers of the Orbera balloon—and limited its utilization. The Obalon balloon is not currently being manufactured. Newly FDA approved is the Spatz balloons. The Elipse Balloon is yet to be FDA approved.

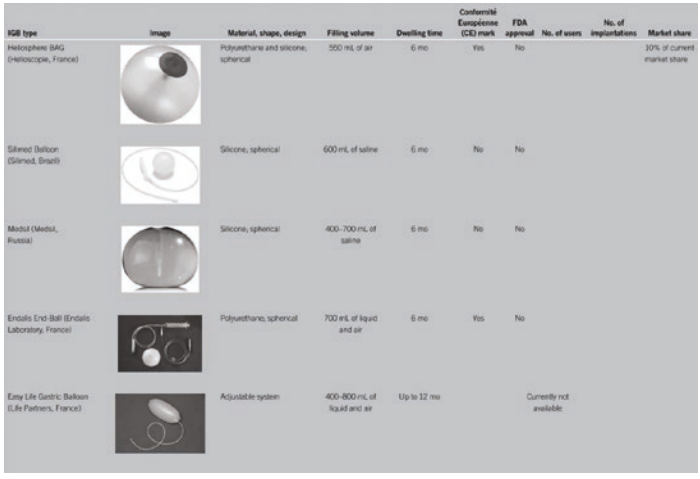

FIGURE 36.1 International Intragastric Balloon Characteristics. (Reused from Bazerbachi F, Vargas EJ, Abu Dayyeh BK. Endoscopic Bariatric Therapy: A Guide to the Intragastric Balloon. *Am J Gastroenterol*. 2019;114(9):1421-1431. doi:10.14309/ajg.0000000000000239)

The Orbera Intragastric Balloon System, formerly known as the BioEnterics Intragastric Balloon, is a single silicone balloon that can be filled with saline (400–700 mL). The balloon is placed and removed via endoscopy after being left in place for 6 months. It was studied comprehensively worldwide in over 220,000 patients before its approval in the USA [4] with its approval coming after a multicenter, prospective randomized comparative study in 2015 showed a total body weight loss (TBWL) of 10.2% vs. a control of 3.3% [5]. Of note, studies performed outside the US showed larger amounts of weight loss. A large meta-analysis by the American Society for Gastrointestinal Endoscopy (ASGE) Bariatric Endoscopy Taskforce demonstrated a sustained TBWL of 12.3%, 13.16%, and 11.27% at 3, 6, and 12 months after placement [6].

The Reshape-Duo is also an endoscopically placed device made up of two balloons, each filled with 450 mL of saline. It is left in place for 6 months. It was the first device to meet its primary efficacy endpoints. Its 2015 pivotal REDUCE trial, a multicenter, blinded, sham-controlled trial, was able to show a 7.6% TWBL compared with 3.6% in the control group [7]. In a device asset swap in 2018, Apollo Endosurgery acquired the Reshape Duo Balloon and shelved its manufacturing, essentially halting its use.

The Obalon balloon differs from the first two IGBs in that it does not require endoscopic placement and is gas-filled rather than liquid-filled. The patient swallows a capsule containing the deflated balloon and catheter, and the balloon is subsequently filled with 250 mL of nitrogen mix gas once it is in the stomach. Up to three balloons can be inserted over 8–12-week period and subsequently removed at 6 months. An initial feasibility study showed a TBWL of 5.9% after 12 weeks [8]. The SMART Trial, a randomized trial, demonstrated a 6.6% TBWL compared to 3.4% of the control [9]. Of note, the Obalon Touch Inflation system, which eliminates a necessary confirmatory radiograph, was approved after these studies were conducted. Endoscopy is required for its removal. At this time, the Obalon is not available due to production issues.

The newest IGB FDA approved device is the Transpyloric Shuttle. It is the only IGB approved for up to 12 months of treatment, twice as long as the other IGBs. It is unique in that not only is it a space-occupying device, but it also causes intermittent gastric outlet obstruction by occluding the pylorus using a large bulb connected to a smaller bulb by a flexible silicone tether. The larger bulb remains in the stomach while the small bulb can remain in the stomach or travel through the pylorus into the duodenum and delay gastric emptying. The ENDObesity II study showed a 9.5% TBWL compared to the 2.8% among the control group [10].

The Spatz Balloon has been FDA approved: The Spatz Balloon is the first and only adjustable silicone intragastric balloon. It intends to offer adjustments in fill volume to

improve ongoing weight loss when patients experience a plateau. Furthermore, the ability to reduce the volume in the balloon may aid with intolerance of the balloon in the early period after placement. The adjustment in the balloon volume has been shown to improve weight loss in a recent study [11].

The Ellipse is currently being reviewed by the FDA. The Elipse balloon system is similar to the Obalon IGB in that it is a swallowable, fluid-filled balloon that does not require endoscopy for placement. The novelty of this device, however, is that it self-deflates using a release valve and is naturally expelled through the gastrointestinal tract after approximately 16 weeks and does not require endoscopic removal.

Placement and Removal

Placement of an IGB should be performed in at least an outpatient endoscopy center with advanced life support capability and the ability to administer conscious sedation. Airway protection is only needed if deeper forms of sedation are used in conjunction with anesthesia support. Before and during placement of the balloon, an EGD should be performed to evaluate the esophagus, stomach, and duodenum and monitor the location of the balloon with inflation and after release. A good quality preplacement EGD is mandatory and may alter therapeutic plans based on findings as approximately 1% of procedures are aborted because of pathology or anatomy concerns [12]. For balloon removal, it is recommended that patients be on a liquid diet for at least two days prior, followed by a 12-h fasting period due to the expected IGB-induced gastric emptying delay. Removal should be performed in an outpatient endoscopy center with advanced life support and the ability to administer monitored anesthesia care. Aspiration precautions during IGB removal should be observed (left decubitus positioning of the patient with an elevation of the head of the bed).

Anesthesia support for IGB removal with endotracheal intubation to prevent aspiration should be used in select patients. For example, those with clinical suspicion of dietary noncompliance, with continued symptoms of severe delayed gastric emptying, or when a substantial amount of food is found in the stomach during the removal procedure [3].

Absolute contraindications to IGB therapy include previous gastric or esophageal surgery [3], coagulation disorders, a known bleeding lesion in the upper gastrointestinal tract, current pregnancy or plans to become pregnant, alcoholism or drug addiction, severe liver disease, and any contraindications to endoscopy. Relative contraindications include previous abdominal surgery, a large hiatal hernia, inflammatory bowel disease, chronic NSAID use, and uncontrolled psychiatric disorders.

Intragastric balloons are able to induce weight loss via restrictive and slowed gastric emptying mechanisms. Once the balloons are filled, the space-occupying nature of the device mimics the feeling of satiety and satiation, thus leading to weight loss. A study revealed an association between delays in gastric emptying and positive weight loss, specifically in the Orbera intragastric balloon [13]. There are conflicting studies on the hormonal effects, in particular grehlin, and their role in weight loss with IGBs. One study showed weight loss with no effect on ghrelin levels [14], another with decreased ghrelin levels with concordant weight loss [15], and yet another showed increased levels of grehlin [16], corresponding with negative energy balance seen historically. The efficacy of these devices is coupled to traditional and supervised dietary and exercise counseling. In order for weight loss to be significant or sustained, the patient must concurrently incorporate the necessary lifestyle changes, ideally as part of a medical and surgical weight loss center.

Despite good results obtained by some patients, IGBs are not without adverse events. A large portion of patients experiences nausea, vomiting, abdominal pain, burping, reflux, and constipation after placement, secondary to gastric accom-

modation of the device. These symptoms are expected and are usually self-limited; however, approximately 4–7% of patients have persistent symptoms past ten days. This led to an early removal rate of 7% and 9% for the Orbera and Reshape Balloons, respectively [6]. Other serious adverse events include bleeding gastric ulceration and perforation, gastric outlet obstruction, and small bowel obstruction from ruptured balloons [17].

The FDA has issued updates in 2017, 2018, and 2020 on safety profiles of the balloons due to observed deaths and complications from the therapy. The 2017 update communicated the potential risk of hyperinflation and acute pancreatitis with fluid-filled IGBs and later addressed the potential risk of death in the same year and in 2018. The most recent update in 2020 provided an update on the potential risks of spontaneous hyperinflation and acute pancreatitis following balloon therapy. From the Orbera post-approval study, the balloon hyperinflation rate was 2.3% and 83% of those were symptomatic. Of all the reported hyperinflation cases worldwide, 99% of them are attributable to the Orbera balloon.

The exact pathophysiology is unknown in terms of the risk of acute pancreatitis during the use of IGBs. Proposed mechanisms include pressure from the balloon and distended stomach causing direct injury to pancreatic parenchyma, compression of the pancreatic duct, and indirect injury through a duodenal obstruction. The Orbera balloon had no cases of pancreatitis in the post-approval study; however, the Reshape duo had a 1.3% rate. Worldwide, 67% of reports were attributable to the Orbera balloon. There were no deaths reported in the Orbera and Reshape post-approval studies. However, neither study was powered to detect rare events such as death. Since their approvals, the FDA has received 18 total deaths, 8 of them in the US (5 with Orbera and 3 with Reshape). The deaths were from gastric perforation, esophageal perforation, pulmonary embolism, and unanticipated death [18].

Conclusion

IGBs, with proper patient selection, coaching, and follow-up can attain weight loss that is beneficial to the patient. Their low mortality rate, adaptability with other weight loss regimens, and wider inclusion criteria allow them to fill a void for a specific subset of overweight and obese patients. Continued long-term studies need to be completed for effects and risks as well as safety for the newer balloons yet to be approved.

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Chapter 37
Endoscopic Liners (Duodenojejunal Bypass Liner, Gastroduodenojejunal Bypass Sleeve)

Keith S. Gersin

Introduction

Obesity defined as BMI > 30 kg/m2 affects 42.4% of the United States population (2017–2018 data) [1] and type 2 diabetes mellitus (T2DM) affects 462 million individuals or 6.28% of the population worldwide (2017 data) [2]. Type 2 diabetes and obesity, sometimes called "diabesity," is a global health problem. Nearly a third of all obese people have type 2 diabetes and nearly half of all people with type 2 diabetes are obese: the connection between the two is undisputed [3].

Reduction in body weight has been demonstrated to improve or cure T2DM, cardiovascular risk factors, reduction in comorbidities and decreases in many types of cancers [4]. It is therefore paramount that weight loss and weight maintenance be an integral portion of a healthy lifestyle. Lifestyle intervention and pharmacological intervention produce weight loss of only 10% below baseline [5] and therefore a strong need exists to find solutions that work in concert with lifestyle intervention and medical management to achieve target outcomes [6].

K. S. Gersin (✉)
Atrium Health, Charlotte, NC, USA

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_37

Bariatric surgery may be an option for this subset of patients, however, may be associated with the potential for operative and post-operative complications and death. Many patients have concerns about these risks and this likely contributes to the statistic of fewer than 1% of those eligible for bariatric surgery actually undergoing these procedures.

There is thus a role for a reversible, endoscopic therapy that contributes to weight loss and improvements in T2DM that may be more effective than diets and medications and less invasive than surgery. The EndoBarrier Gastrointestinal Liner System is a single use, sterile, prepackaged intestinal liner and anchor that is delivered and removed endoscopically. The liner provides in essence a duodenal and proximal jejunal bypass.

Implantation/Retrieval

The EndoBarrier is a fluoropolymer, impermeable intestinal liner with an integrated self-expanding nitinol anchor system. The EndoBarrier is meant for a maximum implant period of 12 months. Prior to delivery, the anchor and liner are packaged within the EndoBarrier capsule, which is affixed to a custom co-axial delivery system.

The liner is imbedded with a proximal radiopaque marker. The anchoring system contains two drawstrings for device retrieval. The capsule is endoscopically delivered into the duodenal bulb. Delivery distal to the pylorus helps prevent the self-expanding anchor from crossing the pyloric muscle, which can result in twisting or migration of the anchor. The anchor is therefore delivered as distal into the duodenal bulb as possible. An atraumatic ball at the distal end of the catheter aids in tracking through the intestine which is performed under continuous dynamic fluoroscopy. See Fig. 37.1.

Once the liner has been completely delivered, as evidenced by the proximal radiopaque marker exiting the capsule, the atraumatic ball is released to pass through the gastrointestinal tract. The anchor is then deployed within the duodenal bulb and continuous dynamic fluoroscopy confirms complete deployment. There are bidirectional barbs located

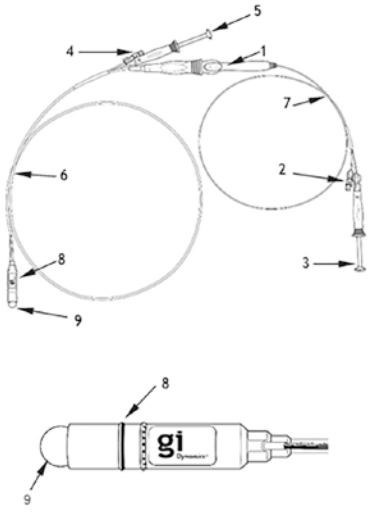

FIGURE 37.1 EndoBarrier Delivery System. The EndoBarrier Delivery System consists of an outer catheter and inner catheter. Initial access to the stomach and duodenum is provided with a standard endoscope through which a guidewire is advanced into the duodenum. After the endoscope is removed with the guidewire left in situ, the EndoBarrier Delivery System is introduced along the guidewire to advance the capsule into the duodenum. Once the capsule is inserted through the pylorus and reaches the duodenum, the guidewire is removed. The endoscope is then reinserted, and the remainder of the deployment of the EndoBarrier Liner from the Capsule is conducted under both endoscopic and fluoroscopic guidance

on the anchor struts that engage the duodenal mucosa and help prevent tilting or migration of the liner/anchor complex. Any crossover of the anchor struts can be uncrossed endoscopically with graspers to ensure a fully deployed anchor sealed against the duodenal bulb wall. The delivery catheters are removed and the liner flushed with dilute contrast to ensure complete deployment of the liner. Visualization of contrast within the jejunal lumen confirms proper liner deployment and patency and helps ensure that there is no evidence of liner obstruction. See Fig. 37.2.

The liner is 60 cm in length and allows for the passage of chyme within the liner while excluding bile and digestive

enzymes that travel on the outside of the liner, between the liner and intestinal mucosa. Chyme exits at the end of the liner where it then mixes with the digestive enzymes and bile for digestion. In this manner, the EndoBarrier mimics the duodenal proximal jejunal bypass created with a Roux-en-Y bypass surgical procedure. See Fig. 37.3.

At the conclusion of therapy, the liner and anchor are removed endoscopically utilizing continuous dynamic fluoroscopy. A custom retrieval hood is placed on the tip of the endoscope. See Fig. 37.4. One of the two anchor drawstrings is

FIGURE 37.2 EndoBarrier Liner. The EndoBarrier liner that is preloaded in the EndoBarrier Delivery System is comprised of the following materials: A self-expanding nitinol anchor mechanism, two polyethylene drawstrings and a fluoropolymer (FEP/ePTFE) 60 cm liner

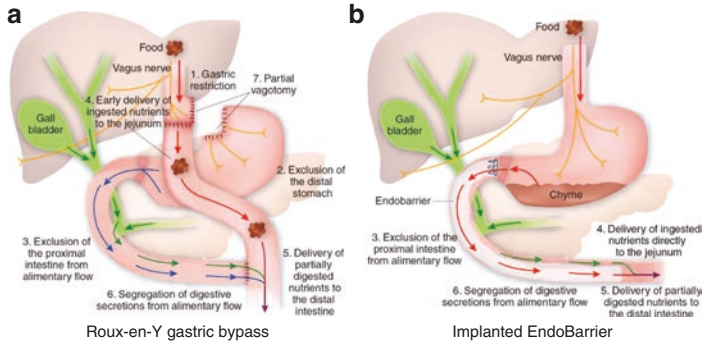

FIGURE 37.3 Intestinal bypass. (**a**) describes the mechanisms of action of a RNY bypass; (**b**) describes the ways in which the EndoBarrier mimics the mechanisms of action of the RNY bypass. The EndoBarrier liner allows chyme to bypass the duodenum and proximal jejunum, thereby mimicking a portion of the intestinal bypass created with a Roux-en-Y gastric bypass

FIGURE 37.4 EndoBarrier retrieval system. The EndoBarrier liner is removed with the EndoBarrier retrieval system. During EndoBarrier liner removal, the EndoBarrier retrieval hook is advanced through the working channel of a standard endoscope. The retrieval hood is fitted and secured to the distal end of endoscope and covers the proximal anchor barbs to prevent tissue trauma during removal

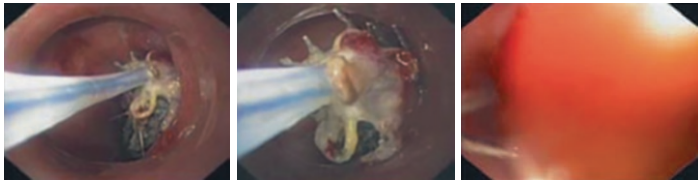

Figure 37.5 Endoscopic anchor collapse and capture. Once the anchor mechanism is radially collapsed and properly positioned within the retrieval hood, the EndoBarrier anchor and attached liner are removed by withdrawing the endoscope through the patient's mouth. Concurrently, continuous dynamic fluoroscopy provides the endoscopist visualization of collapsed anchor within the retrieval hood and withdrawal from the upper GI tract, thus confirming successful EndoBarrier liner retrieval

grasped with a custom hook, the liner struts retracted and the collapsed anchor withdrawn into the custom hood. See Fig. 37.5.

The proximally facing anchor barbs should all be encased within the hood to prevent damage to the gastrointestinal tract during retrieval. Once confirmed, the anchor and liner are removed trans-orally. Proctoring of endoscopists early in device adoption is critical to help mitigate adverse events such as bleeding, laceration and perforation that can occur during implantation or removal.

Pre-Implantation/Post-Implantation Considerations

Anticoagulants (aspirin, heparin, NSAIDs, etc.) should be held for 10 days prior to liner placement and for the duration of treatment. To reduce the potential for infection, a single 2-g dose of ceftriaxone (or equivalent) should be administered intravenously 1–2 h prior to EndoBarrier placement.

Individuals with known allergies or hypersensitivity to ceftriaxone, cephalosporins or penicillins, should seek an equivalent, long-acting, broad-spectrum antibiotic. To ensure safe deployment, a general anesthetic should be administered. A thorough gastroscopic examination of the stomach, pylorus, and duodenum should be performed prior to placement to ensure that the patient's alimentary canal is free of abnormalities which could interfere with the delivery, function, and removal of the implant. Patients are typically discharged the day of the implant or explant and instructed to follow the dietary guidelines similar to those patients who have undergone Roux-en-Y gastric bypass.

Indications/Contraindications

The EndoBarrier can be considered as an adjunct therapy to lifestyle and medications in those adult patients with type 2 diabetes, type 2 diabetes with obesity (BMI $\geq$ 30 kg/m^2), or obesity (BMI $\geq$ 30 kg/m^2). The EndoBarrier is indicated for a maximum implant duration of 12 months. Serial implantation may be considered after an explant "holiday," however, there are no clinical trials to date to support this use of the device.

EndoBarrier Is Contraindicated in the Following Patients

Women who are pregnant or plan to become pregnant while implanted with the EndoBarrier liner, previous GI surgery that could preclude the ability to place the device or affect its function, known history of renal or liver disease (e.g., viral, autoimmune, fibrosis/cirrhosis etiology, but not including incidental fatty liver), prior history of an abscess requiring hospitalization, intravenous antibiotics or drainage, diagnosis of type 1 diabetes mellitus or having any history of ketoacidosis, male patients with serum creatinine (Cr) >1.5 mg/dl or

female patients with Cr >1.4 mg/dl, iron deficiency anemia with hemoglobin ≤12 g/dL and uncorrectable bleeding diathesis, platelet dysfunction, thrombocytopenia with platelet count less than 100,000/microliter or known coagulopathy. Other less common contraindications include hypersensitivity to the device itself, psychological disorders precluding its use and hypersensitivity to cephalosporins, penicillins and all equivalents.

Clinical Outcomes/Efficacy

The published weight loss effects and changes in HbA1c are seen in several studies (Table 37.1). Cumulative data from the six studies showed a significant decrease in HbA1c from baseline to 12 months in T2DM patients. The decreases in mean HbA1c were 1.2% at 3 months, 1.1% at 6 months, 1.3% at 9 months, and 1.2% at 12 months after device placement. In addition, the effects on gastrointestinal hormones on glucose metabolism have included increases in ghrelin and peptide YY and decreases in fasting leptin concentrations and cholecystokinin response [7, 8]. Finally, total serum cholesterol and LDL-cholesterol were significantly lower after duodenal-jejunal bypass liner (DJBL) implant. Paradoxically, HDL-cholesterol levels were also significantly lower in the DJBL group [9].

The clinical effects noted above are usually associated with a reduction in required antidiabetic medication therapy and many of these positive effects on metabolism can be demonstrated up to 6 months after EndoBarrier explantation [10]. Serial implantation after an explant "holiday" has also been demonstrated as safe with the benefits of additional weight loss [11].

Table 37.1 Summary of OUS weight loss and T2DM clinical trials

Study Characteristic	Study 06–6	Study 07–1	Study 07–1 (Crossover)	Study 08–2	Study 10–1	Study 08–1	Study 09–3
Indication	Type 2 diabetes	Type 2 diabetes	Type 2 diabetes	Type 2 diabetes	Type 2 diabetes	Weight loss	Weight loss
Geographic region	Brazil	NL	NL	Brazil	UK	Chile	Chile
Number of patients implanted with EndoBarrier	22	34	28	20	45	43	19
Number of control patients	NA	39	NA	NA	NA	NA	NA
Study design	Single arm Non-randomized	RCT-diet control	Open label extension	Single arm Non-randomized	Single arm Non-randomized	Single arm Non-randomized	Single arm Non-randomized

(continued)

TABLE 37.1 (continued)

Study Characteristic	Study 06–6	Study 07–1	Study 07–1 (Crossover)	Study 08–2	Study 10–1	Study 08–1	Study 09–3
Primary efficacy objective	% excess weight loss; improvement in type 2 diabetes (variations in glucose, HbA1c, and insulin levels)	% of patients with a ≥ 0.5% reduction in HbA1c at 6 months or time of explant	% of patients with a ≥ 0.5% reduction in HbA1c at 6 months or time of explant	Glycemic control at 52 weeks assessed by HbA1c; change in anti-diabetes medications	HbA1c change, reduction in diabetic medications, absolute weight loss, quality of life (SF 36v2)	% excess weight loss	% excess weight loss at week 52 or last assessment
Primary safety objective	Incidence and severity of AEs	Incidence and severity of AEs	Incidence and severity of AEs	Incidence of adverse events	Incidence and severity of AEs	Incidence and severity of AEs	Incidence and severity of AEs

Eligibility BMI (kg/m^2)	40–60	30–50	NA	26–50	30–50	40–60 w/o comorbidity; 35–60 w/ comorbidity	NA
Eligibility HbA1c (%)	Not defined[a]	7.5–10	NA	7.5–10	7.5–10	NA[b]	NA[b]
Implant duration	52 weeks	24 weeks	24–52 weeks	52 weeks	52 weeks	52 weeks	52 weeks
Post-removal follow-up	24 weeks	24 weeks	24 weeks	52 weeks	24 weeks	24 weeks	24 weeks

[a] Study 06–6 did not include a specific eligibility criterion for baseline HbA1c

[b] Study #'s 08–1 and 09–3 were specifically aimed at weight loss and therefore did not have an eligibility criterion regarding T2DM or HbA1c

Mechanisms of Action

The mechanism of action is likely via the delayed onset of digestion and hormonal changes altering appetite and glucose homeostasis. Implantation of the DJBL has demonstrated decreases in gastric emptying. Average gastric retention was greater after DJBL implantation compared with the baseline (first hour, 74 ± 16.3%, $p = 0.001$; second hour, 45 ± 25%, $p < 0.001$; fourth hour, 15.8 ± 15%, $p < 0.001$). There was no difference between the baseline and 4 weeks after device removal (fourth hour, $p = 0.057$) [12]. In addition, the duodenal bypass created by the liner causes numerous hormonal changes, some of which are also known to occur after Roux-en-Y gastric bypass surgery. Weight loss may relate to changes in gut hormones affecting appetite, such as GLP-1 and PYY. In contrast to the reduction in ghrelin levels seen after Roux-en-Y bypass procedures, patients who have undergone liner implantation have increased levels of this hormone [13].

Malabsorption has not been proven. Throughout the clinical data for EndoBarrier, there has been no reports of short gut syndrome, which results in compromised absorption of not only drugs, but also of fluids, macro- and micronutrients. Medications with a narrow therapeutic window such as digoxin or lithium could potentially have their bioavailability affected, however, this patient cohort is excluded from EndoBarrier trials.

Complications

Adverse events tend to be mild and include pain, nausea and vomiting in up to 50% of patients implanted. There have been no instances of permanent clinical sequelae from adverse events. Most observed adverse events have been mild, and have involved expected GI symptoms (abdominal discomfort, nausea, vomiting, diarrhea, or constipation) See Table 37.2.

Table 37.2 Summary of OUS adverse events over time

2011	2012	2013	2014	2015	2016	2017	Total	
# implanted	96	286	653	779	388	199	142	2543
Hepatic abscess	0	1	8	12	11	4	3	39
Hepatic abscess rate	0.00%	0.35%	1.23%	1.54%	2.84%	2.01%	2.11%	1.53%
Intolerance	12	24	20	16	4	1	0	77
Intolerance rate	12.50%	8.39%	3.06%	2.05%	1.03%	0.50%	0.00%	3.03%
Liner obstruction	6	4	3	10	2	0	0	25
Liner obstruction rate	6.25%	1.40%	0.46%	1.28%	0.52%	0.00%	0.00%	0.98%
GI bleed	9	8	9	22	11	1	0	60
GI bleed rate	9.38%	2.80%	1.38%	2.82%	2.84%	0.50%	0.00%	2.36%

(continued)

Table 37.2 (continued)

2011	2012	2013	2014	2015	2016	2017	Total	
Migration/ movement	13	3	6	16	17	2	1	58
Migration/ movement rate	13.54%	1.05%	0.92%	2.05%	4.38%	1.01%	0.70%	2.28%
Pancreatitis	0	4	2	9	0	0	0	15
Pancreatitis rate	0.00%	1.40%	0.31%	1.16%	0.00%	0.00%	0.00%	0.59%
Perforation	0	0	5	3	3	2	0	13
Perforation rate	0.00%	0.00%	0.77%	0.39%	0.77%	1.01%	0.00%	0.51%
Surgical removal	1	0	10	0	0	0	1	12
Surgical removal rate	1.04%	0.00%	1.53%	0.00%	0.00%	0.00%	0.70%	0.47%

Although available safety data is reassuring and there have been no deaths reported from the use of EndoBarrier, serious adverse events can occur, including hepatic abscess, GI tract perforation, and liner/intestinal obstructions. With ongoing training and expertise, liner obstructions and perforations can be greatly mitigated. The hepatic abscess rate is also being decreased by the decreased use of proton pump inhibition, which may have led to alkalinization of the gastric milieu and promotion of bacterial translocation. To date, all serious adverse events have been successfully managed. The cumulative rates of GI bleeding and intolerance that resulted in device removal were 1.4% and 7.6%, respectively. Although significant and sustained weight loss has been observed in patients implanted with a DBJL, the higher frequency of complications precludes implant recommendations beyond 1 year [14].

Summary

The EndoBarrier has been demonstrated to provide a non-surgical and successful option for the treatment of T2DM and obesity. The procedure has several advantages in that it is a non-permanent and easily reversible procedure performed as an out-patient in the majority of cases. The serious adverse events, although infrequent, have all been managed successfully to date with no deaths attributable from the use of the EndoBarrier. Ongoing research trials are helping to mitigate many of these adverse events and better define the role of EndoBarrier in the armamentarium for the treatment of T2DM and obesity. Further considerations for serial implantation, effects on microvascular and macrovascular events and long-term effect on cardiovascular risk factors will require additional controlled studies.

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Chapter 38
Endoscopic Sleeve Gastroplasty

Aayed R. Alqahtani

Introduction

Therapeutic endoscopy gained rapid momentum during the past two decades including endoscopic suturing that has evolved over the past years. Technical advances in endoscopy enabled physicians to perform natural-orifice, minimally invasive procedures that otherwise required surgical intervention.

Endoscopic sleeve gastroplasty (ESG) is a novel, incisionless technique whereby the effective gastric lumen is reduced by approximately 70% using lines of full thickness sutures **(**Fig. 38.1**)** along the greater curvature of the stomach [1, 2]. Several large, independent studies have assessed the safety and efficacy of ESG, and systematic reviews have illustrated that ESG can safely induce up to 15–20% total weight loss (TWL) in 1–2 years with satisfactory resolution of comorbidities [3]. Additionally, a recent single center study of 216 patients has shown that at 5 years, 90% and 61% maintained 5% and 10% of TWL, respectively [4]. Our experience with more than 3441 ESG patients shows a mean TWL of 14% at 3 years of follow-up.

A. R. Alqahtani (✉)
Department of Surgery, New You Medical Center, Riyadh, Saudi Arabia

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_38

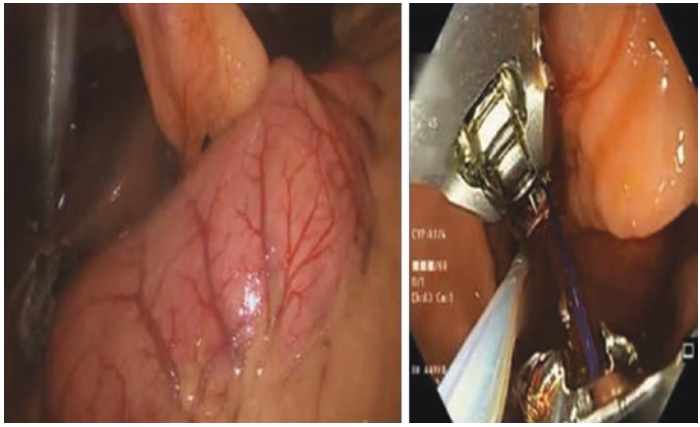


Figure 38.1 Dual view of ESG: Laparoscopic & Endoscopic

While metabolic/bariatric surgery (MBS) is the most effective intervention for inducing significant weight loss, only 1% of eligible patients ultimately undergo surgery. Several factors including access to care, concerns over complication risk, fear, and patient preference prevent more widespread adoption of MBS [5–9]. For such patients, ESG provides a less invasive, incisionless option that could fill a critical gap in the treatment of obesity. Current literature shows that ESG also offers patients the advantages of repeatability and reversibility with a good safety margin [4].

Indication

The indications for ESG are based on obesity parameters, with a BMI > 27.5 to 35 kg/m^2 and previous failed attempts at non-invasive weight loss, or in patients with a BMI > 35 kg/m^2 who declined surgery or are not suitable surgical candidates. Additionally, ESG can be employed as a revisional procedure for weight regain after MBS. In our center, ESG is offered for patients with BMI > 27 kg/m^2 which is the lower cut-off according to the Brazilian Consensus on ESG [10] (Table 38.1).

Table 38.1 Patient selection guidelines for those considering ESG

Patient selection guideline
Inclusion/indication criteria
• Age: 10–65+ years
• BMI: 27 kg/m^2 & above
• Committed to procedure & follow-up with MDT
Exclusion criteria
• Neoplastic pathology.
• Family history of gastric cancer.
• Cirrhosis or esophageal/ gastric varices.
• Esophageal strictures.
• Active peptic ulcer disease.
• Presence of hiatal hernia >3 cm.
• Uncontrolled/untreated psychiatric disorder.

Contraindications

The procedure is contraindicated in patients with bleeding disorders, chronic use of anticoagulants, cirrhosis / esophageal or gastric varices, esophageal strictures, presence of a large hiatal hernia greater than 3 cm, neoplastic pathology, and active peptic ulcer disease. Also, patients with uncontrolled/ untreated psychological disorders should be excluded. (Table. 38.1).

BMI Body mass index, *MDT* Multidisciplinary team

How ESG Induces Weight Loss

ESG reduces gastric capacity by creating a restrictive tubular sleeve-like configuration through a series of full thickness sutures extending from the prepyloric area to below the gastroesophageal junction. Additionally, evidence has shown

that changes in gastric emptying time post-endoscopic bariatric intervention could correlate with weight loss [11]. Abu Dayyeh et al. conducted a study to assess the metabolic and physiologic alterations of ESG. The study demonstrated that gastric emptying time post-ESG is delayed in solids showing retention of 32% of the meal in the gastric fundus cup, 4 h post-meal with no effect on emptying of liquids [11]. No significant change was observed in leptin, glucagon-like peptide-1, and peptide YY levels [11]. Similar delay in solid emptying was also demonstrated by Vargas et al. [12].

Setup/Tools Requirement (Table 38.2)

We use a flexible endoscopic suturing system (OverStitch®; Apollo Endosurgery, Austin, TX) composed of a needle driver, a catheter-based suture anchor, and an actuating

Table 38.2 Endoscopic sleeve gastrectomy setup tools

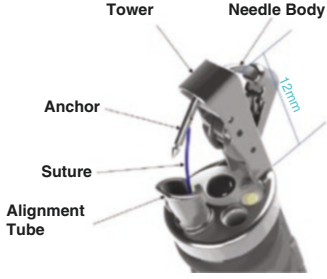
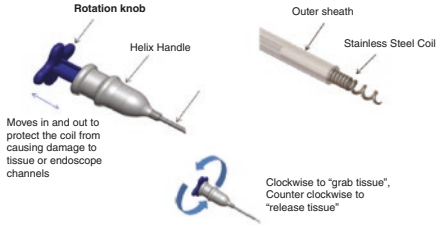
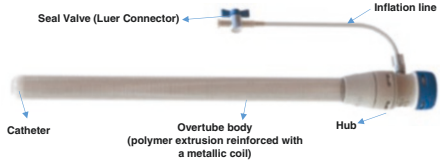
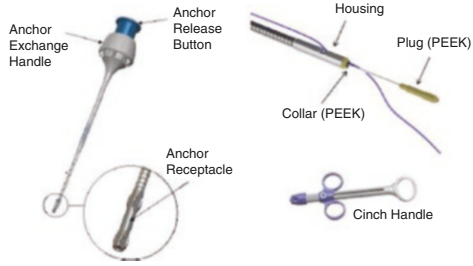
Tools	Image
Double-channel gastroscope Fig. 38.2b	 Olympus EXERA GIF-2T160 Video Gastroscope.  Compatible with Olympus GIF-2T160 Olympus GIF-2TH180 Olympus GIF-2T240 Fuji EI-740D/S • 13.2mm Olympus GIF-2T160 • 12.2mm Olympus GIF-2TH180 •11.8mm Olympus GIF-2T240
Overstitch endoscopic suturing system Fig. 38.2c	

Table 38.2 (continued)

Tools	Image
Tissue helix Figure 38.4	
Overtube (US endoscopy, Mentor, Ohio) Figure 38.5	
Suture Figure 38.6	
Needle holder Figure 38.7	

handle, attached to a double-channel therapeutic upper endoscope (Fig. 38.2a–c) (GIF- 2TH180; Olympus, Center Valley, PA). Apollo OverStitch® is a suturing device that fits on the end of a double-channel endoscope or single channel endoscope (Fig. 38.3) with different platform inserting into the

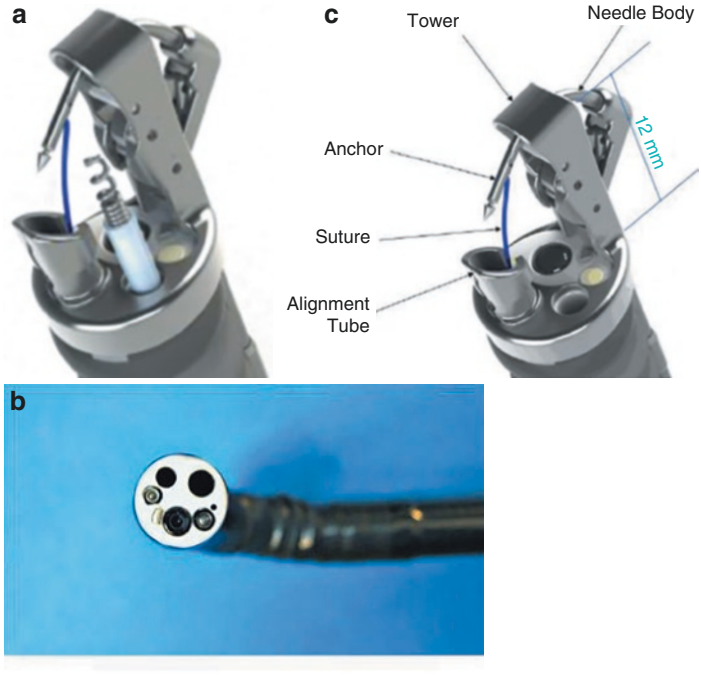


FIGURE 38.2 (**a**) OverStitch ™ Double-channel endcap. (**b**) Double-channel gastroscope. (**c**) Overstitch endoscopic suturing system

FIGURE 38.3 OverStitch ™ Single- & Double- channel endoscopic suturing system

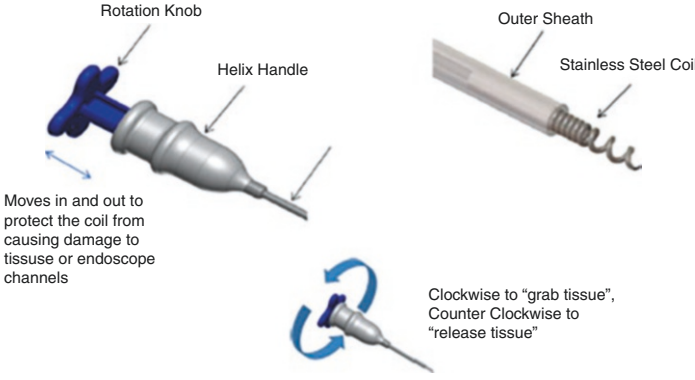


FIGURE 38.4 Tissue Helix

larger channel, with a curved needle driver allowing full thickness sutures to be placed in an interrupted or running fashion. This system also uses an instrument to grasp tissue called the tissue helix (Fig. 38.4) which is passed through one of the channels. Esophageal over tube (US Endoscopy, Mentor, Ohio; Fig. 38.5) is used to facilitate the safe passage of the double-channel upper gastroscope during the procedure.

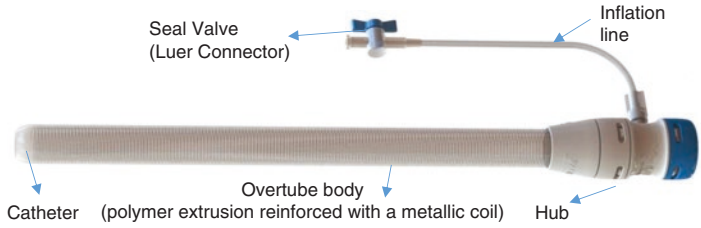


FIGURE 38.5 Overtube (US Endoscopy, Mentor, Ohio)

Device Overview

Intended for endoscopic placement of suture(s) and approximation of soft tissue.

Technique

The aim of the technique is to reduce the effective volume of the gastric lumen using lines of full thickness 2/0 non-absorbable sutures (Fig.38.6) created along the greater curvature of the stomach. Under general anesthesia (GA), patients are placed in the left decubitus or supine position (operator preference) (Table 38.3). Initially, a diagnostic esophagogastroduodenoscopy (EGD) is performed to rule out contraindications to ESG, including ulcers, neoplastic pathology, and hiatal hernia >3 cm in size. An Overtube is then inserted using the double-channel scope and the Overstitch System (Fig. 38.2a, b, and 38.5) is installed on this gastroscope. The tissue helix and sutures are loaded on the system.

Suturing starts distally at the level of the incisura angularis and finishes at the fundus. Sutures are loaded without

Figure 38.6 Suture

Table 38.3 Procedure: set-up

Anesthesia	**General**
Position	**Left lateral (Supine)**
Diagnostic EGD performed at the time of the procedure	**Pylorus, GE junction measurement**
Overtube	**placed with diagnostic scope**
APC (optional)	Marking starting point (anterier and posterior line)

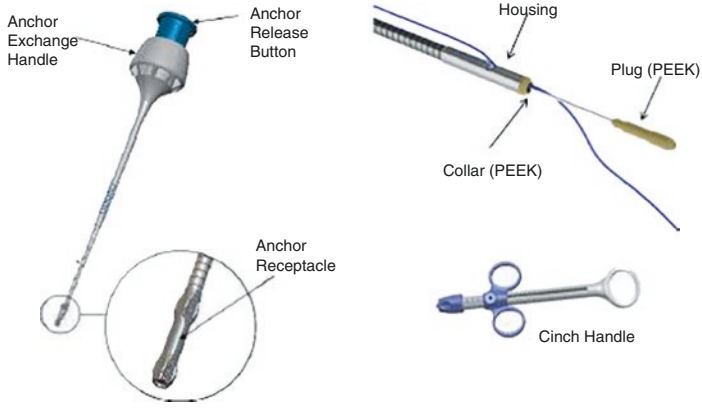


FIGURE 38.7 Needle holder

endoscope removal using the needle holder (Fig. 38.7). The tissue helix is passed in the second channel of the scope to grasp and draw the stomach wall into the jaws of the Overstitch perpendicularly to have a full thickness bite (Fig. 38.8). 2-rows-per-suture pattern is placed beginning at the anterior wall, followed by bites at the greater curvature, before taking final bites at the posterior wall. This pattern (anterior wall, then greater curvature, then posterior wall) is then repeated in reverse (posterior wall, then greater curvature, then anterior wall). Each row consists of 4–6 closely spaced bites depending on the available surface area and the level of the row. The sutures are tightened and secured using a cinch to close the gap (Fig.38.9). Typically, an average of 4–6 sutures are placed in each patient. A small fundus is left to function as a pouch, which may prolong satiety and delay gastric emptying (Fig. 38.10). It is debatable if suturing the fundus will contribute more to weight loss. However, it should be known that it carries more risk of complication considering how thin fundus tissue is and the possibility of the helix drawing tissue from outside the stomach, including the adjacent splenic hilum.

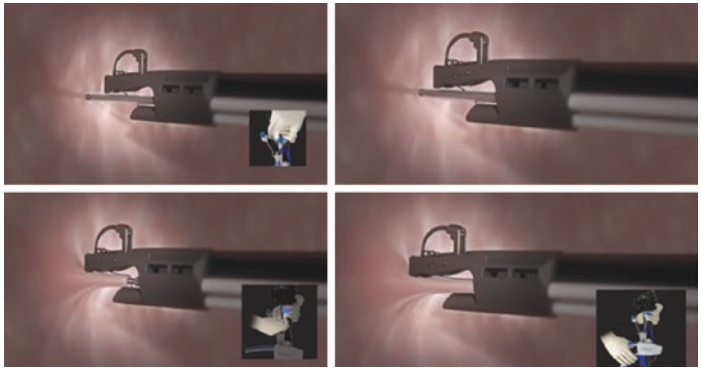


FIGURE 38.8 Endoscopic intraoperative view of ESG

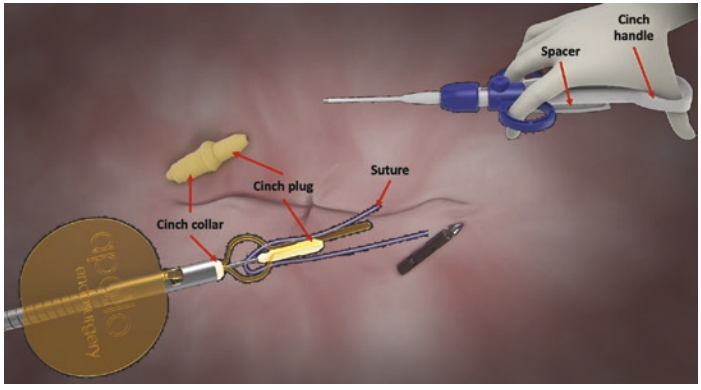


FIGURE 38.9 Cinch

Alternate Suturing Patterns

1. **Square pattern:** Starting at the anterior wall just at the incisura then going distally to incorporate part of prepyloric area followed by bites at the greater curvature at the same level, before taking final bites at the posterior wall. This pattern (anterior wall, then greater curvature, then posterior wall) is repeated in reverse (posterior wall, then greater curvature, then anterior wall) (Fig. 38.11a).

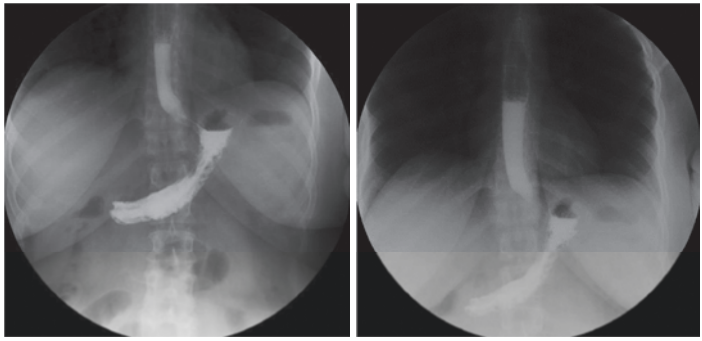


Figure 38.10 Overstitch Endoscopic Sleeve Gastroplasty: Post-ESG view of small fundus

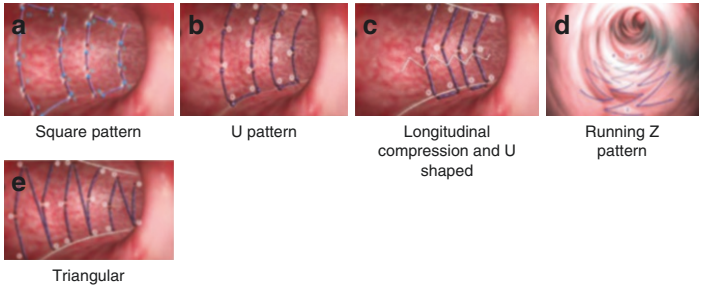


Figure 38.11 Suture patterns commonly used in Endoscopic Gastroplasty. (**a**) square pattern. (**b**) U pattern. (**c**) longitudinal compression and U shaped. (**d**) Running Z pattern. (**e**) Triangular pattern

2. **U pattern**: Suturing begins at the anterior wall, proceeding to the posterior wall, and returning to the anterior wall using approximately 4–6 sutures (Fig. 38.11b).
3. **Longitudinal compression and U pattern**: Two longitudinal compression sutures along the greater curvature of the stomach; the first suture starts at the proximal antrum and terminates in the mid-body along the greater curve, and the second suture starts at the mid-body and progresses into the fundus along the greater curve. A second parallel

U-shaped layer of interrupted plications is formed (Fig. 38.11c).

4. **Running z pattern:** Using four sutures proceeding from the gastric incisura to the fundus in a running "Z" pattern with a distance of 1.5–2 cm between stitches. A total of four rows of sutures with this stitch pattern are placed: two of each along the greater curve, one along the posterior wall and another one along the anterior wall of the gastric body (Fig. 38.11d).
5. **Triangular pattern**: Three parallel (anterior, greater curvature, and posterior, then anterior followed by greater then posterior and cinch) starting at the incisura and extending proximally to the gastroesophageal junction with an average of 16 sutures (Fig. 38.11e).

Systematic review comparing different types of suturing pattern namely triangular, Z pattern, U- pattern, and combination of longitudinal compression and U-shaped suturing pattern showed no association between TBWL and suturing pattern at 6 months. Additionally, there is no statistically significant difference between suturing patterns and adverse event rates [13].

Reinforcement

In light of current evidence from systematic reviews and meta-analyses, a layer of interrupted reinforcing stitches was performed in majority of the studies [14]. It has been stipulated that a layer of reinforcement stitches correlates with better efficacy and durability, however, total number of reinforcement sutures is not fixed ranging from 2 to 9 sutures [14]. This depends on the suturing pattern being performed. In our practice, we perform square suturing pattern (Fig. 38.11a). We do not add a layer of reinforcing stitches due to multiple bites that are taken per row. Additionally, we are particularly careful to close adjacent gastric tissue, leaving no pockets or gaps in between to be reinforced.

ESG in Pediatric Age Group

The latest guidelines from the American Academy of Pediatrics recommend metabolic/bariatric surgery (MBS) to children and adolescents in selected cases. Current guidelines recommend consideration of surgery for adolescents with BMI higher than 140% of the 95th percentile (Class III obesity) and to those with a BMI higher than 120% of the 95th percentile (Class II obesity) if they also have co-morbid conditions. At the time of writing this chapter, we have performed ESG in more than 200 children and adolescents in our center from which we published the first cohort of 109 with similar outcomes as in adults in terms of weight loss and safety [15]. Children and adolescents with obesity were enrolled in our comprehensive pediatric weight management program. The multidisciplinary, multistage program includes family-focused educational workshops, multidisciplinary assessment and management, and interventions. Patients are allocated to different treatment pathways according to the severity of their obesity and co-morbid status. Those with obesity are enrolled in the interventional protocol if they fail to lose satisfactory weight during a treatment period of at least 6 months. Options included endoscopic bariatric therapy, which involves intragastric balloon and ESG, and bariatric surgery for those with co-morbidities or Class III obesity. The choice of intervention is made after thorough counseling on benefits, risks, expectations and commitment, and with input from all caregivers across specialties. We adopted relevant parts of our protocol for ESG in adult patients with drug dose adjustment for pediatric patients as indicated. The mean TWL at 12 and 18 month was 14.4% and 15.4, respectively. There were no adverse events, bleeding, mortality, or unplanned admissions [15].

Perioperative Protocol for Patients Undergoing ESG

Complete lab workup should be done prior to ESG. Preoperatively, patients are required to fast for 8 h and take Netupitant/Palonosetron 8 before the surgery (Table 38.4). In addition, patients are required to take proton pump inhibitors for 4–5 days prior to the procedure. On admission patients are started on IV fluids, prophylactic antibiotics, and 8 g of

Table 38.4 Clinical pathway for endoscopic sleeve gastroplasty

Preoperative protocol

Before the day of the surgery

Dietary/behavioral

- Liquid diet for the last 24 h before the procedure.
- NPO 8 h prior to surgery.

Medical

- Netupitant 300 mg/Palonosetron 500 microgram (Akynzeo®) capsules + scopolamine patch at 6 pm the evening before ESG
- Complete blood workup (CBC, renal profile, liver profile, coagulation profile, blood group, blood sugar), (ECG, CXR, hemoglobin A1C, as indicated)
- Clinical assessment with all findings should be clearly documented

On the day of the surgery

Medical

- 500 cc of 0.9% normal saline solution IV
- PPI 40 mg IV.
- Antibiotic, e.g., cefuroxime 1.5 g IV.
- Ondansetron 8 g IV.

(continued)

Table 38.4 (continued)

Intraoperative protocol

Medical

- Standard general anesthesia protocol including fentanyl 100–200 μg IV.
- IV fluid maintenance.
- Acetaminophen 1 g IV.
- Dexamethasone 16 mg IV.
- Compazine suppository/ Promazine IV/ IM.

Postoperative protocol

Medical

- Antibiotic as per protocol.
- PPI 40 mg IV.
- Scopolamine IV/patch Q12H.
- Promethazine 25 mg Q6H/Compazine suppository.
- Pethidine 50–100 mg IM Q6H PRN.
- Acetaminophen 1 g IV Q6H.
- Ondansetron 8 mg Q8H.

Dietary/behavioral

- Start sips of water 4–6 h post-procedure as tolerated, according to pain and nausea.
- Encourage early ambulation.
- Incentive spirometry.

Discharge

Dietary/ behavioral

- Day 0–3: Clear liquid diet.
- Day 3–7: Full liquid diet.

Table 38.4 (continued)

- – Start protein drinks.
- – Start chewable multivitamins.
- – 60 g protein daily

- Day 7-onward:
  - – Pure diet.
  - – Progress to low fat, low carbohydrate, balanced diet.

- Monthly follow-up with MDT as convenient.

Medical

- Tramadol 50–100 mg orally QH8 PRN for 1 week.
- Ondansetron 8 mg Q8H.
- Acetaminophen-codeine orally Q6H PRN for 1 week.
- Omeprazole 40 mg for 1 month.

NPO nothing by mouth, *ECG* electrocardiogram, *CXR* chest X-ray, *hemoglobin A1C* glycated hemoglobin, *mg* milligrams, *IV* Intravenous, *PPI* Proton Pump Inhibitor, *IM* Intramuscular, *PRN* when necessary, *MDT* multidisciplinary team

ondansetron intravenously. During the procedure, patients receive 16 mg of dexamethasone, 1 g of acetaminophen, scopolamine as needed, and standard general anesthesia protocol which includes fentanyl 100–200 μg. Postoperatively, patients receive one further dose of antibiotics, 40 mg PPI, 20 mg scopolamine every 12 h and promethazine 25 mg every 6 h intravenously. In addition, ondansetron 8 mg every 8 h is provided and pethidine 50–100 mg IM every 6 h.

ESG is a day case procedure and therefore patients are discharged 6–8 h after the procedure. Patients are encouraged to ambulate, continue with their daily routine, and perform mild physical exercises, such as walking. Endoscopic or radiological follow-up is not performed unless a patient complaint warrants these studies.

Upon discharge, patients typically are prescribed tramadol for 1 week and omeprazole for 1 month. Additionally, patients

receive ondansetron 8 mg, and antibiotic as an option. Patients are placed on a low-calorie diet and monitored by dieticians weekly in the early post-procedure period and monthly thereafter. (Table 38.4).

Results

Impact of ESG on Weight Loss

Outcomes from our cohort of more than 3441 patients who underwent ESG have shown that patients achieved 67.5% EWL and 15% TBWL at 1 year and 14% TWL at 3 years [1].

Similarly, results from more than five international multiple systematic reviews and met-analysis have reported an EWL of up to 50 to 60% at 12 month [16–20]. ESG matches the criteria set by ASGE/ASMBS Task Force for Endoscopic Bariatric Therapy by illustrating TBWL >5%, EWL >25% at 1 year [21]. Furthermore, Sharaiha et al. reported an EWL of 45.1% at 3 years and 45.3% EWL at 5 years with 74% of patients maintaining 25% of EWL [4]. The five-year study demonstrated durability of ESG in maintaining weight loss.

Complications and Management

With regard to post-procedure complaints, a majority of patients reported abdominal pain or nausea that is controlled with IV hydration, analgesia, and antiemetic consistent across studies. The reported pooled estimate adverse event rate for ESG is 2.2% with 95% CI, {1.57%–3.09%} [3]. Upper gastrointestinal bleeding occurs in 0.56% of patients which can be managed with expectant management or blood transfusion. Perigastric collections occur at a rate of 0.47%. The diagnostic test of choice is a CT scan with oral and IV contrast which demonstrates a relatively high sensitivity and specificity. Pulmonary embolism and pneumoperitoneum are among the least common adverse events with a rate of 0.06% each [3]. Table 38.5 summarizes the post-ESG complications and their rates.

Table 38.5 Reported adverse events after ESG; Self-limiting nausea/vomiting occurred in 55% (1909/3441) of patients in our series

Adverse events rate	Literature		Our experience	Management
Vomiting and pain that required admission	1.08%	0.46% (Sharaiha et al) (bridging fibrosis bands)	(0.06%) 2/3441 gastric outlet obstruction due to second suture	Suture removal or IV hydration, analgesia, and antiemetic
Upper GI bleeding (0.56%)	0.56%		(0.23%) 8/3441	Conservative intervention or blood transfusion rarely surgical exploration
Perigastric collection (0.47%)	0.47%		(0.12%) 4/3441	Percutaneous drainage or antibiotic alone in case of small collection
Pulmonary embolism (0.06%)	0.06%		0%	Conservative anticoagulant alone or radiological intervention

(continued)

Table 38.5 (continued)

Adverse events rate	Literature	Our experience	Management
Pneumoperitoneum (0.06%)	0.06%	(0.03%) 1/3441	Conservative
Total adverse event rate	2.2%	0.45%	

All cases responded to IV hydration, analgesia, and antiemetic. However, other authors disregarded these symptoms as minor without need for monitoring. Additionally, bringing patients on second post-operative day for IV hydration and medications decreases threshold for ER visit. **Akynezeo was utilized initially in our practice it has shown to be effective in preventing N/V

Sources: Sharaiha, R. Z., et el. Five-Year Outcomes of Endoscopic Sleeve Gastroplasty for the Treatment of Obesity. *Clinical gastroenterology and hepatology*: *the official clinical practice journal of the American Gastroenterological Association*, (2020)

Hedjoudje A, et el.Efficacy and Safety of Endoscopic Sleeve Gastroplasty: A Systematic Review and Meta-Analysis. Clinical Gastroenterology Hepatology. 2019

In our cohort we encountered 39/3441 (1.13%) patients that required sutures removal at a median of 18-month post-ESG. Reason for removal was mainly due to pain 20/39 (51%), 9/39 (23%) optimal weight loss, 8/39 (20%) suture removals upon patient request without medical indication.

Conversion to Laparoscopic Sleeve Gastrectomy (LSG) and Redo ESG

Not all patients achieve satisfactory weight loss outcomes after ESG, and some may require conversion to LSG or redo ESG. The choice of revision intervention is reached as an agreement between the endoscopist and the patient, in the context of the results of the workup and expected weight loss with each option. Predictors of weight regain post-bariatric surgery include poor diet adherence, higher preoperative BMI, certain medications, and medical conditions. In our cohort, 36 (1.0%) patients underwent repeat ESG during follow-up due to weight regain at a median of 19 month (Fig. 38.12) and 114 (3.3%) patients underwent revisional LSG post-ESG at median of 20 month. (Fig. 38.13) When performing conversion to LSG the surgeon should avoid placing the stapler over the suture needle/anchors left behind following ESG as these foreign bodies, if caught in the staple line, can negatively impact the function of the stapler.

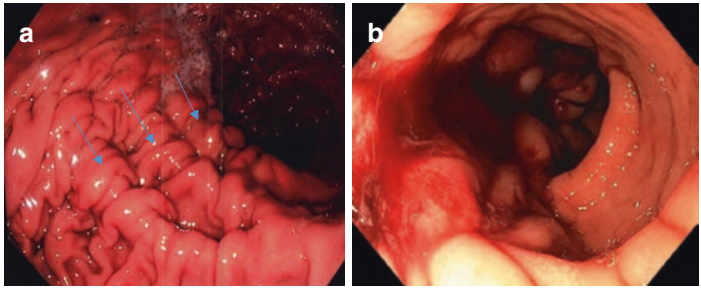


Figure 38.12 (**a**) Redo ESG: arrow indicating prior sutures. (**b**) After redo

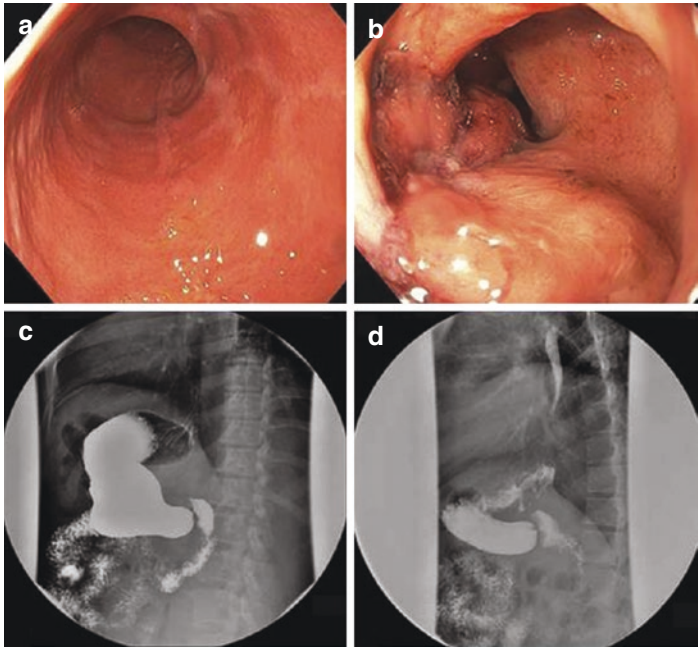


Figure 38.13 Gastric anatomy before (**a**, **c**) and after (**b**, **d**) revisional endoscopic sleeve gastroplasty (R-ESG) of laparoscopic sleeve gastrectomy

ESG as a Revisional Procedure

It is estimated that approximately 10%–30% of patients undergoing LSG and RYGB experience weight regain at 5 years, requiring revision. However, revisional bariatric surgery is associated with a relatively higher adverse event rate compared to primary bariatric surgery. Anastomotic leak, bleeding, mid-gastric stenosis and other complications have been reported after revisional surgery. Additionally, 10–15% of revision patients develop peptic ulcer or significant GERD necessitating re-revision [22–26]. This concern may prompt patients to opt for a less invasive revisional procedure, including ESG. Despite meaningful outcomes as a primary procedure, there is a paucity of evidence on ESG as a revisional

intervention. An international, multicenter study headed by Alqahtani and Abu Dayyeh analyzed data pertaining to patients who underwent revisional ESG and laparoscopic sleeve gastrectomy. Authors found that more than 80% of patients experienced at least 10% total weight loss with a single adverse event in the form of GE junction narrowing that required endoscopic dilation [27].

How Does ESG Compare to Laparoscopic Sleeve Gastrectomy?

While LSG has shown to be one of the most effective treatment for severe obesity, only 1% of eligible patients have access to surgery. Access to care, eligibility criteria, patient preference, and reluctance have limited wide adoption of MBS. ESG could fill this critical gap by providing an incisionless alternative with durable weight loss outcome. We conducted a propensity matched score analysis to compare outcomes of ESG and LSG. A total of 3018 patient pairs who were matched for BMI, age, and gender were included. Results demonstrated that at 3 years %TWL of 14% and 19% was induced by ESG and LSG, respectively. Fourteen ESG patients developed adverse events (0.5%) vs. ten LSG patients (0.3%). Co-morbidity remission rates after ESG vs. LSG were 64% vs. 82% for diabetes, 66% vs. 64% for dyslipidemia, and 51% vs. 46% for hypertension, respectively. Eighty ESG patients (2.7%) underwent revision to LSG for insufficient weight loss or weight regain, and 28 had re-suturing after primary ESG (0.9%) [28].

Barriers and Concerns

There are three learning curves for ESG, the first is learning the scope for those who are not endoscopists. The second is the learning curve of the suturing system. The trainee should attain competence in loading and unloading until it becomes

cognitively intuitive, along with tissue feeling. The third is for the trainee to apply the sutures in place in an appropriate pattern and symmetrical manner (which is the most difficult one and critical in determining the outcome). That being said, initially a trainee should attain safety skill level by performing ten cases under supervision, then fair proficiency by performing 50–100 cases. Full proficiency level can be attained by performing above 100 cases.

Pearls in Performing ESG

ESG Technical Principles

- Goal of suturing pattern is to reduce the size (and the length) of the stomach by approximately 60–70%.
- Strength of the construct depends mainly on achieving full thickness bites more than the suturing pattern (Fig. 38.14).
- Suturing pattern depends on the local experience adopted.

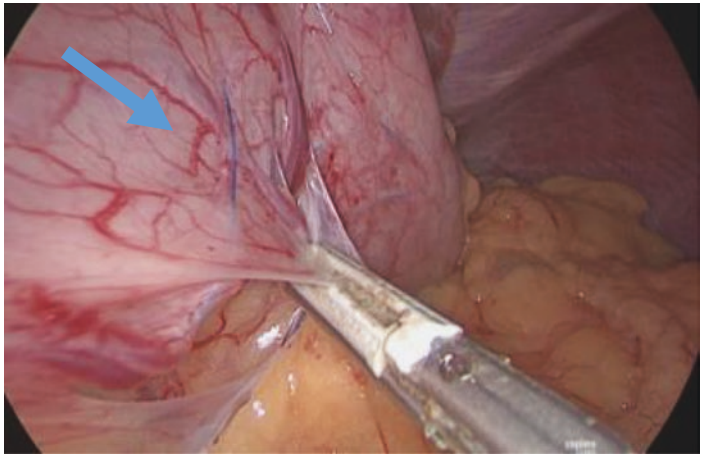


Figure 38.14 OverStitch suture shown running through gastric wall indicating full thickness suture

- Number of bites per suture is not fixed/ our aim is to plicate all the tissue leaving no gaps in between to be closed.
- 4–6 sutures are placed depending on the surface area of the stomach and suturing pattern.
- Fundus should be touched and closed partially and cautiously with minimal insufflation to reduce the risk of complication. Wall thickness is in this area is less than the rest of the stomach, this should be taken into consideration.
- At the distal part of the stomach three turns of the helix is acceptable but not at the body and fundus. At the body and fundus of the stomach two full turns and a third turn can be added after initially pulling the wall toward the system.
- Adding a layer of reinforcement is a matter of controversy.
- Tighten the sutures but not too hard as the needles and the anchor can erode through gastric wall with time (Fig. 38.15).

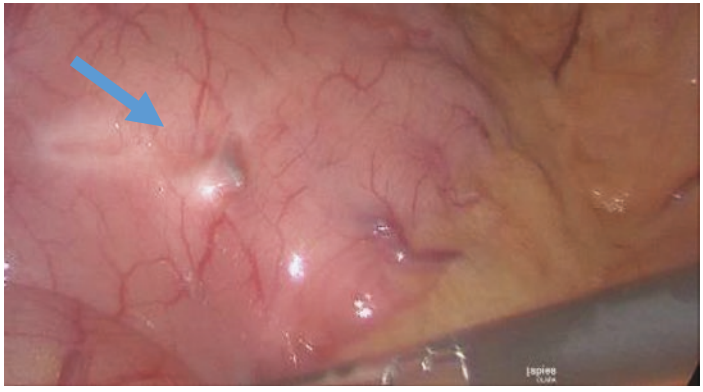


Figure 38.15 OverStitch anchor eroding through gastric wall

Improve Visualization and Orientation

- Use of APC is a matter of choice and depends on experience, usually used in the first few cases to mark the site of starting point at the level of the incisura anteriorly (anterior and posterior walls of the greater curvature).
- Use of CO2 insufflation is mandatory.
- Use CO2 insufflation intermittently to reduce adverse events such as postop pain and vomiting. Additionally, this will reduce the chance of catching nearby structures during the procedure.
- Water pump irrigation is mandatory.
- IV Scopolamine is sometimes useful to control excessive contractions and improves visualization especially at the site of first suture distally.

Conclusion

Endoscopic sleeve gastroplasty (ESG) offers a viable option to treat obesity in numerous patients with varying degrees of obesity. ESG use as a primary bariatric procedure or as a revisional option demonstrates its versatility in treating the obesity pandemic. ESG's statistically significant longer term weight loss outcomes solidify its importance as well. Future considerations such as evolving technology and various suturing patterns will come into play as ESG gains much more traction throughout the surgical and medical communities. Longer term data will be necessary to fully evaluate durability of this procedure.

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Chapter 39
New Technologies to Treat Obesity and Related Comorbidities

Vitor Ottoboni Brunaldi and Manoel Galvao Neto

Introduction

The escalating obesity pandemic has recently gained an appropriate neologism: globesity. As of 2016, 39% of American adults were obese, accounting for more than 93 million individuals [1]. Despite all information on the associated health and economic burden, population-based data show that the prevalence continues to increase over time [2]. Worldwide, the WHO estimates that half a billion people currently suffer from obesity [3].

V. O. Brunaldi (✉)
Gastrointestinal Endoscopy Unit, University of São Paulo Medical School, São Paulo, Brazil

Surgery and Anatomy Department, Division of Gastrointestinal Surgery, Faculty of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil
e-mail: vitor.brunaldi@usp.br

M. Galvao Neto
ABC Faculty of Medicine, Department of Surgery, Santo Andre, Brazil

Endovitta Institute, Sao Paulo, Brazil

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_39

Obesity is a well-known risk factor for several types of cancer, cardiovascular diseases, type 2 diabetes (T2D), and metabolic syndrome [4]. Moreover, the recent coronavirus pandemic has also been pointed out as a predictor of poor COVID-19 outcomes [5].

Bariatric surgery has long been the most effective therapy to address moderate and Severe Obesity in the long term [6, 7]. Also, it may adequately control T2D and metabolic syndrome, thus reducing morbidity and mortality [8]. However, only a tiny portion of patients with indications undergo surgery [9]. Fear from complications, restricted access, costs, and misinformation are some factors that might explain such a disparity between people in need and people treated [10].

This gap fostered novel, less invasive alternatives to surgery in the last decades [11]. Several types of gastric-filling devices - each with its particular mechanism of action, intestinal coats, mucosal devitalization, and even the combination of different devices in the same patient are some compelling examples. This chapter aims to describe the most recent endoscopic procedures to address Obesity and T2D and bring future perspectives on the minimally invasive bariatric treatment.

Duodenal Mucosal Resurfacing (DMR)

T2D is one of the metabolic diseases most commonly associated with obesity [12]. Thus, the best therapeutic strategy usually involves treating both conditions simultaneously [13]. Bariatric surgery, especially procedures that bypass the duodenum, effectively achieves both T2D and obesity control. Notably, procedures that lead to weight loss without bypassing the foregut are less effective in normalizing glycemic levels [14]. Animal and human studies investigating this observation found that the duodenal food transit exclusion improves T2D independent of weight loss [15, 16].

Experts hypothesized that diabetic patients develop cellular-level alterations in the duodenal mucosa that impair

the adequate endocrine and paracrine downstream signaling [11]. Ultimately, there is an imbalance between hormones that increase insulin secretion and peripheral insulin sensitivity—known as incretin gut hormones, and their counterparts—the anti-incretin hormones. Bypassing the duodenum in patients with T2D might reestablish the incretin balance, thus ameliorating glycemic levels.

Instead of excluding the duodenum from food transit, the novel duodenal mucosal resurfacing (DMR) procedure promotes hydrothermal ablation of the mucosa to trigger healing with newer healthy cells. Animal data suggest this process is stem-cell mediated [17]. Those cells are more efficient at incretin hormone production and release, therefore improving T2D.

The DMR consists of a catheter-based sequential ablation controlled by endoscopy and fluoroscopy. After reaching the Ligament of Treitz with a pediatric colonoscope, the endoscopist leaves a guidewire in the proximal jejunum and removes the scope. Then, the catheter (Figs. 39.1 and 39.2) is inserted over the wire, and the first ablation begins at the descending portion of the duodenum, immediately distal to the papilla.

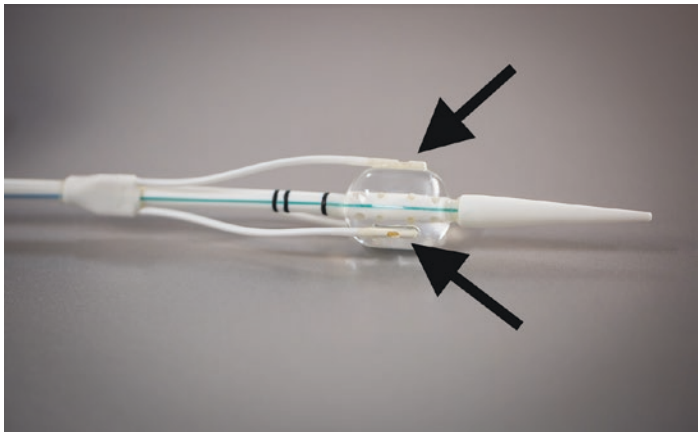

FIGURE 39.1 The Duodenal Mucosal Resurfacing catheter. Black arrows show to the needle ports

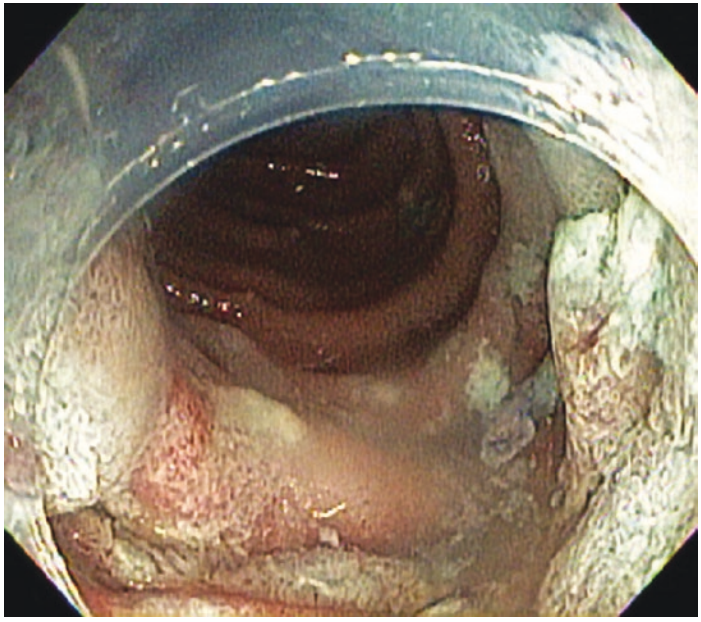

Figure 39.2 The endoscopic control after the duodenal mucosal resurfacing procedure showing the distal limit of the ablated area

Three needles attached to the device perform submucosal injections before the balloon delivers hydrothermal energy by circulating hot water. This protects the underlying muscle and decreases the full thickness injury rate. Five ablations covering 2 cm each should be accomplished for a total of 10 cm [18].

After preclinical safety studies were complete, human studies were conducted (Fractyl Laboratories Inc., Lexington, MA, USA) [18]. The first-in-human proof-of-concept trial enrolled 44 patients and demonstrated a 1.2% average reduction in HbA1c 6 months after DMR [19]. This trial by Rajagopalan et al. also demonstrated a better response in the long segment ablation cohort (five sequential ablations) as compared to three ablations. Consequently, a five ablation/10 cm technique has become the standard of practice and is being used in follow-up clinical trials of DMR [19].

More recently, the first open-label multicenter study enrolling 46 individuals demonstrated only modest technical success: 37 of the 46 proposed procedures were completed (80%), mostly due to catheter-related difficulties (7/9). One additional patient was excluded due to inadequate medication adjustment during follow-up. Of the 36 patients analyzed, per-protocol analysis showed significant reductions in HbA1c (−0.9% ± 0.2%), fasting plasma glucose (−1.7 ± 0.5 mmol/L, $p < 0.001$), and improvement in Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score (−2.9 ± 1.1) 24 weeks after DMR. Moreover, there was modest but statistically significant weight loss (−2.5 ± 0.6 kg, $p < 0.001$), and the alanine transaminase levels decreased by 9 U/L and 10 U/L at 24 weeks and 12 months, respectively. As to safety, 52% of patients in whom DMR was initiated experienced at least one adverse event (24/46). However, there was only one related serious adverse event requiring hospital admission. Of note, this trial enrolled only non-insulin-dependent patients and excluded individuals with low endogenous insulin production (fasting C-peptide <0.333 nmol/L) [20].

Van Baar et al. also investigated the effect of DMR on insulin-dependent type 2 diabetic patients. The investigators studied the effects and feasibility of a single DMR ablation session, treatment with a glucagon-like peptide-1 receptor agonist (liraglutide), and lifestyle counseling on the ability to discontinue insulin. Sixteen patients were enrolled in this single-center, single-arm feasibility study. At 6, 12, and 18 months, 69%, 56%, and 53% of patients were off insulin, respectively, with HbA1c levels ≤7.5%. Additionally, the authors demonstrated significant weight loss, as well as a reduction in BMI, FPG, and improvements in mean HOMA-IR score and liver proton density fat fraction value. In their latest series, van Baar et al. reported 100% technical success and no serious adverse events [21]. In contrast with the above-mentioned multicenter trial [20], such better technical and safety-related outcomes might point either to results of a learning curve in the first study [20] or to a selec-

tion bias in the latter one [21]. Nonetheless, the result is exciting as it broadens the possible future indications of DMR.

Finally, medical literature still lacks sham-controlled trials—a gap that shall be addressed by a large currently ongoing multicenter sham-controlled study. Besides diabetes control, this trial also focuses on the amelioration of metabolic syndrome and non-alcoholic fatty liver disease (NCT02879383). If the results confirm the non-controlled data on DMR efficacy and safety, duodenal ablation might become a central player in the fight against T2D, obesity, and related comorbidities.

Magnetic Anastomosis System (GI Windows Inc.)

In 1957, Equen et al. firstly described magnets' use in gastrointestinal surgery to retrieve ingested metallic foreign bodies [22]. Since then, animal and clinical studies have investigated the application of magnetic force to address several GI disorders, including creating anastomoses [23, 24].

The development of self-assembling magnets and the technique's refinement originated from studies initially addressing gastric outlet obstruction [25, 26]. The acquired experience and technology nurtured the idea of utilizing the same system to address Obesity and T2D. The rationale was somewhat based on the abandoned traditional surgical jejunoileal bypass. Ryou et al. published the animal proof-of-concept study in 2016 [27]. The authors created a partial jejunal diversion, which differs from the surgical technique since the original GI pathway is kept intact. Consequently, only a fraction of food is diverted, mitigating the risk of excessive malabsorption.

To perform the endoscopic magnetic partial jejunal diversion (EMPJD), the operator delivers the first magnet in the proximal jejunum through an upper endoscopy and the distal one in the terminal ileum through a deep colonoscopy. After survival studies concluded the procedure was safe [28],

Machykta et al. conducted the first-in-human project settled in the Czech Republic [29]. Fourteen patients with Obesity were initially enrolled, and 11 ultimately underwent attempted EMPJD. As a pilot study, laparoscopic assistance was allowed per protocol. If the endoscopists could not couple the magnets after 40 mins, the surgeon used graspers to guarantee adequate coupling. Ten procedures were technically successful (one required two attempts) after a mean of 115 mins, but only two cases exempted laparoscopic assistance.

Nine magnets (90%) were naturally expelled by day 13, and the patient with the retained device underwent uneventful endoscopic removal. As to the primary outcomes, patients presented a mean total weight loss (TWL) of 8.2%, 10.6%, and 14.6% at 3, 6, and 12 months, respectively. Accordingly, the mean excess weight loss (EWL) was 21.7%, 28.3%, and 40.2%. Also, diabetic patients experienced a median reduction of 1.9% in HbA1c levels from baseline to 12 months. Finally, there was a significant increase in peptide YY levels at 2 months, suggesting the weight loss was mediated not only through malabsorption but also through the amelioration of gut hormone signaling. Regarding adverse events, nausea, abdominal pain, and diarrhea were frequent. However, all adverse events were managed non-operatively [29].

There is currently another ongoing clinical trial based in Argentina, assessing the safety and effectiveness of the EMPJD (NCT03130244). During the study, the investigators confirmed the exclusive endoscopic coupling to be technically challenging, which prompted the technique's modification to a laparoscopic-assisted fashion.

Intragastric Satiety-Inducing Device (ISD)

The ISD (Full-sense™; BFKW, LLC, Grand Rapids, MI, USA) is a novel endoscopically-placed stent-like device that aims to promote satiety and a feeling of fullness. Its particular shape resembles a standard esophageal metallic stent with a wide disk attached to the distal end.

The endoscopist should place the ISD through the esophagogastric junction (EGJ). The proximal tubular side of the device anchors in the distal esophagus while the distal disk stays in the gastric side of the cardia (Figs. 39.3 and 39.4). By applying continuous pressure to the EGJ, the ISD hypothetically stimulates vagal afferent receptors to induce satiety [30]. Moreover, the disk distends the cardia and part of the gastric fundus, which might also downregulate ghrelin production and release, ultimately suppressing hunger [31, 32].

To date, three animal studies have been published assessing the safety and effectiveness of the ISD. Firstly, Park et al. investigated three types of devices in six porcine survival models: fully covered (A), fully covered with barbs (B), and uncovered with barbs (C). Unfortunately, the authors found migration rates as high as 100% in groups A and B and 67% in group C [33].

Later, Luo et al. assessed the efficacy and safety of two uncovered ISDs: the first type had a single gastric disk (SD)

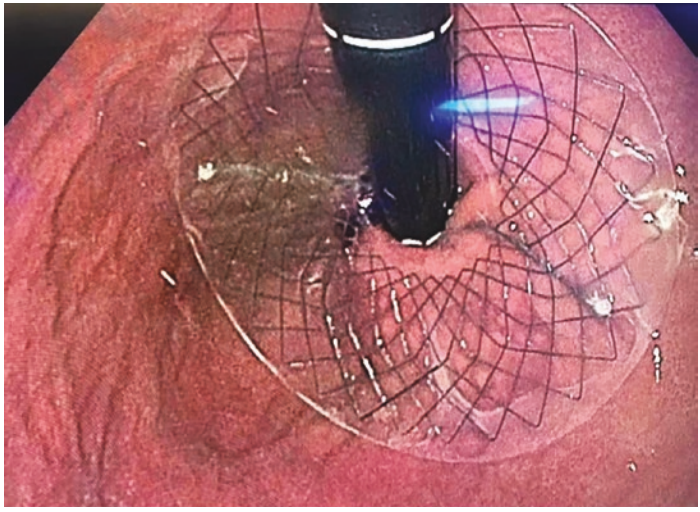

FIGURE 39.3 Radiographic aspect of the intragastric satiety-inducing device placed through the esophagogastric junction

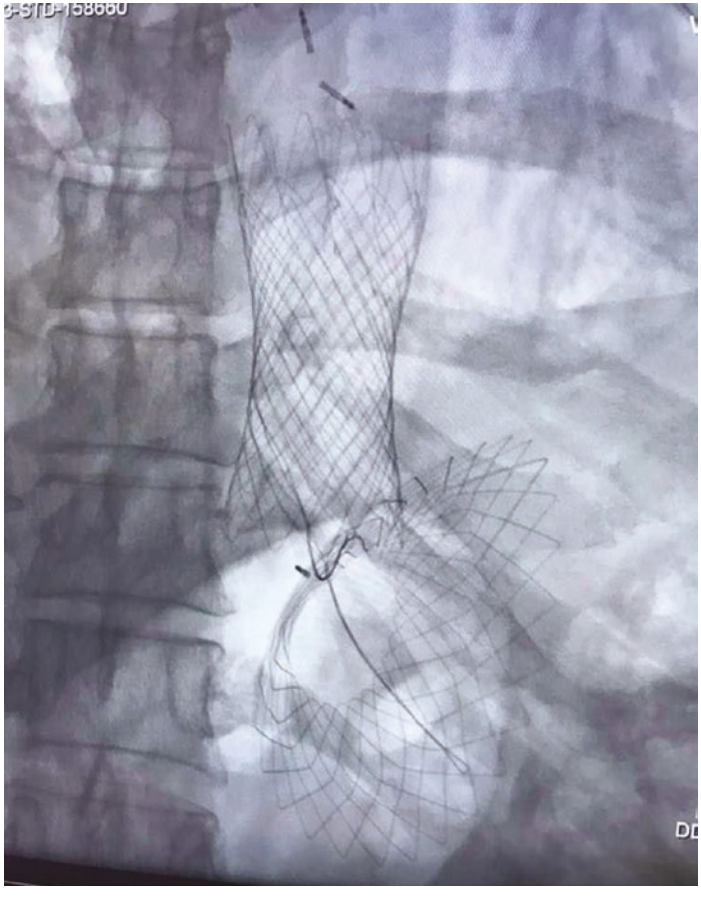

FIGURE 39.4 Endoscopic retroflexion showing the distal disk of the intragastric satiety-inducing device compressing the gastric side of the cardia and fundus

while the other had a double disk (DD). Thirty-two rodents randomly underwent ISD placement (SD or DD), esophageal stenting (ES), or a sham operation. There were no migrations, but all devices had been surgically sutured. The authors found that the food intake and body weight were significantly lower in both SD and DD groups than in sham. However,

there was no significant change in serum ghrelin levels [34], which might indicate another physiological reason for weight loss rather than ghrelin suppression.

Finally, Bakheet et al. published the most recent study comprising five juvenile pigs that received the ISD and three control ones. Although all devices were anchored by a thread attached to the animal's snout, the authors reported two cases of migration (40%). The intervention group experienced lower weight gain rates compared to the control group from week 1 to week 6, when the device was removed. Moreover, ghrelin levels were also lower in ISD pigs. Immunohistochemical studies showed fewer interstitial cells of Cajal in animals undergoing ISD placement, suggesting that gastric motility alterations could be overlapping hormonal changes [35].

After several modifications and refinements in the device to mitigate the high migration rate, the first-in-human study was recently initiated in India. If proven safe and effective in clinical studies, the ISD might become another tool in the armamentarium against Obesity.

Sleeveballoon

The Sleeveballoon is a novel intragastric balloon-like device that aims to mimic the Roux-en-Y gastric bypass procedure's exact effect. It consists of a balloon that occupies 2/3 of the gastric lumen, which is attached to a duodenal liner. The gastric portion of the device carries a central channel that allows progressive passage of food through the sleeve (jejunal portion) and delivers food to the mid-jejunum (Fig. 39.5).

To date, there is only one animal physiology study assessing the clinical and metabolic effect of the Sleeveballoon compared to RYGB and sham operations. Thirty rats were randomly allocated to one of the procedures mentioned above on a 1:1:1 ratio. Most of the organic responses to the Sleeveballoon and RYGB procedure were similar. Namely, improvement in hepatic and whole-body insulin sensitivity sustained weight loss and reduction of visceral and subcuta-

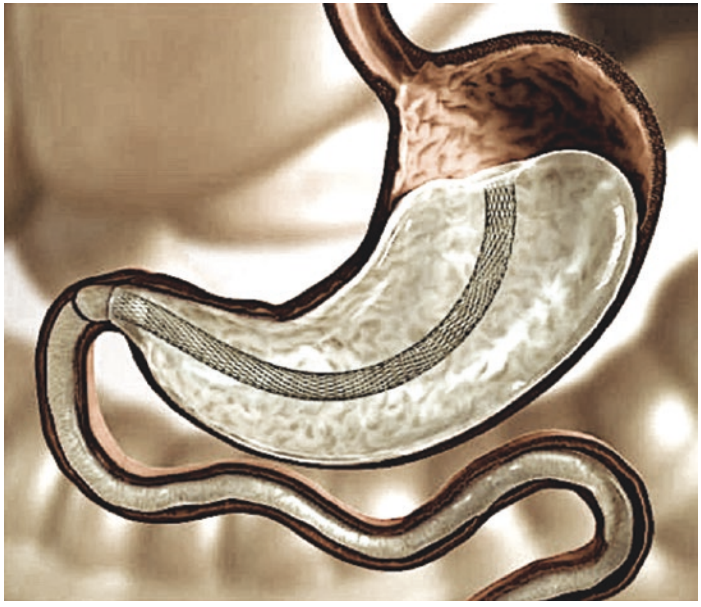

FIGURE 39.5 Schematics of the Sleeveballoon device

neous fat, and a postprandial peak of GLP1. However, the Sleeveballoon was delayed while RYGB accelerated gastric emptying compared to sham, which did not affect weight-related outcomes [36].

The industry is currently working on capitalization to start human projects. In the meantime, the exciting results of the physiology article broaden future perspectives on the endoscopic approach of Obesity and metabolic diseases.

Gastric Mucosal Devitalization (GMD)

This novel procedure employs the renowned argon plasma coagulation (APC) to ablate the internal gastric surface. Based on the hypothesis that the gastric mucosa is an independent regulator of obesity-related comorbidities, initial

studies investigated the impact of ablating 70% of the gastric surface with APC. Using a high-fat diet rat model, Oberbach et al. compared GMD to vertical sleeve gastrectomy (VSG) and sham procedure. The authors found that GMD promoted significant reductions in visceral and subcutaneous adipose tissue, body weight, and hepatic steatosis. Furthermore, lipid metabolism improved after GMND in rates similar to VSG and to a greater degree than after the sham procedure [37]. A further study demonstrated that GMD also improves blood pressure, renin, and cardiovascular lipid deposition in obese mice [38].

Posteriorly, Kumbhari et al. developed a porcine model with an analogous design and confirmed the efficacy of the GMD in non-human settings. Twenty-three pigs were included in the study, of which 9, 7, and 7 underwent GMD, sleeve gastrectomy, and sham operation, respectively. There were no unexpected adverse events, and all pigs were euthanized per protocol at 8 weeks. The endoscopic procedure elicited more pronounced weight loss at 4 and 8 weeks compared to placebo. Accordingly, visceral adiposity markedly reduced in GMD at 2 months. Comparing GMD to SG, there was no difference regarding weight loss at 4 weeks, but the latter resulted in a 29% greater relative loss at 8 weeks ($p < 0.05$).

The authors concluded that gastric mucosal devitalization is feasible and effective in the short term at promoting weight loss in a porcine model. Future human studies are warranted to confirm such effectiveness, which might add another exciting and broadly available procedure to the endoscopic armamentarium against Obesity.

Conclusion

The escalating obesity pandemic is outpacing the healthcare system's capacity to offer treatment. New technologies and novel endoscopic alternatives are evolving to help in addressing this global crisis. Newly developed devices and procedures to treat excess weight and metabolic diseases, primarily

type 2 diabetes, are revealing new promising frontiers and the use of multiple end effectors in the endoscopic management of clinically severe obesity.

Conflicts of Interest Dr. Brunaldi has no conflict of interest to declare. Dr. Galvao Neto isa consultant for APOLLO ENDOSURGERY, FRACTYL LABS, GI WINDOWS, GI DYNAMICS, USGI, COLUBRIS MX, KEYRON, MEDTRONICS, OLYMPUS, ETHICON ENDOSURGERY, ALACER BIOMEDICA, CMS/SCI-TECH, AND MI TECH outside the submitted work.

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Chapter 40
Endoscopic Bariatric Revisional Procedures

Jennifer Colvin and Stacy A. Brethauer

Introduction

The prevalence of obesity has been increasing, and it is estimated that 18 million adults have a BMI >40 kg/m^2 [1]. As the only durable treatment of obesity, metabolic, and bariatric surgery becomes increasingly important in treating the obesity epidemic, with over 250,000 procedures performed in the USA in 2018 [2]. Of these patients, approximately 10–20% have insignificant weight loss or experience weight regain [3]. As such, revisional procedures have also increased drastically from 9480 cases in 2011 to 38,971 cases in 2018 [2]. This demonstrates the need for adjunctive treatment modalities to manage this chronic disease.

Weight recidivism is complex and requires a thorough evaluation of behavioral, nutritional, and anatomical details to deliver safe and effective treatment [4]. A multi-disciplinary approach should be taken when evaluating any patient for revisional bariatric procedures. Complete and detailed assessments by registered dieticians and psychologists specializing

J. Colvin · S. A. Brethauer (✉)
Department of Surgery, Division of General and Gastrointestinal Surgery, The Ohio State University, Columbus, OH, USA
e-mail: Jennifer.Colvin@osumc.edu; stacy.brethauer@osumc.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_40

in obesity are fundamental [5]. This includes a review of clinical history, medications, social stressors, and eating behaviors and psychiatric co-morbidities. A complete evaluation of the surgical history and current anatomy is also crucial before any surgical or endoscopic intervention. Large gastrojejunal anastomosis, dilation of the gastric pouch, and gastrogastric fistula may all contribute to weight regain [6, 7]. As such, contrast studies and upper endoscopy can give valuable information regarding postoperative anatomy [6, 8].

While there are multiple options for surgical revision after a sleeve gastrectomy, the options after Roux-en-Y gastric bypass are limited, given the anatomy. Traditionally, common channel shortening or reduction of the size of the gastrojejunal anastomosis was offered to these patients [9]. However, revisional surgery is associated with significantly higher morbidity compared to primary procedures [10]. Therefore, endoscopic therapies are emerging as a less-invasive alternative to revisional surgery in the long-term management of obesity.

Endoscopic Procedures and Devices

Transoral Outlet Reduction (TORe)

Transoral outlet reduction procedures place sutures around the gastrojejunal anastomosis to reduce the stoma's size to <1 cm diameter [4]. The intent is to re-create gastric restriction and delay emptying from the gastric pouch after eating. The RESTORe trial, the first large trial evaluating this concept, was a multi-center randomized controlled trial comparing a sutured outlet using the Endocinch® device versus a sham group in patients who had regained weight after gastric bypass. While the trial demonstrated the safety and short-term efficacy of the procedure using a suction-based partial-thickness endoscopic suturing device, the results were not durable, and the primary endpoint of the study was not met. In the final analysis, patients had only an average of 3.5% total weight loss at 1 year post-procedure. [11]

A newer platform was subsequently developed that placed full-thickness sutures (Overstitch device, Apollo Endosurgery, Austin, TX). Studies using the Overstitch (Fig. 40.1) resulted in superior weight loss outcomes compared to partial-thickness sutures [12]. In a study of 130 patients who had a 25% weight regain from their nadir after gastric bypass and underwent a TORe procedure, the average weight loss at 6, 12, and 18 months were 9.31 ± 6.7 kg ($N = 84$), 7.75 ± 8.4 kg ($N = 70$), eight ±8.8 kg ($N = 46$) ($p < 0.01$ for all three-time points), respectively. In a meta-analysis of 330 patients undergoing the same procedure, the pooled weight loss at 12 months was 8.4 kg. Nausea and pain were commonly reported after these procedures, but no major adverse events occurred in these studies [13]. Fig. 40.2 shows a dilated gastrojejunal anastomosis pre- and post-TORe procedure.

Mucosal ablation using argon plasma coagulation (APC) was then added to optimize weight loss outcomes after these revisional procedures [14]. APC utilizes radiofrequency energy in the form of ionized gas as a form of non-contact

Figure 40.1 Overstitch device

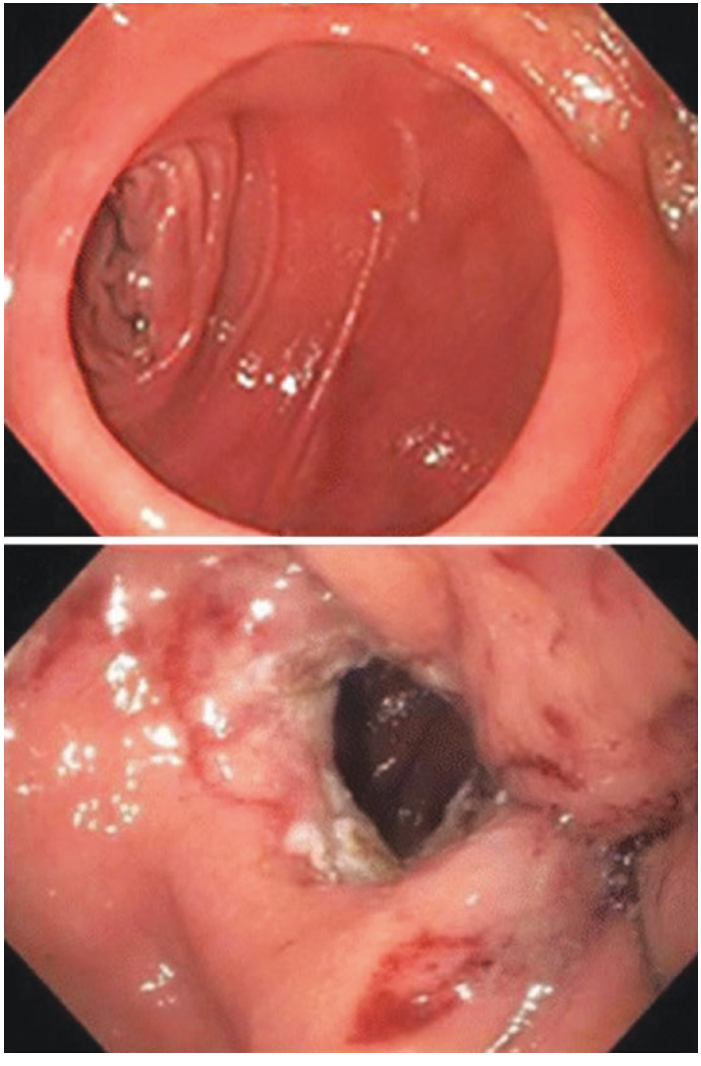

FIGURE 40.2 Gastrojejunal anastomosis pre and post-TORe

cautery [15]. In a prospective series, the mucosa of the gastrojejunal anastomosis was ablated circumferentially using APC prior to full-thickness TORe using the Overstitch device. Plication sutures were also placed in the distal pouch to reduce pouch volume if deemed necessary. At 1 -year follow-up, total weight loss was 9.5 ± 0.9% [14]. Durability of these procedures has remained a concern. Like any treatment for obesity, there will be responders, partial responders, and non-responders. As techniques evolve and experience grows, though, it appears that the majority of carefully selected patients will have a favorable response to a TORe procedure when performed by an experienced endoscopist. The longest follow-up to date for TORe is reported in a study by Jirapinyo et al. They reviewed outcomes of 342 TORe procedures in 331 RYGB patients with a pre-TORe BMI of 40 kg/m^2 and an average gastrojejunal anastomosis measuring 23.4 ± 6.0 mm. After mucosal ablation with APC, the majority of procedures (76%) used a purse-string closure, and post-TORe anastomotic diameter was 8.4 ± 1.6 mm. In this study with 83% follow-up rate at 5 years, patients experienced 8.8% ± 12.5% total weight loss (TWL). [16]

Since the overstitch device allows for multiple bites and multiple sutures to be placed without exchanging the scope, different suture patterns (purse-string, interrupted, continuous running) have been used. Patel et al. compared different suturing techniques using the overstitch device in combination with circumferential APC ablation of the gastrojejunostomy. There was a greater reduction of stoma diameter with the purse-string technique (84.2 ± 5.1% vs. 76.8 ± 8.5%, $p = 0.01$). There was also a trend towards greater weight loss using the purse-string technique, but this failed to reach statistical significance [17].

StomaphyX (EndoGastric Solutions, Redmond, WA) was another method of natural orifice surgery that was used for both gastric pouch and stoma outlet reduction. This system used 7-mm, 3–0 polypropylene H-fasteners to create full-

thickness, serosal-to-serosal tissue approximation [18, 19]. Goyal et al. utilized the StomaphyX device to perform endoscopic gastric pouch plication without stoma outlet reduction. Long-term weight loss results were poor, with an average weight loss of 1.7 ± 9.7 kg (4.3 ± 29.8% excess body weight loss) at 24–48 months post-procedure [20].

When StomaphyX was utilized to reduce the size of both the gastric pouch and the stoma, weight loss results were improved. In this technique, fasteners were placed circumferentially, starting 1 cm above the gastrojejunostomy and proceeding proximally to 1 cm below the gastrojejunal anastomosis [18, 21]. Stoma diameter was reduced from 22 mm to 9 mm, and gastric pouch size was reduced by 33% on average [21]. At 12-month follow-up, average weight loss was 10.0 kg (range 2.3–29.5 kg), which corresponded to 19.5% excess body weight loss (range 5.7–38.0%) [18]. Other studies have failed to show significant weight loss with the StomaphyX device. In fact, a randomized controlled trial comparing StomaphyX vs. sham surgery was terminated early due to failure to achieve clinically meaningful weight loss in the treatment group. At 12 month follow-up, patients in the treatment group lost an average of 7.8 ± 10.7% excess weight [19]. This device did add to our knowledge about endoscopic revisional procedures but is no longer available for use.

Based on the available literature, endoscopic pouch plication alone does not result in adequate weight loss. Data also suggests that suturing is superior to plication for TORe. Full-thickness, purse-string suturing techniques combined with APC of the gastrojejunal anastomosis have shown the best long-term results with regards to weight loss. This technique can be combined with plication of the gastric pouch if necessary to reduce pouch volume to 15–30 mL.

Restorative Obesity Surgery Endoscopic (ROSE)

The ROSE procedure uses the incisionless operating platform (IOP) to reduce the size of both the gastric pouch and

stoma by placing expanding tissue anchors to create tissue folds [4, 22]. The IOP system is introduced into the pouch, and circumferential folds are placed around the stoma to reduce the size of the gastrojejunostomy outlet. Tissue folds are then placed proximally in order to reduce the size of the gastric pouch [22, 23]. Average weight loss at 6 months was 6.6 ± 6.5 kg in one study [22]. Another retrospective study showed a total weight loss of 4.2 ± 4.7 kg, which corresponded to a total weight loss of 4.7 ± 5% at follow-up [23].

Argon Plasma Coagulation of the Gastrojejunal Anastomosis

As mentioned previously, circumferential ablation of the gastrojejunal anastomosis was shown to be beneficial in terms of total weight loss when combined with endoscopic suturing to reduce the stoma size [14]. APC has also been used successfully in the absence of endoscopic suturing. Aly first published a case report of successful APC ablation of the gastrojejunal anastomosis in a patient that was a poor candidate for revisional surgery [24]. In 2015, Baretta et al. published their results, in which they demonstrated the safety and efficacy of APC ablation of the gastrojejunal anastomosis. In their series, patients were required between one and three sessions to decrease the stoma size to the goal diameter of <12 mm. Long-term weight loss data, however, was not available [25]. Moon et al. published a larger retrospective review analyzing the efficacy of APC ablation for the treatment of weight regain. Stoma size was able to be reduced by 10.4 ± 6.3 mm, and total weight loss at 12 months was 8.3 ± 0.4% [25].

The settings for APC ablation, however, are not standardized. Jirapinyo et al. compared the efficacy of low and high-dose APC for treating weight regain. APC was performed using a 7 French StraightFire APC catheter probe (ERBE, USA) using either low-dose settings (pulsed APC, flow 0.8 L/min, effect of 2, maximum 45–55 W) or high-dose

settings (forced APC, flow 0.8 L/min, maximum 70–80 W). At 12 months, weight loss was higher in the high-dose group (9.7 ± 10% vs. 5.1 ± 8.5% total weight loss, $p = 0.008$). In addition, fewer sessions were required to reach the goal stoma size of 10 mm in the high-dose group (1.4 ± 0.7 vs. 2.4 ± 1.5 procedures per patient) [26].

One advantage of the APC-only technique is that it is easier to perform and takes less time per session. In one study, the average procedure time was 5–10 mins [15]. In comparison, the average procedure times using the Overstitch device to perform TORe were up to 79.0 ± 33.9 mins in one study [27]. Similarly, the average procedure time using the StomaphyX device was 35 mins [18]. There is also a steeper learning curve with endoscopic suturing. Currently, though, APC is used mainly as an adjunct to suturing procedures.

Endoscopic Sclerotherapy

Endoscopic injection of sodium morrhuate has been used as a sclerosing agent in order to decrease the size of the gastrojejunostomy. In this technique, sodium morrhuate (50 mg/mL) is injected in 2 mL aliquots circumferentially around the dilated gastrojejunostomy [28]. Most patients require repeated sessions in order to achieve the desired result [28–31]. In one of the largest studies analyzing sodium morrhuate sclerotherapy, the average weight loss at 6 months was 4.5 ± 7.2 kg (4.4% total body weight loss) [28]. However, other studies have shown poor long-term weight loss with the technique. In one study, the average weight loss at long-term follow-up at 22 ± 14 months was only 1.4 ± 8.9 kg [29]. In another study, almost one-third of patients gained weight after treatment, and another third maintained a stable weight [30].

Based on the available data, endoscopic sclerotherapy results in less weight loss compared to other techniques such as APC and endoscopic suturing. However, sclerotherapy does have the advantages of being widely available, easy to perform, and lower cost compared to other techniques [28].

One disadvantage is that it can take repeated sessions to achieve an acceptable stoma size. In fact, it took up to six procedures to achieve the desired results in one study [31]. In comparison, most studies looking at APC only required one to three sessions on average [25].

Future Directions

Endoscopic procedures to arrest weight gain or promote additional weight loss after gastric bypass have been available for over a decade but have had modest results and questionable durability. The most current technology, though, does provide a more "surgical" approximation of the tissue. Promising evidence of effectiveness and durability is now emerging from centers with extensive experience performing these procedures.

Because revisional options for weight regain after bypass are limited, endoscopic techniques and procedures will continue to evolve for this indication. Currently, though, sleeve gastrectomy is the most commonly performed bariatric procedure in the USA, and some of these patients will also experience weight regain. There are currently no endoscopic revisional options for sleeve gastrectomy, likely because there are viable surgical options, but there may be a role for endoscopy in patients who are poor surgical candidates or don't want a conversion operation. As suturing procedures are now available to perform primary weight loss procedures (endoscopic sleeve gastroplasty), it is possible that these techniques could be used to revise a sleeve gastrectomy in the future.

Many challenges remain for the future of endoscopic bariatric procedures. More data for efficacy and durability is needed to support revisional procedures like pouch and stoma reduction in order for them to be widely accepted. Additionally, the advanced endoscopic skills required to perform these procedures are not common among most bariatric surgeons or gastroenterologists in the USA. Lastly, insurance coverage for these procedures can be difficult to obtain, and most of these procedures are currently paid for by the patient.

Summary

The endoscope remains an important tool for bariatric surgeon. Revisional endoscopic procedures can be performed safely and provide additional short-term weight loss in the majority of patients. Currently, purse-string suturing of the gastrojejunostomy appears to be the most effective technique to manage weight regain after gastric bypass endoscopically. Despite some promising 5-year results, further evidence is needed to support the durability of these procedures.

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Chapter 41
ERCP and the Bariatric Patient

Aurora D. Pryor and Kevin K. Seeras

Introduction

The management of biliary tract disease in the bariatric patient has been a challenging and evolving process throughout the history of metabolic surgery. Difficulties are well described when considering the approach to biliary tract diseases in a patient who has undergone intestinal bypass resulting in impaired access to the biliary tree. This chapter will describe approaches and outcomes of various techniques to perform endoscopic retrograde cholangiopancreatography (ERCP) in patients who have undergone intestinal bypass procedures. It is well known that rapid weight loss results in an alteration in bile composition, with reduced concentrations of bile acids and increased concentration of calcium, mucin, and cholesterol [1]. These factors, combined with biliary stasis, commonly lead to the formation of cholesterol gallstones in post-bariatric surgery patients.

A. D. Pryor (✉)
Long Island Jewish Medical Center, Northwell Health, New York, NY, USA
e-mail: aurorapryor@icloud.com

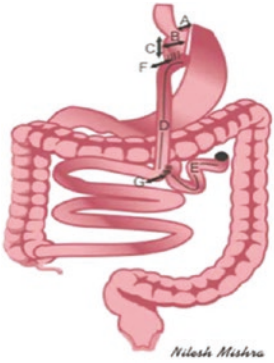
K. K. Seeras
HCA West Florida Division, Tampa, FL, USA

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_41

The development of cholelithiasis and choledocholithiasis post-Roux-en-Y gastric bypass (RYGB) is well described with an incidence between 13–42% and 0.22–0.44%, respectively [2–5]. The incidence of new gallstone formation was shown to be reduced from 32% to 2% in a blinded, randomized, placebo-controlled trial at 6 months with the use of prophylactic Ursodeoxycholic Acid. However, this study did not focus on symptomatology or the need for cholecystectomy in these patients [6]. Many randomized trials and meta-analyses have also demonstrated a reduction in gallstone formation with pharmacologic prophylaxis, but the clinical benefits pertaining to the prevention of biliary complications remain inconclusive. Other issues with the use of Ursodeoxycholic Acid are high costs, side effect intolerance, and patient non-compliance, making its current use a point of controversy [7–13]. The rate of cholelithiasis and its complications after BPD-DS in patients treated with prophylactic Ursodeoxycholic Acid have been investigated, revealing a 12.1% cholecystectomy rate in the long-term postoperative period [14]. With rates of prophylactic cholecystectomy for intestinal bypass procedures declining over recent years, the management of common bile duct stones in these patients with limited access to the biliary tree must be fully understood.

Commonly encountered bariatric procedures are sleeve gastrectomy (SG), adjustable gastric banding (AGB), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with duodenal switch (BPD-DS), one anastomosis gastric bypass (OAGB), and single anastomosis duodeno-ileostomy with sleeve gastrectomy (SADI-S). Of the mentioned procedures, access to the biliary tree with conventional ERCP is not likely with the bypass procedures; RYGB, BPD-DS, OAGB, and SADI. The following briefly describes the anatomy and ERCP difficulties associated with these procedures.

RYGB (Fig. 41.1)



A = 1-2 cm	Distance from esophagogastric junction
B = 3 cm	Width of created gastric pouch (approx.)
C = 3-4 cm	Length of created gastric pouch
D = 50-150 cm	Length of Roux-en-Y limb
E = 50-150 cm	Length of biliopancreatic limb
D+E = 200 cm	
F = 1.2-1.5 cm	Width of gastroenterostomy
G = 3-4 cm	Width of enteroenterostomy
V = <30 cc	Volume of gastric pouch

Roux-en-Y Gastric Bypass (RYGBP)

FIGURE 41.1 The standard access to the ampulla of Vater is compromised with the bypass of the remnant stomach. Note that the distance to D2 can exceed 300 cm peroral endoscopy. (From Mohit Bhandari. Reprinted with permission from Springer Nature)

OAGB (Fig. 41.2)

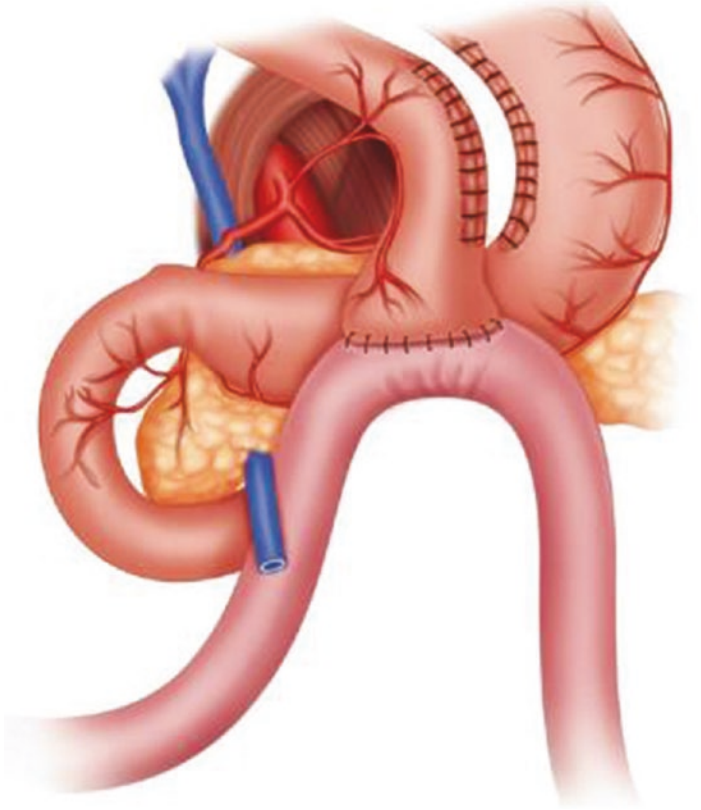


Figure 41.2 The standard access to the ampulla of Vater is compromised with the bypass of the remnant stomach. Note that the distance to D2 can exceed 200 cm per oral endoscopy. (From Billy, Bashah, and Fairley. Reprinted with permission from Springer Nature)

BPD-DS (Fig. 41.3)

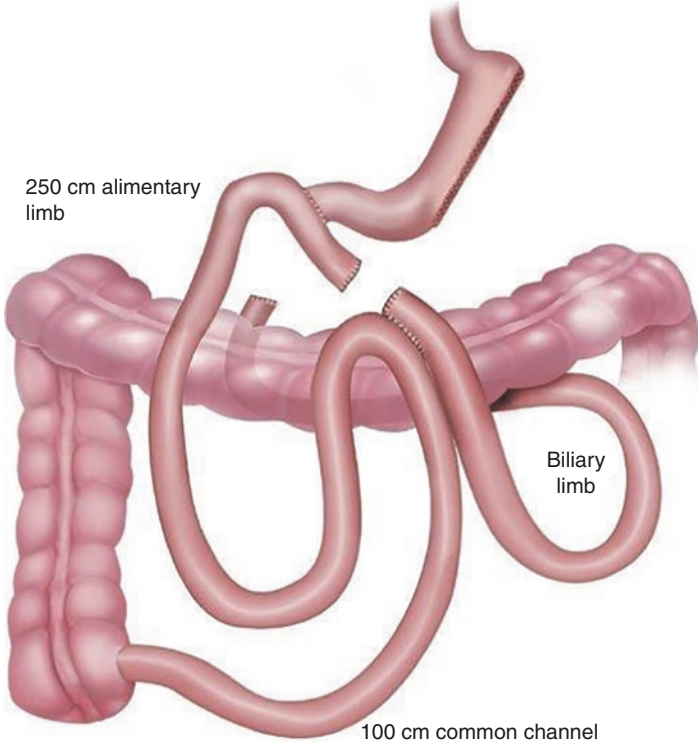


FIGURE 41.3 The standard access to the ampulla of Vater is compromised with the bypass of the second portion of the duodenum. Note that there is no excluded remnant stomach connecting to the duodenum as in the RYGB. (From Sudan and Podolsky. Reprinted with permission from Springer Nature)

SADI-S or OADS (Fig. 41.4)

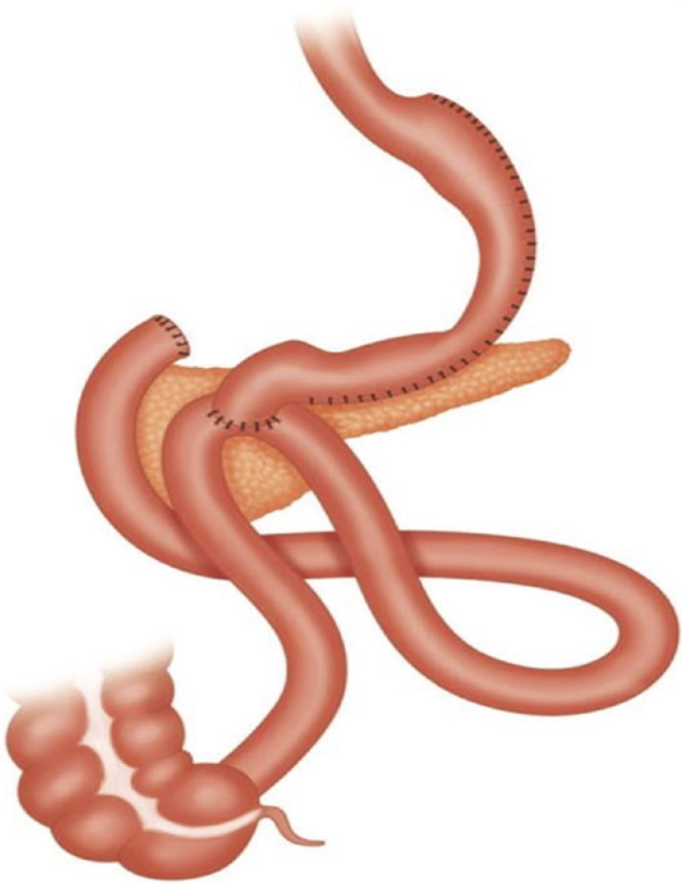


FIGURE 41.4 The standard access to the ampulla of Vater is compromised with the bypass of the second portion of the duodenum. Note that there is no excluded remnant stomach connecting to the duodenum as in the RYGB. (From Bradley and Reavis. Reprinted with permission from Springer Nature)

Management

When considering altered intestinal anatomy, several methods can be utilized in evaluating and treating biliary pathology, which involve endoscopic, surgical, and percutaneous techniques alone or in combination. Techniques described are deep enteroscopy with retrograde ERCP, surgical transgastric ERCP, surgical transenteric ERCP, percutaneous transgastric ERCP, percutaneous transhepatic cholangiography (PTC), surgical common bile duct exploration (transcystic vs. transcholedochal), and gastro-gastric fistula formation with ERCP.

Management of the common bile duct in intestinal bypass patients is a complex decision. In terms of RYGB and OAGB patients, there are far more options to access the biliary tree when compared to the BPD-DS and SADI-S techniques. Although we will not incorporate PTC and surgical common bile duct exploration into our discussions as it is beyond the scope of this chapter, we must be aware of the indications for these techniques. Surgical common duct exploration, in particular, has seen major recent advances in technology and acceptability and often may be first-line therapy, especially with the gallbladder in situ. If these techniques are not feasible, based on training, equipment, or anatomic reasons, ERCP is frequently preferred. In the following chapter, we will describe and critique various techniques for a successful ERCP in the intestinal bypass patient.

Enteroscopy-Assisted ERCP

Purely endoscopic access to the biliary tree has been described in cases of RYGB. The use of a standard endoscope is rarely successful, with the highest rate of cannulation achieved on patients with short limb bypasses not typical of current bariatric operations [15]. Longer scopes, such as a push enteroscope or a pediatric colonoscope, have reported suc-

cess rates of approximately 50% in longer limb bariatric patients [16]. Balloon endoscopic technology, which was originally introduced in 2001 for small bowel examination, has been applied to ERCP techniques and is now commonly referred to as enteroscopy-assisted ERCP or e-ERCP. These are technically challenging procedures that are deemed time-consuming and have a steep learning curve. Single or double-balloon endoscopes (Fig. 41.5) are used, and technical success

Figure 41.5 Double-balloon endoscopy system (From Takano and Yamataka. Reprinted with permission from Springer Nature)

rates vary in the literature and are generally more successful in gastrojejunostomies not done for weight loss.

E-ERCP performed for long-limb bariatric patients has a therapeutic success rate of about 60%. Further analysis revealed that total limb length was the primary factor associated with e-ERCP success rates: (88% vs. 25%), Roux + BP limb length <150 cm and > 150 cm, respectively. For Roux + BP limb >225 cm, there were no successful e-ERCP therapies completed [17, 18]. Another technique of e-ERCP is the use of spiral enteroscopy, in which a rotating overtube is installed over a push enteroscope and used to reach the ampulla (fig. 41.6 and video 1). Results are promising, with an 86% success rate when done for bariatric length Roux en-Y anatomy [19].

In general, these e-ERCP enteroscopes are classically 200 cm long and are forward viewing. A limitation of the traditional length scopes with a 2.8 mm working channel is that conventional ERCP accessories will not be adequate, and specialty equipment is required. Accessory catheters should be at least 230 cm long, and their corresponding wires should be double that length. Most conventional ERCP interventions (sphincterotomy, balloon dilation, stone extraction, small-caliber plastic stent placement) can be performed through these devices, with the exception of through-the-scope metal stents and 10 Fr plastic stents. As technology continues to evolve, we will continue to strive for larger diameter working channels, as demonstrated in the short single-

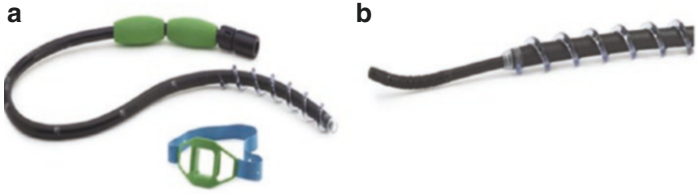


Figure 41.6 Spiral endoscope overtube (**a**), with tip detail (**b**). (From Ali MF et al., Gastrointestinal Endoscopy 2018 May;87(5):1241–1247. Reprinted with permission from Elsevier)

balloon enteroscope (sSBE) with a length of 152 cm and working channel of 3.2 mm, allowing for metallic stent placement [20]. These methods are considered low risk, with the majority of complications related to the ERCP procedure itself and the most serious adverse events being small bowel perforation, a rare event.

The above data can be extrapolated into the other intestinal bypass procedures. With extreme difficulty, e-ERCP may be performed in patients with Roux + BP limbs >150 cm. Thus we can conclude that this technique would be largely ineffective in cases of OAGB (typical afferent BP limb length of 200 cm), BPD-DS (roux + BP limb = 450 cm) and SADI (afferent BP limb approaching 300 cm).

Transgastric ERCP

In the cases of RYGB and OAGB, the remnant stomach is left in situ affording potential indirect access to the second portion of the duodenum. Cannulation of the remnant stomach can be accomplished surgically, percutaneously, and endoscopically.

Surgical Transgastric ERCP

Laparoscopic or open surgical access to the remnant stomach is the most commonly described method in current practice for transgastric ERCP. The technique typically involves laparoscopy and requires 2–4 ports. Lysis of adhesions may be performed to identify the remnant stomach and a purse-string suture, or transabdominal support sutures are placed on the remnant stomach along the greater curvature. Additional stay sutures are placed as needed to anchor the remnant stomach to the abdominal wall. A gastrotomy is created, and a 15 mm port is introduced into the stomach. Through this gastrostomy port, an ERCP is performed with the standard duodenoscope (Fig. 41.7). Upon completion of

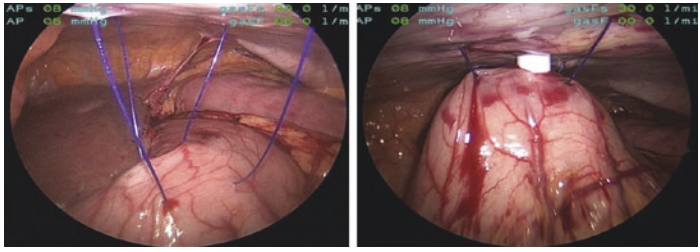


Figure 41.7 Trocar cannulating the remnant stomach with stay sutures on tension resulting in its opposition to the anterior abdominal wall. (From Katherine Habenicht Yancey et al., Journal of Obesity Published 2018 Mar 21. Article ID: 8275965, 4 pages)

the ERCP, the gastrostomy site is closed with sutures or a laparoscopic stapler. Alternatively, a large caliber gastrostomy tube can be placed if subsequent access to the biliary tree is anticipated.

Laparoscopic-assisted transgastric ERCP for the treatment of biliary tract disease in RYGB patients has an excellent success rate of 98.9%, with complications reported as high as 14%. The majority of these adverse events were minor and related to gastrostomy (wound infection) or post-ERCP pancreatitis [21].

Percutaneous transgastric ERCP - There are two percutaneous methods that can be employed for gastric remnant access and subsequent ERCP:

A gastrostomy tube is placed radiographically (CT or fluoroscopy-guided with or without ultrasound guidance) into the remnant stomach with subsequent ERCP through the fistula. This will require a period of 3–4 weeks to allow the tract to mature prior to performing the ERCP. In addition to a waiting period, radiographically guided gastrostomy tubes have adverse events in the range of 20–25%, thus making this a less attractive option for most patients [22, 23].

EUS-guided sutured gastropexy for transgastric ERCP (ESTER) is a technique published in 2015 by Attam and colleagues (Fig. 41.8). This is a percutaneous procedure that allows for ERCP to be completed at the time of remnant

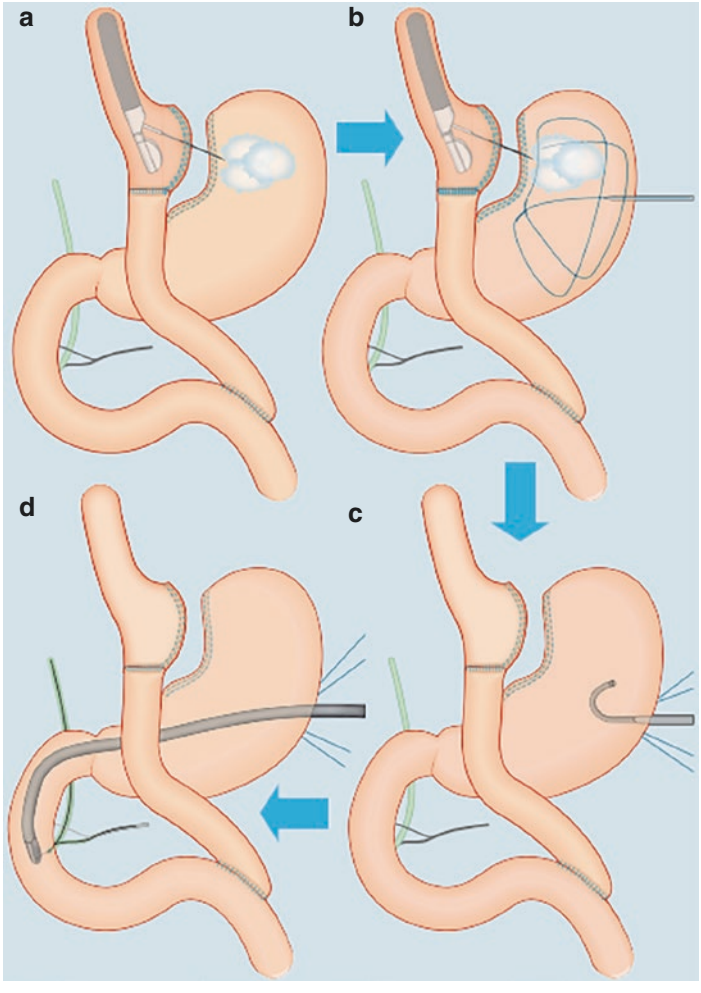


Figure 41.8 For EUS assisted transgastric access, the gastric remnant is accessed using an aspiration needle (**a**) and the remnant is inflated. Under flouroscopic guidance, as guidewire is placed in the remanant (**b**). Using seldinger technique, access is then obtained to the remnant and the endoscope placed (**c**). The ERCP is then performed (**d**). (From Attam, Leslie, Arain, Freeman, and Ikramuddin. Reprinted with permission from George Thieme Verlag KG publishing)

gastrostomy creation, thus foregoing the delay in treatment associated with tract maturation. It begins with a EUS-guided puncture of the remnant stomach from the gastric pouch with subsequent insufflation under fluoroscopy. The tract then undergoes serial dilation to accommodate a small-caliber endoscope which is then introduced into the remnant stomach. Endoscopic suturing utilizing a 2 mm laparoscopic suture passer is performed to pexy the stomach to the abdominal wall. The tract is then dilated to accommodate a 15 mm trocar, and the ERCP is performed using a conventional duodenoscope. Once therapy is completed, a 20-Fr ballooned gastrostomy tube is left in place. This case series consisted of ten patients, 9 of which the ESTER technique was successful. There were no immediate complications. The one failure was a patient with an ante-gastric Roux limb, preventing safe percutaneous puncture of the insufflated remnant stomach due to overlying bowel [24]. In theory, the modifications to anchor the stomach in the ESTER approach can be accomplished without EUS.

Endoscopic Ultrasound-Directed Transgastric ERCP (EDGE)

This technique was published in 2014, by Kedia and associates, as a method of transgastric ERCP with the sole use of endoscopy (Fig. 41.9 and video 2). The procedure begins by locating the gastric remnant with EUS from the gastric pouch or proximal roux limb jejunum. A 19-gauge needle is used to access the remnant stomach, and it is distended with contrast under fluoroscopy to confirm correct positioning. A wire is then passed, the tract is balloon dilated, and a 15 mm fully covered lumen-apposing metal stent (LAMS) is placed. The distal and proximal stent flanges are deployed under fluoroscopic guidance and direct visualization respectively to secure the stent, thus creating a gastrogastric or jejunogastric fistula. The stent is subsequently balloon dilated to accommodate the duodenoscope. Depending on the indication for

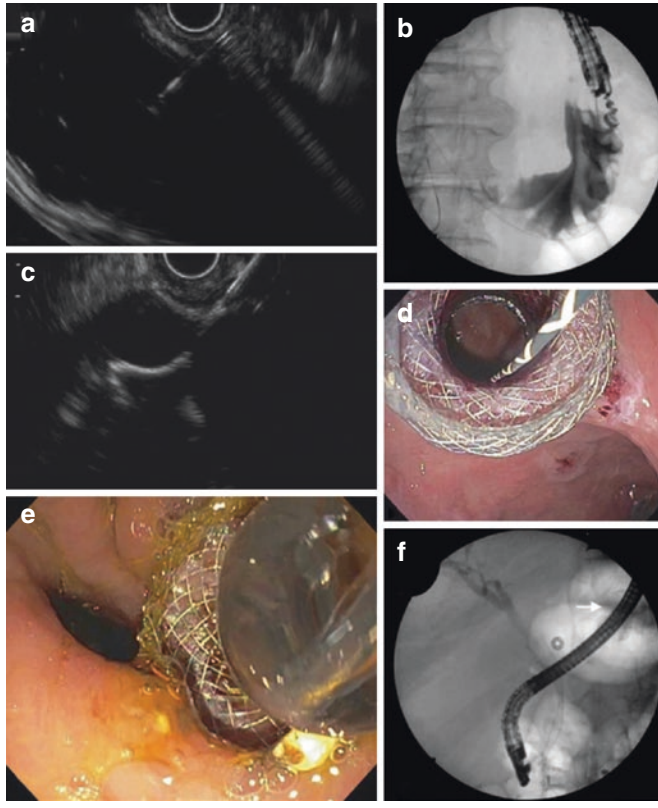


Figure 41.9 Pictorial summary of the EDGE procedure. (**a**) An Endosonographic image of the excluded stomach was accessed with a EUS needle from the remnant gastric pouch. (**b**) Fluoroscopic image showing a wire coiled within the lumen of the excluded stomach after being advanced through the EUS needle. (**c**)Endosonographic image of the distal flange of the LAMS after being deployed into the excluded stomach. (**d**) Endoscopic image of the proximal flange of the LAMS after being deployed into the proximal afferent jejunal limb. (**e**) Endoscopic image showing the lumen of the LAMS dilated with a 15-mm dilating balloon. (**f**) Fluoroscopic image showing a duodenoscope through the LAMS (arrow) with the successful placement of self-expanding metal stent in the bile duct. LAMS, Lumen-apposing metallic stent. (From Bukhari, Kowalski, Nieto, Kunda, Ahuja, Irani, Shah, Loren, Brewer, Sanaei, Chen, Ngamruengphong, Kumbhari, Singh, Aridi, and Khashab. Reprinted with permission from Elsevier Publishing)

ERCP, the procedure can be carried out at the index operation or in several weeks after the fistula tract has matured. If ERCP is performed at the index procedure, care must be taken when withdrawing the duodenoscope from the LAMS to prevent stent dislodgement. If delayed ERCP is undertaken, the patient will return for the procedure weeks later. The stent will be removed endoscopically after no further biliary tree instrumentation is required and the tract is mature. The fistula tract is then either closed (endoscopic clips or sutures), treated with argon plasma coagulation (APC), or left alone. Failure of fistula closure is the primary concern with this procedure. Longer-term follow-up is needed to demonstrate lack of weight regains or new marginal ulcer formation after this type of access.

Short- and mid-term results of the EDGE procedure are promising. The technical success of ERCP utilizing this technique is excellent, ranging from 90 to 100%. Perioperative adverse events have been reported from 0 to 24% and are commonly due to stent migration and bleeding. Management of these complications is accomplished endoscopically in the majority of reported cases with minimal morbidity. A feared long-term complication is the risk of persistent gastrogastric fistula and resultant weight gain, as well as the possible development of anastomotic ulceration. Retrospective data has shown that most fistulas will close spontaneously and are even more likely to close when suturing/clip closure or application of APC at the time of stent removal if performed [25–29]. However, endoscopic closure of peristent fistulae has been poor, and this could be a significant complication of the EDGE technique. Low-level evidence supports the following techniques to prevent stent migration: the use of a 20 mm stent as opposed to a 15 mm stent and/or LAMS fixation with endoscopic sutures prior to the passage of the duodenoscope when considering one-stage ERCP. ERCP did weeks after the initial procedure ensures tract maturation prior to endoscopic manipulation of the LAMS; this has been shown to decrease the risk of stent migration [30, 31].

A case report does describe the use of EUS-guided gastroenterostomy creation for ERCP with a LAMS in a patient

with prior BPD-DS (video 3). The patient's BP limb was distended with a contrast-saline mix, and a wire was passed into the limb under fluoroscopy via the previously placed PTC catheter. This allowed easier identification of the BP limb with EUS from the gastric sleeve. The procedure was then conducted in a similar fashion as the previously described EDGE technique with successful cannulation of the biliary system [32]. A multicenter retrospective study evaluating the use of this technique in patients with surgically altered anatomy not secondary to an RYGB was recently published. A total of 18 patients were included with a 94.4% success rate and a 5.6% adverse event rate [33]; this technique needs to be further evaluated for outcomes, techniques, and applications to other intestinal bypass procedures such as the SADI-S.

Surgical Transenteric ERCP

In the cases of SADI-S and BPD-DS, where there is no remnant stomach to afford access to the second portion of the duodenum, an ERCP must be accomplished with a surgically assisted enterostomy. This may also apply to RYGB or OAGB, in which the remnant stomach has previously been resected.

A literature review is limited considering biliary pathology after BPD-DS is an infrequent disease process encountered by the modern surgeon as it is the least commonly performed standard metabolic operation performed around the world. Case reports demonstrate successful laparoscopic-assisted transjejunal ERCP in patients who have undergone previous BPD with or without DS. Published in 2007, Mutignani et al. described the following technique [34]: The procedure begins with laparoscopic access and port placement. A purse-string is placed on the jejunum of the BP limb 40 cm distal to the ligament of Treitz. An enterotomy is made, and the BP limb is cannulated with a trocar sized to accommodate the ERCP scope (Fig. 41.10). The patient had a laparoscopically placed guidewire into the cystic duct to traverse the common bile

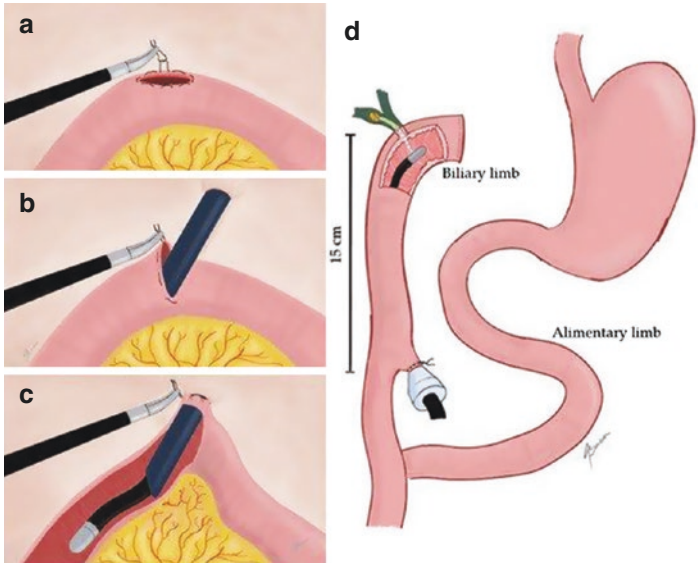


FIGURE 41.10 (**a**) Purse-string suture around enterotomy; (**b**) trocar insertion through enterotomy; (**c**) intestinal limb pulled in close contact to the abdominal wall and purse-string tightening; (**d**) endoscope insertion through the biliary limb. (From Baca-Arzaga AA et al., Medicina [Kaunas]. 2019;55(8):483)

duct and enter the duodenum. This helped facilitate to the identification of the ampulla of Vater. Utilizing a rendezvous technique, the transcystic wire is then used to guide the ERCP catheter into the bile duct. Cholangiography with or without interventions is performed, and the cholecystectomy is then completed. The final step involves closing the enterotomy with a laparoscopic stapler or sutures. Marchesini and colleagues described a very similar technique in two of their cases with technical success and minimal morbidity [34]. Other small case series presents successful cannulation of the bile duct with transjejunal ERCP in patients that have altered intestinal anatomy from various disease processes other than metabolic surgery that resemble the anatomic difficulties of a BPD-DS [35, 36].

Laparoscopic-assisted transjejunal ERCP can also be applied to RYGB and OAGB patients. Utilization of this technique is uncommon and rarely reported in the literature as transgastric ERCP through the remnant stomach has been the mainstay of treatment for the complicated biliary disease in these patients. The transjejunal technique is reserved for cases in which the remnant stomach has been resected, or anatomic factors preclude its safe cannulation. Several cases are reported in the literature, with the majority performed on patients who underwent Roux en-Y reconstructions done for reasons other than weight loss. Like the BPD-DS cases, they also demonstrate high rates of technical success with low perioperative morbidity [37–39].

Evidence-Based Algorithm for Choledocholithiasis Post-RYGB

As described above, there are many options to access the biliary tree in an RYGB patient. The decision to perform one procedure over another will be based on factors such as technical capabilities of the operating surgeon, access to specialty equipment, the clinical status of the patient, pertinent surgical anatomy with a review of prior operative reports, and costs related to the technique.

Multiple studies have recently been published comparing the different methods of transgastric ERCP in RYGB patients.

A retrospective review published by Schreiner and colleagues compared laparoscopic-assisted (LA) and balloon enteroscopy-assisted (BEA) ERCP in RYGB patients [17]. They demonstrated a success rate of 100% vs. 58% for LA-ERCP and BEA-ERCP, respectively with similar morbidity and length of stay. The success rate for BEA-ERCP was 88% vs. 25% for Roux + BP limb less than 150 cm and greater than 150 cm, respectively. The authors conducted a cost analysis comparing when BEA or LA ERCP was used first. They concluded that when BEA-ERCP is used first in patients with Roux-BP limb lengths of greater than 150 cm, there was an

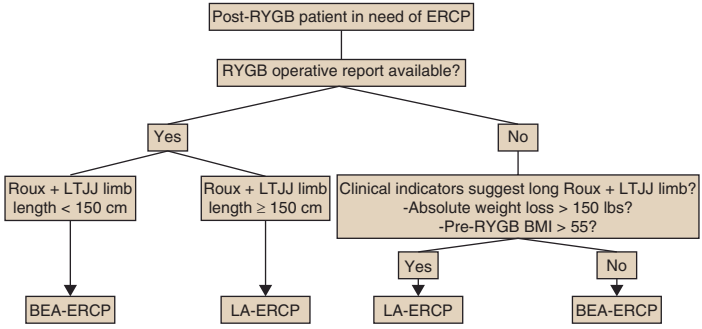


FIGURE 41.11 Proposed algorithm is equipped centers. (From Schreiner MA et al., Gastrointestinal Endoscopy. 2012;75(4):748–756. Reprinted with permission from Elsevier)

increased cost due to the high failure rate and subsequent need for LA-ERCP. BEA-ERCP is cost-beneficial when used first in patients with Roux-BP limb lengths of less than 150 cm. The authors concluded that if the patient has a reliable operative report and the limb lengths are known, it should be used to direct the initial therapy (Fig. 41.11).

A recent meta-analysis of 26 studies was conducted comparing enteroscopy-assisted (EA) and laparoscopy-assisted (LA) ERCP in RYGB patients. The endoscopic techniques included single and double balloons as well as spiral enteroscopy. The results demonstrated a success rate of 97.9% vs. 73.2%, adverse events of 19% vs. 6.5%, and mean procedure time of 158.4 and 100.5 minutes when comparing LA-ERCP and EA-ERCP, respectively. This study demonstrated the LA-ERCP has a significantly higher technical success rate but with an increase in adverse events and procedure time [40]. A limitation of these two studies in the modern era is that they did not include a comparison with the EDGE procedure.

Kedia et al. recently published the outcomes of four tertiary care centers regarding EDGE vs. LA-ERCP [41]. Technical success was impressive for both procedures, with rates of 96.5% and 97.7% for EDGE and LA-ERCP, respectively. Adverse events were similar between the two groups,

Table 41.1 Depicts outcomes between the two procedures

	e-ERCP (n = 30)	EUS-GG-ERCP (n = 30)	*P* value
Technical success ERCP, %	60.0	100	<.001
Mean procedure time, min, ± SD	90.7 ± 34.9	49.8 ± 26.5	<.001
Median length of hospital stay, days (IQR)	10.5 (1.5-13)	1 (1-3)	.02
Mean weight change, kg, ± SD	.07 ± 4.9	−1.1 ± 6.1	.42
Adverse events			
All	3 (10)	2 (6.7)	1.00
Mild	1 (33.3)	1 (50)	
Moderate	1 (33.3)	1 (50)	
Severe	1 (33.3)	0	
Death	0	0	

Values are n (%) unless otherwise defined.
e-ERCP, Enteroscopy-assisted ERCP; *EUS-GG-ERCP*, EUS-guided gastrogastrostomy-assisted ERCP; *SD*, standard deviation; *IQR*, interquartile range.

(From Bukhari M et al., Gastrointestinal Endoscopy. 2018;88(3):486–494. Reprinted with permission from Elsevier Publishing)

but procedure time and LOS were significantly reduced with the EDGE technique. However, longer-term follow-up was lacking.

Bukhari et al. published an international multicenter trial comparing EDGE and E-ERCP [18]. This study demonstrated significant superiority of EDGE when compared to E-ERCP in terms of technical success and shorter procedure time. Adverse events were comparable between the two groups (Table 41.1).

A single-center retrospective review was recently published comparing EDGE, LA-ERCP, and EA-ERCP. Technical success rates were 100% vs. 94% vs. 75% for EDGE, LA-ERCP, and EA-ERCP, respectively. Procedure time was significantly shorter for EDGE when compared to LA-ERCP and EA-ERCP with comparable adverse events [42].

A recent systematic review with meta-analysis was conducted to compare EDGE, LA-ERCP, and BEA-ERCP. Success rates were achieved in 95.5% vs. 95.3% vs. 71.4% for EDGE, LA-ERCP, and BEA-ERCP, respectively. Adverse events were comparable between EDGE and LA-ERCP; however, BEA-ERCP had a much lower rate (Table 41.2). This study concluded that EDGE is a comparable alternative to LA-ERCP and is superior to BEA-ERCP in terms of technical success [43].

Table 41.2 Outcomes of EDGE vs. LA-ERCP vs. BE-ERCP

Pooled rates of technical success, clinical success and adverse events of EDGE, LA–ERCP and BE-ERCP.

(95% CI, I2%, *P* value in comparison to EDGE)	EDGE	LA-ERCP	BE-ERCP
Technical success	95.5% (84.2–98.8, 0)	95.3% (91.3–97.5, 46.3, *P* =0.98)	71.4% (51–85.7, 87, *P* =0.01)
Clinical success	95.9% (81.2–99.2, 0)	92.9% (83.9–97.1, 84.2, *P* =0.65)	58.7% (27.6–84.1, 0, *P* =0.001)
All adverse events	21.9% (14.6–31.4, 21.2)	17.4% (14–21.5, 18.1, *P* =0.32)	8.4% (5–13.6, 0, *P* =0.001)
PEP	2.2% (0.6–7.4,0)	6.8% (5.3–8.8, 0, *P* =0.07)	6.3% (3.7–10.4, 0, *P* =0.12)
Bleeding	6.6% (3.3–13,0)	3.7% (2.6–5.4, 5.8, *P* =0.15)	1.5% (0.4–5, 0, *P* =0.04)
Perforation	2.2% (0.6–7.4,0)	2.2% (1.3–3.7, 0, *P* =0.99)	1.8% (0.7–4.7, 0, *P* =0.79)
Stent migration	13.3% (5.7–28.1, 57.6)	NP	NP
Infection	NP	5.8% (4.4–7.6, 0)	1.9% (0.7–5.2, 0, *P* =0.04 as compared to la-ERCP)

LA-ERCP, laparoscopic endoscopic retrograde cholangiopancreatography; BE-ERCP, balloon endoscopic retrograde cholangiopancreatography; EDGE, endoscopic ultrasound-directed transgastric retrograde cholangiopancreatography; PEP, post-ERCP pancreatitis; NP, not provided

(From Dhindsa BS et al., Endoscopy International Open. 2020;8(2): E163-E171. doi:10.1055/a-1067-4411)

Conclusion

There are many alternatives for ERCP access in patients with altered anatomy from bariatric surgery. In RYGB patients we can safely conclude that LA-ERCP is a reliable method for the treatment of biliary tract pathology. Recent studies have shown the EDGE technique to be comparable to LA-ERCP with decreased cost and procedural time; however, longer-term follow-up is needed to determine the consequences of

iatrogenic gastrogastric fistula creation. EA-ERCP has consistently been shown to be less successful when compared to the other techniques of ERCP but is a cost-effective option in patients with short Roux-BP limb lengths.

In BPD-DS patients, there is less conclusive data on optimal management of the biliary tree. There have been many reports of successful ERCP with the laparoscopic-assisted transjejunal method [44]. Further investigation into EUS-guided gastroenterostomy ERCP in patients with BPD-DS is warranted as this may be a feasible option in the future. PTC and surgical common duct exploration have a more significant role in the case of BPD-DS as ERCP in these patients is more difficult to perform when compared to the RYGB patient.

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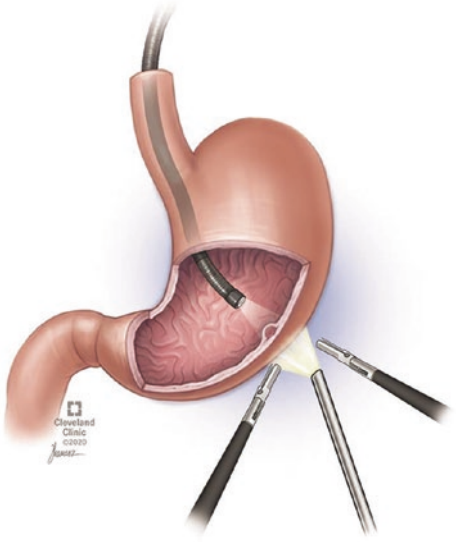
Chapter 42
Hybrid Laparoscopic and Endoscopic Techniques: Upper Gastrointestinal Tract

Abhiram Kondajji and Matthew Allemang



A. Kondajji · M. Allemang (✉)
Cleveland Clinic-Digestive Disease and Surgical Institute, Cleveland, OH, USA
e-mail: kondaja@ccf.org; allemam@ccf.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_42

Introduction

Flexible endoscopy continues to evolve and has become a vital tool for surgeons and gastroenterologists. The endoscope, which started as a diagnostic instrument, now offers therapeutic capabilities through working channels within the gastrointestinal lumen. Combining these new capabilities with the capacity of laparoscopic surgery has further advanced the field of minimally invasive surgery. This chapter describes the most frequently used laparoscopic and endoscopic hybrid surgeries to treat upper gastrointestinal tract tumors.

Gastric Lesions

Hybrid endoscopic and laparoscopic surgery shows promising results for submucosal tumors (SMT) and early gastric cancer (EGC) [1–8]. Ludwig et al. first described a hybrid procedure in 2002 where the endoscopist provided direct intragastric visualization of the tumor while the laparoscopic surgeon performed the wedge resection [9]. In 2008 Hiki et al. published the first paper to describe laparoscopic and endoscopic cooperative surgery (LECS or classic LECS) for GIST [10]. As the LECS technique gained momentum, modified versions of the hybrid surgery developed. The inverted-LECS, as developed by Nunobe et al., was the first of the modifications and prevented exposing the gastric lumen to the peritoneal cavity [8]. Soon after, the non-exposed endoscopic wall-inversion surgery (NEWS) procedure developed to treat early gastric cancer while allowing full-thickness resection without exposing the tumor or gastric lumen to the peritoneal cavity [11]. Inoue et al. developed the combined laparoscopic endoscopic approach to neoplasia with a non-exposure technique (CLEAN-NET) to maintain mucosal integrity and prevent tumor spread and gastric exposure [12]. Lastly, Kikuchi et al. described the closed LECS to address SMT with potential early gastric cancer use [13].

Gastrointestinal Stromal Tumor (GIST)

Gastrointestinal stromal tumors are the most common mesenchymal tumors, often expressing KIT (CD117)-tumor marker. GISTs arising from the Cajal cells can occur anywhere along the gastrointestinal tract, with 60% of occurrences noted in the stomach and 4–5% in the duodenum. Most patients are over the age of 50 [14]. Metastatic potential depends on the tumor size and number of mitoses per 50 high-power field described [15, 16]. The National Comprehensive Cancer Network (NCCN) currently recommends GIST resection for tumors greater than two centimeters with complete gross resection with an intact pseudocapsule and negative margin of 1–2 cm [15, 17]. Rutkowski et al. underscored the value of negative margins for better recurrence-free survival and the benefit of imatinib for R1 resections [17].

Gastric Cancer

Gastric cancer is currently the fifth most frequently diagnosed cancer and the third leading cause of cancer-related death worldwide. Frequently gastric cancer is diagnosed at an advanced stage; however, early detection through screening allows for diagnosis and treatment of early gastric cancer in Japan and Korea. Current NCCN guidelines recommend staging scans and endoscopic ultrasound to determine tumor depth [18]. Early gastric cancer (EGC) is a tumor confined to the mucosa or submucosa regardless of nodal involvement [19]. These early gastric cancers are candidates for minimally invasive procedures such as endoscopic mucosal resection [20], making them great candidates for hybrid laparoscopic and endoscopic procedures [8, 12, 20, 21]. Current NCCN guidelines for margin negative resections extend up to 6 cm proximally and four centimeters distally for T3 and T4 tumors, but there was not enough evidence to provide margins for early gastric cancer [22]. Kim et al. demonstrated margins greater than 1 mm to be adequate for EGC resection [23].

Gastric Hybrid Procedures

Patient, Surgeon, and Endoscopist Positioning

The following positioning is typical for the hybrid laparoscopic and endoscopic procedures. The patient is in the supine or lithotomy position with the laparoscopic surgeon to the patient's right, the assistant to the patient's left, and the endoscopist at the head of the bed. Standard laparoscopic port placement techniques are used to access the abdomen using the Veress, optical entry, or Hasson cut-down technique at the umbilicus. A camera port is placed near the umbilicus, followed by an additional 12 mm and 5 mm port in the right abdomen and typically two 5 mm ports in the left abdomen for the assistant. Finally, a liver retractor of choice is employed to manage the left lobe of the liver. Laparoscopic insufflation is maintained at 12–15 mm Hg. A soft bowel clamp can be placed on the proximal jejunum to limit insufflation to the gastric lumen and duodenum. This may require an extra port depending on the assistant's participation.

Classic LECS (Laparoscopic and Endoscopic Cooperative Surgery)

After establishing laparoscopic entry into the peritoneal cavity, the endoscopist enters the stomach using CO_2 insufflation and an endoscope fitted with the transparent cap. The endoscopist identifies the lesion, and the laparoscopic surgeon can identify the area of interest by endoscopic transillumination. Local blood supply to the tumor is controlled using the harmonic vessel sealing device or other laparoscopic energy devices of choice.

Argon plasma coagulation (APC) with a 20-watt coagulation current is directed at the tumor base mucosa with 5 mm margins to demarcate the tumor. A 10% glycerin solution is injected at the submucosal plane and used to elevate the

tumor. The insulated-tip knife (IT-2 Olympus, Tokyo, Japan) starts the cutting process by going to the submucosal layer and encircling the tumor. The endoscopist then changes to the needle-knife with 100-watt endo-cut mode and pushes through the seromuscular layer under laparoscopic guidance. The IT-2 is pushed through the perforation, and dissection is completed primarily by the endoscopist with laparoscopic assistance (Fig. 42.1). Any remaining dissection is completed using the laparoscopic harmonic or electrocautery device. The specimen is placed into an endobag and removed laparoscopically through the 12 mm port site.

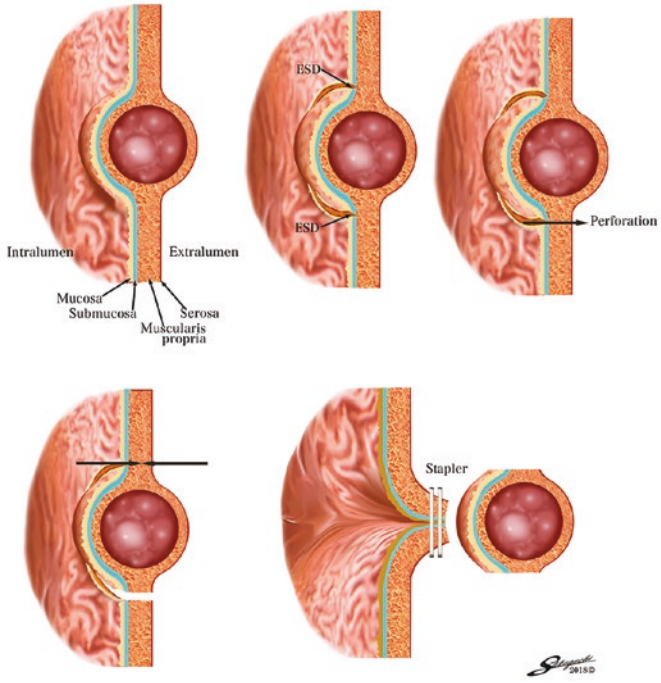


Figure 42.1 Classic Laparoscopic and Endoscopic Cooperative Surgery. From: Hiki et al. [24]. Adapted and reprinted with permission from John Wiley and Sons

The gastric defect is approximated with laparoscopic suturing and final closure completed with a linear laparoscopic stapler. Laparoscopic suturing is definitive closure for lesions close to the pylorus or gastroesophageal junction (GEJ) in an effort to prevent stenosis. A final air-leak test and hemostasis are confirmed at the end of the procedure [10, 24].

Inverted LECS

Endoscopic dissection is started using the IT-2 with 1 cm margins using the forced 20-W coagulation current. The marked area is cut to the submucosal layer circumferentially using the ITK-2 on 80-W Pulse-Cut slow mode. The tip of the knife is then visible through the thinned seromuscular layer. The ITK-2 tip perforates through the seromuscular layer using the 100-W endo-cut mode. A suture placed on the tumor without disrupting the tumor capsule provides countertraction and inverts the tumor into the gastric lumen. Additional endo-closure laparoscopic sutures are placed on the marked dissection plane's outer periphery to tent the gastric wall and provide a bowl (Fig. 42.2a). The laparoscopic harmonic device is advanced through the perforation and used to cut the tumor on the pre-established dissection line while the stomach is tented and the tumor on traction involutes into the stomach.

The tumor is pulled into the gastric lumen and removed per-orally without risking contamination to the peritoneal cavity. The endo-close sutures are approximated and provide temporary closure. The stomach defect is then closed using the laparoscopic stapler or hand-sewn with intracorporeal laparoscopic suturing (Fig. 42.2b) [8, 24].

NEWS (Non-exposed Endoscopic Wall-Inversion Surgery)

Endoscopic APC is used to mark the tumor margins on the mucosa. Then the endoscopic transillumination guides the

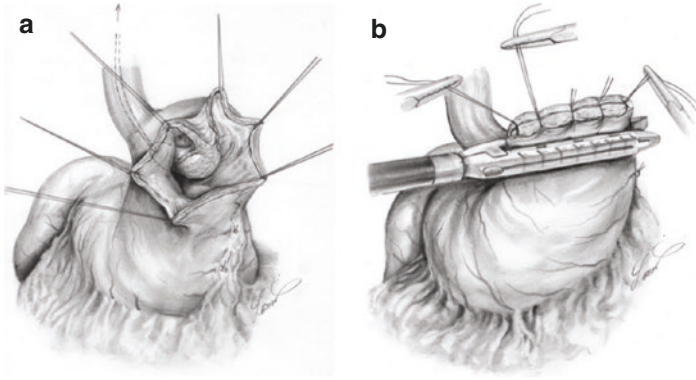


FIGURE 42.2 Inverted LECS. (**a**) To prevent contact between the tumor and the visceral tissue, the tumor is inverted to face the intragastric cavity using the traction of the stitch at the edge of the resected specimen, and the resection line of the stomach is pulled up like a bowl by several stitches. (**b**) The incision line is then properly closed using a laparoscopic stapling device with particular care paid to the direction and margin of the suture line. From: Nunobe et al. [8]. Reprinted with permission from Springer Nature

laparoscopic serosal marking. Sodium hyaluronate with indigo carmine dye endoscopically injected into the seromucosal layer delineates the tumor. The injection provides an additional protective layer and indicator for the laparoscopic seromuscular dissection. The serosal dissection is completed using the harmonic ligature device without invasion into the gastric lumen. The seromuscular layer outside of the dissection line is approximated with sutures at 5 mm intervals, and the lesion is inverted into the gastric lumen (Fig. 42.3).

The mucosal and submucosal dissection is completed using the endoscope with the indigo carmine dye acting as a guide. The tumor is then retrieved per-orally, and the mucosal edges are closed using endoscopic clips, and the stomach is checked for leaks [11, 24].

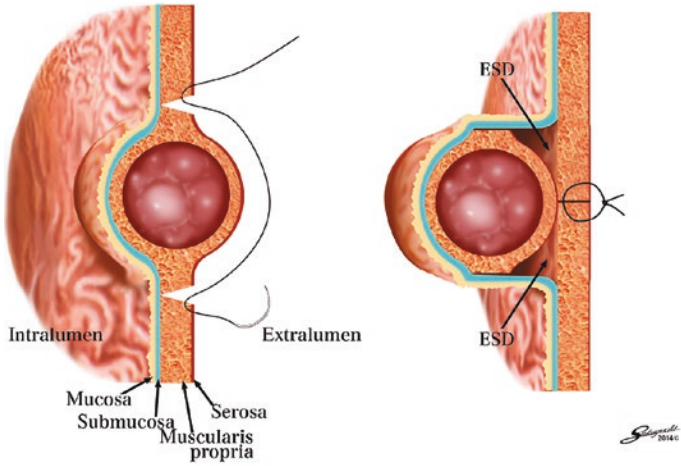


FIGURE 42.3 Non-exposed Endoscopic Wall-inversion Surgery (NEWS). From: Hiki et al. [24]. Adapted and Reprinted with permission from John Wiley and Sons

CLEAN-NET (Combined Laparoscopic Endoscopic Approach to Neoplasia with a Non-exposure Technique)

The tumor margins are marked on the mucosa using the IT-2 while maintaining the mucosa's integrity. The mucosa provides a barrier (a clean net) from exposing the tumor or gastric content into the peritoneal cavity. Four stay sutures are placed laparoscopically around the specimen with endoscopic guidance to affix the mucosa to the seromuscular layer. The sutures are elevated with laparoscopic forceps, and the seromuscular dissection outside the sutures is completed with laparoscopic electrocautery. As the specimen is dissected, the mucosa starts to involute into the specimen, and

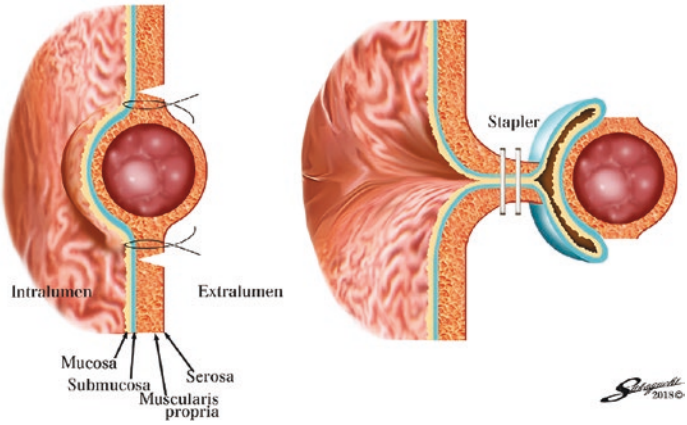


FIGURE 42.4 CLEAN-NET. From: Hiki et al. [24]. Adapted and Reprinted with permission from John Wiley and Sons

the laparoscopic stapler transects the full-thickness specimen (Fig. 42.4). An endobag retrieves the specimen through the port site [12, 24].

Closed LECS

The procedure starts by completing a circumferential endoscopic submucosal dissection around the tumor (Fig. 42.5a), followed by corresponding laparoscopic serosal markings under endoscopic light guidance (Fig. 42.5b). Laparoscopic sutures are placed outside the marked region at 5 mm intervals, and the lesion is inverted with the aid of a spongy spacer (Fig. 42.5c, d). Endoscopic seromuscular dissection of the tumor against the sponge completes the resection (Fig. 42.5e). The lesion and sponge are removed per-orally.[13].

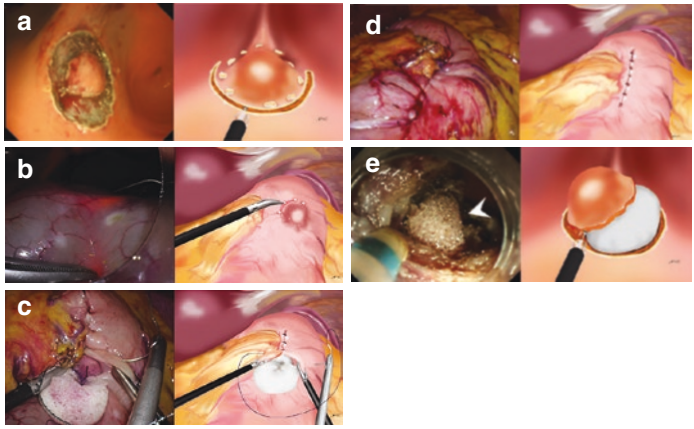


Figure 42.5 Closed LECS. From: Kikuchi et al. [13]. (**a**) Circumferential endoscopic submucosal resection around the tumor by the endoscopic submucosal dissection technique. (**b**) Laparoscopic serosal marking on the sides corresponding to the submucosal dissection line under guidance by endoscopic light. (**c**, **d**) Seromuscular suture with inversion of the marked lesion into the inside of the stomach in such a way to bury a spongy spacer, Securea (Hogy Medical, Tokyo, Japan). (**e**) Endoscopic seromuscular dissection. The spacer extended the space between the sutured seromuscular plane and the serosal surface of the inverted lesion (arrowhead), and facilitated the seromuscular dissection. Reprinted with permission from Springer Nature

Discussion

Gastric Lesions

The development of minimally invasive surgery continues to push the boundaries of gastrointestinal surgical techniques. Studies support that laparoscopic and endoscopic procedures provide adequate tumor margins, decrease blood loss, decrease tissue loss, and shorten hospital stay compared to traditional open procedures [5, 25, 26].

Hybrid laparoscopic and endoscopic surgery starting with the classic LECS shows promising surgical treatment for GIST and EGS. Current laparoscopic-only procedures do not provide adequate visualization of the lesion within the gastric lumen, and the endoscopic procedures alone cannot provide a full-thickness resection. By combining the endoscopic visualization of the mucosal surface, a smaller margin is established around the tumor while the laparoscopic component provides a full-thickness resection. All procedures previously described can be used for submucosal tumors (SMT) such as leiomyomas and GIST resection less than 5 cm and some for EGC; however, each has its limitations and may require modifications accommodating for tumor location or size [5, 27]. Table 42.1 provides a summary of the procedures.

The classic LECS procedure is versatile because it is not limited by the tumor location or suturing techniques. Tumor size is a limiting factor based on the current understanding that GIST greater than 5 cm has increased potential for malignancy, and those patients benefit from more aggressive treatment modalities [15]. The procedure has limited blood loss and can be used for SMT like GIST near the pylorus or GEJ, where laparoscopic hand suturing is required. The major limitation with this procedure is the risk of exposing gastric content or tumor to the peritoneal cavity, which is prohibitory for gastric cancer resection and some ulcerated GISTs [2, 10, 24, 27].

The inverted LECS addresses gastric exposure's potential by creating a bowl and retracting the tumor into the gastric lumen. Given the inherent gastrostomy created, this procedure is not ideal for EGC, where there still is potential for spillage. There is limited data on this procedure after the initial procedure by Nunobe et al. [8, 24, 27]. Additional studies are needed to determine the procedure's feasibility and long-term outcomes.

Non-exposure techniques such as NEWS addressed the potential for gastric contamination and tumor seeding to the peritoneal cavity. The NEWS procedure's significant limitations include tumor size less than 30 mm for per-oral retrieval

Table 42.1 Comparison of procedures

Procedure	Candidate lesion(s)	Size limits (mm)	Tumor location	Specimen retrieval	Closure
Exposed techniques					
Classic LECS	SMT	50	Any location	Transabdominal	Laparoscopic stapler or hand suture
Inverted LECS	SMT± EGC	30	Any location	Per-oral	Laparoscopic stapler or hand suture
Non-exposed techniques					
NEWS	SMT, EGC	30	Except EGJ or pylorus	Per-oral	Hand suture
CLEAN-NET	SMT, EGC	50	Except EGJ or pylorus	Transabdominal	Laparoscopic stapler
Closed LECS	SMT, EGC	30	Any location	Per-oral	Hand suture

LECS Laparoscopic and endoscopic cooperative surgery, *NEWS* non-exposed endoscopic wall-inversion surgery, *CLEAN-NET* combined laparoscopic and endoscopic approach for neoplasia with non-exposure technique, *SMT* submucosal tumor, *EGC* early gastric cancer (T1a, T1b), *EGJ* Esophagogastric junction

given the potential for pseudocapsule rupture for GIST and prolonged surgical time close to 5 h [11, 24, 27].

CLEAN-NET provides an alternative non-exposure technique with a larger tumor size given the transabdominal removal; however, tumor location is the limiting factor because of the need for a laparoscopic stapling device. Tumors on the gastric cardia or posterior wall are not easily exposed, making the laparoscopic stapling difficult. Lastly, the resection line is determined from the serosal side, which may not provide adequate EGC resections margins [2, 12, 24, 27].

Lastly, the closed LECS provides the benefits of non-exposure, better surgical margin, and full-thickness resection compared to the other procedures. There is no limitation to the tumor location because of the need for laparoscopic suturing. Limitations are the per-oral retrieval, limiting tumor size to 30 mm, and the need for a spongy spacer [2, 24, 27].

Yin et al. compared the current surgical options for GIST <5 cm in 91 patients and found LECS was comparable to laparoscopic resection alone and endoscopic submucosal dissection (ESD). Notable differences were shorter intraoperative time and less blood loss for ESD than the laparoscopic and LECS groups [28].

As previously mentioned, the NCCN currently recommends a 1–2 cm resection margin with an intact pseudocapsule for complete oncologic resection for GIST. GIST less than 5 cm can be approached with minimally invasive techniques, whereas larger tumors benefit from more invasive procedures [15]. These guidelines are based on the current widely used surgical management methods for these tumors. Laparoscopic wedge resections do not provide real-time visualization of the tumor's intragastric component, and submucosal dissections do not provide a full-thickness specimen. Tumor location may limit resection options if the tumor is not easily accessed by the laparoscopy or endoscopy alone, or if the wider resection leads to stricturing [29]. As demonstrated through the hybrid laparoscopic and endoscopic cooperative surgery studies, narrower margins can provide complete

oncologic resections without significant tissue loss [30]. These smaller margins are feasible due to the intragastric visualization, marking, and dissection provided by endoscopy, while the laparoscopic component allows for a full-thickness specimen and visualization of the peritoneal components.

Duodenal Lesions

LECS's success in the gastric lumen led to its extension to the duodenum, commonly known as D-LECS. There is considerably less data for this technique compared to gastric SMT resections. Sakon et al. first described the use of the D-LECS on two patients in 2010. Both patients had 20 mm non-ampullary tumors. After establishing laparoscopic access, the surgeon mobilizes the duodenum from the retroperitoneum. As described in the classic LECS, the D-LECS starts with mucosal markings of the tumor margin, and the submucosal dissection started using the ESD technique. The seromuscular layer is partially perforated under laparoscopic guidance. The tumor is tented with laparoscopic forceps, and the remaining dissection is completed with a laparoscopic harmonic or electrocautery knife. The tumor is retrieved with an endoscopic bag and the duodenal defect closed with transverse laparoscopic intracorporeal suturing. Sakon et al. noted negative margins and decreased operative time compared to ESD for similar pathology [31]. One of the concerns for ESD on duodenal tumors is delayed leaks from the resection with resultant morbidity and mortality. Candidate lesions for ESD are also a candidate for D-LECS. D-LECS is limited to the first and second portion of the duodenum that does not involve the ampulla. Additionally, tumors need to be less than 30 mm to allow laparoscopic suturing of the duodenal defect [25].

Nunobe et al. evaluated the safety and feasibility of D-LECS on 206 patients with tumors on the first, second, and third portions of the duodenum. The team employed two procedures: D-LECS with full-thickness resection (150

patients) or D-LECS with ESD and laparoscopic reinforcement of the duodenal wall (56 patients) by suturing the seromuscular layer. They demonstrated en-bloc resection for 96% and R0 resection for 95% of the patients. The average operative time was 180 mins, with 5.3% of cases requiring conversion to an open procedure. The most common complications were delayed emptying, followed by stenosis. Most impressively, no patients demonstrated recurrence [32].

Finally, in comparing D-LECS to ESD alone, Ojima et al. found D-LECS to be an ideal treatment option for low-risk tumors with no short-term complications noted. Low-risk tumors encompassed tumors less than 50 mm, adenomas, mucosal cancer, neuroendocrine tumor, or SMT [33].

Future

As robotic surgery continues to expand its utility in gastrointestinal surgery, it is no surprise that robotic-assisted cooperative surgery is the next step in the evolution of minimally invasive cooperative surgery. Shi et al. evaluated a third space robotic and endoscopic cooperative surgery (TS-RECS). Twenty patients with endoscopically confirmed GIST were enrolled. This technique preserves the mucosa and limits tissue destruction. The steps as described by Shi et al. are as follows: Robotic laparoscopic set-up with endoscopic visualization of the tumor. The lesion is then lifted by endoscopic submucosal injection of 10% glycerol fructose and 4% methylene blue solution, which creates a third space. Using the injected dye as a circumferential tumor-marker, robotic dissection is started into the seromuscular layer and continued until the tumor is removed from the mucosal layer of the gastric wall. The specimen is placed in an endoscopic bag for removal, and the serosal defect is closed with robotic hand suturing or stapler device [34].

The short-term data is promising, with 100% of patients with R0 resection and no recurrence for the 10-month median follow-up period. Additionally, the shorter operative

time of 115 mins [34] and technical ease make TS-RECS alluring when compared to NEWS (252 mins), CLEAN-NET, or CLOSED-LECS (253 mins).[2, 27] Given these promising early results, this technique may be adapted for duodenal lesions that are candidates for D-LECS or EGS.

Conclusion

The last two decades have seen a remarkable evolution of minimally invasive surgery with the advancement of flexible endoscopy and robotic surgery. Much of the data regarding surgical management for GIST and EGC comes from Japan and Korea where tumors are often found in the early stages due to robust screening. Hybrid laparoscopic and endoscopic surgery has proven to be a safe and feasible option for patients who present with GIST or EGS. As data continues to support the use of these procedures, they may become the new standard of care and provide patients with complete and less destructive tumor resections.

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Chapter 43
Hybrid Laparoscopic and Endoscopic Techniques: Colon and Rectum

Lameese Tabaja and Shafik Sidani

Colorectal polyps, specifically adenomatous polyps, are considered precursors of malignant tumors, making complete resection necessary. Endoscopic polypectomy is the standard of care for the treatment of colon and rectal polyps. This also allows for pathologic examination to rule out underlying malignancy [1].

Traditionally, several techniques are available for endoscopic polypectomy, including snare polypectomy, endoscopic mucosal resection (EMR), and endoscopic submucosal dissection (ESD). Difficult polyps may not be technically amenable to endoscopic resection and have a high risk of complications. By definition, difficult polyps are those that are large (>2 cm) or occupy more than one-third of the bowel circumference or two haustral folds, broad-based lesions (flat and sessile polyps), those located in tortuous colonic segments, flexures, or the ileocecal valve, and those positioned

L. Tabaja (✉) · S. Sidani
Section of Colon and Rectal Surgery, Digestive Disease Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, United Arab Emirates
e-mail: TabajaL@clevelandclinicabudhabi.ae; SidaniS@ClevelandClinicAbuDhabi.ae

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_43

on the mesenteric side of the colon [2–4]. Cancer is present in about 18% of these polyps [5].

Difficult polyps that are not amenable to endoscopic polypectomy were historically referred for segmental resection. Despite advancements in laparoscopic surgical technique and expertise, as well as the development of enhanced recovery protocols that markedly improved surgical morbidity and costs, surgery is still associated with significantly higher morbidity as compared to endoscopy. Both endoscopy and laparoscopy have their respective limitations. Combining both techniques can overcome these limitations.

Feared complications of endoscopic polypectomy are bleeding, perforation, and incomplete polypectomy that may predispose to local recurrence or, ultimately, malignancy [4]. In the last decade, advancement in endoscopic expertise, as well as instrumentation, facilitated the development of the innovative Combined Endoscopic and Laparoscopic Surgery (CELS) to ensure complete resection of complex polyps with colonic preservation.

CELS was first described in 1993 by Beck and Karulf, who performed complete excision of premalignant polyps avoiding colon resection. Several variations of the hybrid technique have since been described, including laparoscopic-assisted endoscopic polypectomy, endoscopic-assisted wedge resection of the colon, endoscopic-assisted translumenal resection, and endoscopic-assisted laparoscopic segmental resection.

Current indications for the hybrid technique include benign-appearing polyps that are soft with regular contours, have no central depression or ulceration, no irregular vascularity or pit pattern on narrow-band imaging, and can be lifted with submucosal injection. The hybrid technique is particularly useful for difficult right-sided polyps, where endoscopists tend to be less aggressive due to the higher risk of bleeding or perforation as a result of its thin wall [6].

There are several benefits of the hybrid approach. Laparoscopic-assisted endoscopic polypectomy allows for inspection of the colon during polypectomy and immediate repair of any colonic partial or full-thickness injuries. If polyps are not completely resectable endoscopically, a limited laparoscopic wedge or full-thickness local excision can be attempted with precise simultaneous endoscopic localization. If local excision is not possible, or if the polyp demonstrates concerning endoscopic features, a formal oncologic resection can be performed, avoiding the need for future procedures. Despite the advantages of CELS, it has not been adopted as a standard option in most clinical practices [7]. Described below are several options and variations of hybrid endoscopic and laparoscopic polyp resections.

Laparoscopic-Assisted Endoscopic Polypectomy (LAEP)

Of the CELS procedures, LAEP is the least invasive option and allows for lysis of adhesions, bowel mobilization, and extraluminal manipulation to position the colon in a configuration that facilitates endoscopic polyp resection. Early case series demonstrated successful simple endoscopic polypectomy in the sigmoid colon facilitated by laparoscopic mobilization.

Endoscopic-Assisted Wedge Resection

In this procedure, local excision of anti-mesenteric polyps can be performed in a tangential fashion under endoscopic guidance. The polyp is initially localized endoscopically. The endoscope is then advanced beyond the lesion to prevent

stenosis when the laparoscopic stapler is applied. This is particularly important when the polyp is near the terminal ileum. Intubation of the terminal ileum can be done to avoid its inclusion in the staple line. Resection is performed in a wedge configuration using a laparoscopic linear stapler.

Laparoscopic-Assisted Transluminal Resection

When lesions are located on the mesenteric aspect of the colon or are not amenable to laparoscopic wedge resection, laparoscopic-assisted translumenal resection can be attempted. Translumenal laparoscopic resection of the polyp is performed after creating a colotomy laparoscopically. Subsequently, the colotomy is closed using sutures or a linear laparoscopic stapler [7].

Endoscopic-Assisted Laparoscopic Segmental Resection

For circumferential or extensive lesions, endoscopic-assisted limited laparoscopic segmental resection can be performed without complete colon mobilization or lymphadenectomy. Again, consideration of this option hinges on the confidence of the benign nature of the lesion to avoid the need for reoperation to accomplish an oncologic resection.

The success rate of CELS ranges from 67 to 89% in numerous retrospective studies. To date, there are no prospective studies comparing CELS with laparoscopic colonic resection for endoscopically unresectable polyps [7]. On the other hand, Wilhelm et al. reported the success rate of

CELS as 95%. Postoperative complication rates ranged from 8 to 25%. The most commonly reported complications were ileus, bleeding, and urinary retention [8]. Reoperation is quite rare, and there are no reports of immediate postoperative mortality. Lee et al. noted no difference in the success of LAEP based on the location of polyps. Additionally, polyp size did not consistently correlate with the success or failure of LAEP [9]. Rates of invasive cancer on final pathology ranged from 3.3 to 11%. This is lower than the expected rates of cancer in advanced polyps found in previous studies, providing further evidence that cancer rates for these patients are not as high as historically believed, necessitating continued development of less morbid procedures. It also emphasizes the importance of accurately characterizing polyps prior to attempting a CELS procedure. The largest study with long-term follow-up shows a 0% local recurrence rate at a median of 5.4 years [10]. Other long-term follow-up studies have reported a local recurrence rate as high as 12%. All recurrences remained benign on pathology.

A recent systematic review includes 18 studies with a total of 532 patients [11]. EMR, ESD, and full-thickness excisions were performed in this heterogeneous group of studies. Successful CELS resection ranged from 58% to 100%, with studies including more than 20 patients demonstrating higher success rates (74–91%). The rate of conversion to an open procedure was less than 5%. Length of stay ranged from 0 to 7 days, and postoperative complications occurred in 0 to 18% of cases. The available data suggest that CELS is a safe and effective option for patients with a benign-appearing polyp that is unresectable by endoscopy alone (Table 43.1) [12].

TABLE. 43.1 Hybrid colorectal resection-summarized studies

Study	Patients (polyps)	Age	Polyp size	Success	OR time (min)	Postoperative complications	LOS (d)	Invasive cancer rate	Local recurrence rate
Franklin and Portillo	176 (251)	75	3.7	89%	All cases: 97	9%	1.1	10%	0% at 5.4 y
Wilheim et al	146 (154)	64	-	5%	All cases: 100; LAEP: 75	25%	8	11%	0.9% at 2.9 y
Lee et al	65 (65)	69	3	74%	All cases: 145	9%	1 (LAEP) vs 5 (colectomy)	7.60%	12% at 5.4 y (Benign)
Crawford et al	30 (30)	64	4	67%	All cases: 72	10%	2	3.30%	3.3% at 0.8 y
Goh et al	30 (30)	64	4	67%	All cases: 72	10%	2	3.30%	3.3% at 0.8 y
Cruz et al	30 (30)	65	1.4	73%	LAEP: 105	13%	2 (LAEP) vs 5.5 (colectomy)	6.70%	0% at 1.7 y

Abbreviations: *LAEP* Laparoscopic-assisted endoscopic polypectomy, *OR* Operating room, *OS* Length of stay

Preoperative Preparation

Patients with benign polyps that are not resectable by simple polypectomy but considered amenable to the hybrid technique should be scheduled electively. A proper review of the colonoscopic images, as well as the pathology report and slides, is necessary. For lesions in the left colon, an office-based flexible sigmoidoscopy is useful to better localize and characterize the polyp, as well as confirm the absence of malignant features.

The patient should be evaluated by an anesthesiologist for review of comorbidities and proper risk stratification in anticipation of the possibility of an abdominal operation. Counseling regarding the possibility of a laparoscopic colon resection should there be an intraoperative suspicion of malignancy or in case the lesion is not resectable by CELS is mandatory, and informed consent is obtained accordingly. Furthermore, it must be clear that if a final pathological examination reveals malignancy even after a successful CELS procedure, then further oncologic colon resection may be required.

Preoperative administration of subcutaneous unfractionated or low molecular weight heparin is recommended. Parenteral antibiotics should be administered within one hour of the surgical incision.

Operative Setup

CELS can be logistically challenging and requires coordination of a multidisciplinary team including anesthesiologist, surgeon, endoscopist, endoscopy technicians, as well as operating room staff and setup. After the administration of general endotracheal anesthesia, the patient should be positioned in modified lithotomy to allow simultaneous access to the anus for colonoscopy and the abdomen for laparoscopy. Both arms should be tucked, and proper padding and support should be used. An orogastric tube and foley catheter should

be inserted. Bilateral pneumatic compression devices must be applied. All the endoscopic and laparoscopic equipment, as well as the required support staff, must be available in the operating room. Equipment required for segmental colon resection should be readily available should the need arise.

Laparoscopic monitor positioning depends on the location of the lesion. For right-sided lesions, the monitors should be on the right side of the patient as the surgeon stands to the patient's left. The opposite setup applies to left-sided lesions. For transverse colon lesions, the monitors should be placed at the head of the bed (Fig. 43.1). The endoscopist usually stands

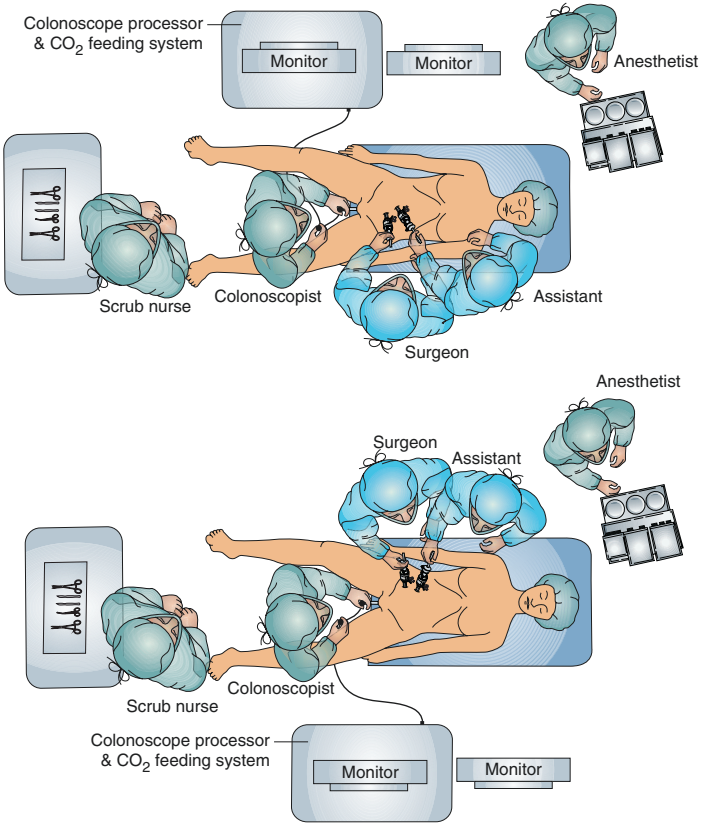

Figure 43.1 Operative setting

between the legs of the patient, and the endoscopy cart should be positioned close to the laparoscopic monitor; however, this can be adjusted to suit the comfort of the endoscopist and surgeon.

Operative Procedure

Colonoscopy (Fig. 43.2)

The endoscopist begins the procedure by identification of the target lesion. Carbon dioxide is used for endoscopic insufflation. Carbon dioxide is superior to room air as it is absorbed 150 times faster than room air, allowing minimal dilation of the colon and more working space for the simultaneous procedure [13]. Early experience with hybrid procedures using air insufflation reported more difficulty with laparoscopic assistance [13]. The polyp should be inspected to confirm its location and size, as well as the absence of any concerning features for malignancy such as ulceration, depression, and

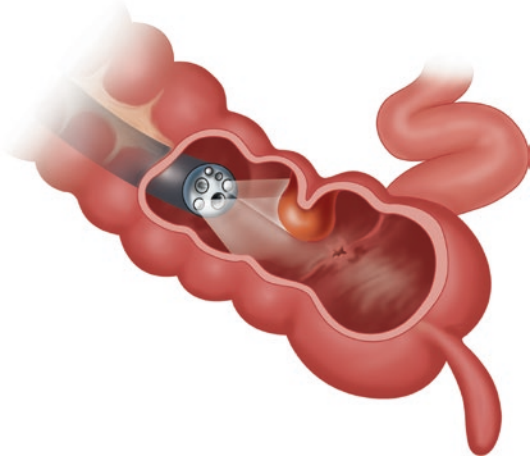

FIGURE 43.2 Colonoscopic visualization of right colon polyps

hardness, before the surgeon proceeds with the abdominal approach and port placement. Beginning with colonoscopic evaluation is critical as a polyp deemed endoscopically unresectable by the referring endoscopist may be readily resectable by the current endoscopist.

The procedure proceeds with the lifting of the polyp by submucosal injection of a dilute solution of methylene blue or indigo carmine with saline or another solvent of choice. The submucosal injection creates a plane between the polyp and the underlying muscular layer, creating a buffer layer to facilitate endoscopic dissection and minimize the risk of full-thickness injury. It also allows delineation of the polyp edge from the adjacent normal mucosa and aids in localization of the polyp laparoscopically.

Failure of the lesion to lift may suggest injection into a deeper layer which will require the slow withdrawal of the needle while slowly injecting to identify the correct plane. It may also indicate scarring from the previous biopsy or attempted endoscopic resection, particularly if the polyp appears to be benign. If the polyp has concerning features for malignancy, then failure to lift can indicate underlying malignancy, in which case laparoscopic oncologic resection is required.

Port Placement

Port placement depends on the location of the lesion. Abdominal access can be accomplished through a periumbilical incision and insertion of a 5mm trocar for the establishment of pneumoperitoneum. Two other ports are inserted to triangulate towards the target lesion. For right-sided lesions, ports are inserted in the left lower quadrant and suprapubic locations. For left-sided polyps, right lower quadrant and suprapubic ports are inserted. Transverse colon lesions can be addressed via bilateral upper or lower quadrant port placement. If the passage of sutures or a stapler is needed, one of the ports can be upsized. For laparoscopic-

assisted colonoscopic polypectomy, transillumination by the endoscopist can help with laparoscopic identification of the location of the polyp. Laparoscopic manipulation can then improve exposure for the endoscopist in an area that may have previously been poorly visualized due to folds or kinks in the colon.

Colon Mobilization and Manipulation

One of the greatest advantages of the hybrid procedure is the ability to laparoscopically manipulate the colon to provide the endoscopist better access to the lesion for successful endoscopic resection.

Direct laparoscopic colon manipulation may be required for polyps and lesions poorly accessible endoscopically due to colonic folds. Laparoscopic repositioning can expose the target area for resection. Colon mobilization can also help expose polyps located behind flexures or those located on the mesenteric or retroperitoneal aspects of the colon.

Polypectomy (Figs. 43.3, and 43.4)

The polyp can be removed using the endoscopic snare device while simultaneously manipulating the colon laparoscopically to facilitate the process. Larger lesions may require piecemeal resection. During and after polypectomy, the serosa should be inspected carefully for any thermal injury or perforation. When suspected, immediate laparoscopic reinforcement or repair can be performed. In this way, the option of a laparoscopic repair allows for a more aggressive and complete resection to be accomplished.

Full-Thickness CELS

Full-thickness CELS is indicated for polyps that are difficult to resect endoscopically, particularly those with significant

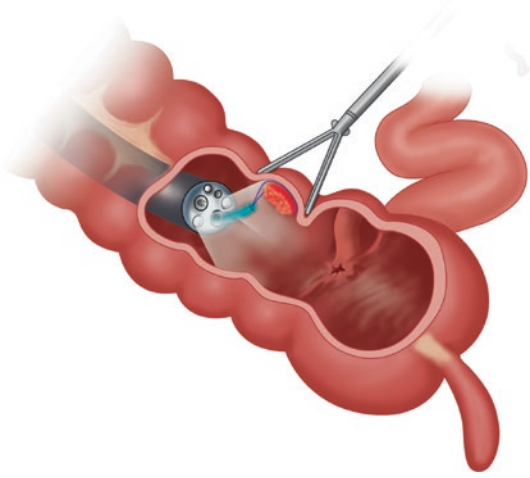

FIGURE 43.3 Laparoscopic-assisted polypectomy

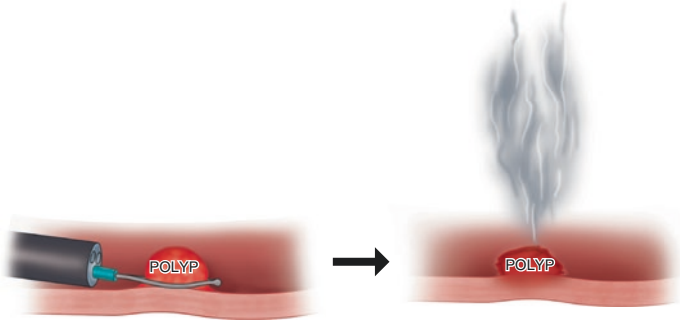

FIGURE 43.4 Hot snare polypectomy

scarring from previous biopsies or attempts at endoscopic resection [13]. The procedure begins with endoscopic lifting when possible. Under endoscopic guidance, the serosal side of the polyp is then circumferentially marked laparoscopically with a monopolar device as an electrocautery hook or scissors. A seromuscular laparoscopic dissection is then performed along the previously marked edge, avoiding any

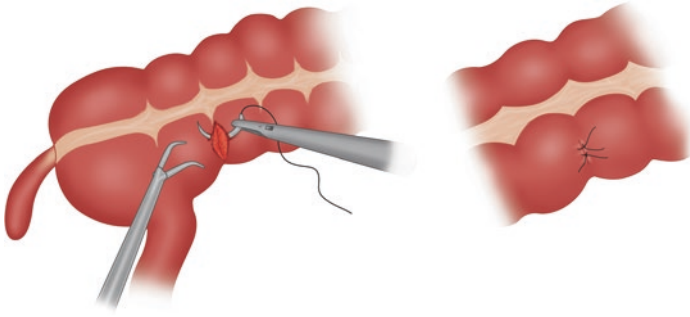

FIGURE 43.5 Laparoscopic suture placement

full-thickness mucosal dissection. The mobilized lesion can then be invaginated into the colon lumen with a laparoscopic grasper while the polyp is snared endoscopically. After the snare is applied and prior to completing the polypectomy, closure of the defect can be performed laparoscopically. The polyp can be collected using a Roth net endoscopically. In the case of piecemeal polypectomy, a trap can be used to retrieve the polyp fragments with suction (Fig. 43.5). An air leak test can be performed to ensure complete closure of the colonic defect. The colonic segment of concern is submerged in saline laparoscopically while insufflating it endoscopically to ensure the absence of air bubble leakage from the repaired defect. The closure can be further reinforced laparoscopically as needed.

Colonoscopic-Assisted Laparoscopic Partial Cecectomy (Fig. 43.6)

This procedure is useful for polyps located in the cecum close to the ileocecal valve or appendiceal orifice. The aim is complete full-thickness resection of the polyp while securing the surrounding structures from injury [14]. The lesion in the cecum is localized colonoscopically. The required margins are confirmed. Laparoscopic ports are

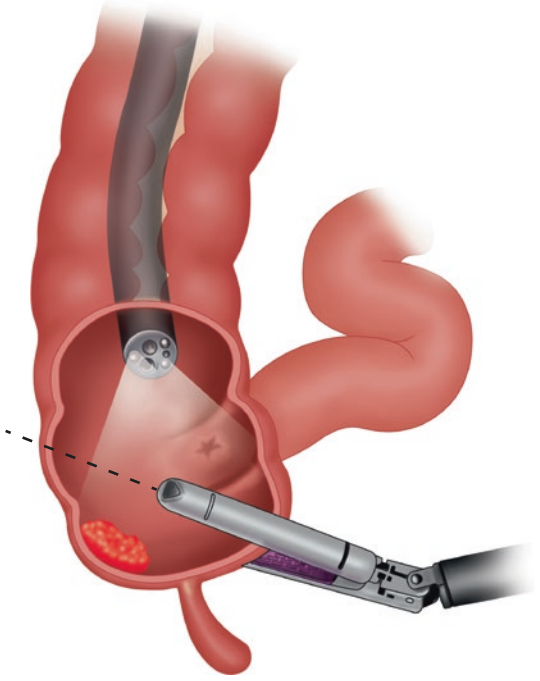

Figure 43.6 Laparoscopic stapled resection of colon polyp

inserted as described previously. A 5mm periumbilical camera port is used along with a 5mm suprapubic port, and a 12mm left lower quadrant port for passage of the laparoscopic linear stapler device. Mobilization of the cecum and ascending colon may be required. As the laparoscopic linear stapler is applied across the cecum, colonoscopy confirms complete inclusion of the polyp and prevents damage to the terminal ileum. Intubation of the terminal ileum can be done to mechanically isolate the terminal ileum from the staple line. The resected specimen can then be retrieved laparoscopically using an Endo-Catch bag. The specimen must be inspected to ensure adequate margins. Oversewing of the staple line is left to the surgeon's discretion.

Intraoperative Frozen Pathology

Currently, there is no consensus on the routine use of frozen sections during hybrid procedures. Obtaining a frozen section can identify malignancy intraoperatively in approximately 2% of cases, and as such, allow for an immediate oncologic colon resection and avoidance of further procedures in the patient's future [9]. On the other hand, there are reports of the false-negative frozen section where benign pathology is preliminarily described intraoperatively with a report of malignancy on final review postoperatively [15]. Therefore, the routine use of frozen sections can be considered time-consuming and costly. We recommend the selective use of frozen sections.

Complications

Several studies have demonstrated the safety of CELS. Franklin and Portillo reported a 9% postoperative complication rate. All complications were minor such as ileus, atelectasis, and seroma [11]. Lee et al. reported a complication rate of 4.2% over a 10-year experience with CELS. The most common complications reported were urinary retention and wound hematoma [9]. Although post-polypectomy bleeding is a well-known complication of endoscopic polypectomy, it has not been widely reported in the published series of CELS. This may be because bleeding is detected and controlled during the procedure. Bleeding encountered during the procedure should be controlled endoscopically using the polypectomy snare and may require epinephrine injection or placement of endoscopic clips. Delayed bleeding can occur up to one-month post-procedure, and management should be supportive. If bleeding persists despite supportive care, endoscopy should be repeated for bleeding control.

Perforation is perhaps the most feared serious complication of endoscopic polypectomy and occurs in less than 1% of

cases [16]. A benefit of CELS is the ability to suture repair a perforation or partial-thickness injury when detected intra-operatively. Suture repair was reported in 10% of laparoscopic-assisted polypectomy cases by Franklin et al. [11].

Complications related to the laparoscopic portion of the hybrid technique are similar to other laparoscopic abdominal procedures and may be even lower if no colonic mobilization is required. These complications include abdominal wall and intra-abdominal visceral or vascular injury related to port placement, grasper trauma, or energy devices.

Postoperative Care

If simple snare polypectomy is performed, the patient can be safely discharged as an outpatient case after a short observation period. In cases where full-thickness resection or partial cecectomy are performed, admission for observation under an enhanced recovery after surgery pathway is generally warranted. Most groups describe a short hospital stay of 1-2 days. However, some other groups report longer stays of 4-8 days [8]. Diet can be advanced as tolerated. The patient should be monitored closely for bleeding, particularly after extensive snare or full-thickness polypectomy. Follow-up is recommended after 7-10 days to discuss the pathology result and determine if further treatment is required.

Follow-Up

Lee et al. and Franklin et al. reported the longest follow-up of 65 months for patients with benign polyps who were successfully resected with the combined procedure. Lee reported a recurrence rate of about 10% [8,] whereas Franklin and Portillo reported no recurrences [11]. In general, a follow-up colonoscopy is recommended 3 months post-procedure after successful resection [9].

Contraindications

Hybrid procedures should not be considered for patients with established malignancy or those with high-risk endoscopic features. Multiple prior abdominal operations resulting in intra-abdominal adhesions may make mobilization of the colon difficult and thus may require surgical resection or even conversion to an open operation, but is not necessarily an absolute contraindication to attempting laparoscopic assistance. Morbid obesity is not a contraindication for the procedure. However special consideration for the use of bariatric trocars and instrumentation as well as port placement is important to ensure proper triangulation to maximize the technical success of the procedure.

Learning Curve

Although a learning curve has not been defined for CELS procedures, the previous series demonstrate that one likely exists. The learning curve correlates with operative time, ability to perform the combined procedure successfully, and the ability to fully resect the polyp endoscopically. Several CELS studies show that those including more than 20 patients resulted in higher success rates [17].

Conclusion

Hybrid laparoscopic and endoscopic procedures were developed to reduce the need and the morbidity associated with laparoscopic or open colon resections in patients with benign-appearing endoscopically difficult polyps. The combined approach is a safe and effective procedure that allows confirmation of complete polyp resection, as well as immediate management of the most feared complications of endoscopic polypectomy, bleeding and perforation. With current endo-

scopic and laparoscopic technology and expertise, the evidence supports its safety and efficacy in appropriately selected patients. Endoscopists performing colonoscopies for difficult polyps, whether gastroenterologist or surgeon, should be encouraged to consider CELS when indicated. Further work is required to define the learning curve and optimal strategies to safely institute CELS procedures into a clinical practice.

Acknowledgements None

Disclosures None

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Chapter 44
Natural Orifice Translumenal Endoscopic Surgery (NOTES™)

Heitham Wady and Salvatore Docimo Jr

Introduction

Natural orifice translumenal endoscopic surgery (NOTES) refers to the application of using the body's natural orifices in a transvisceral approach in order to access body cavities and perform surgical interventions. The benefit of such a method is in the removal of cutaneous body incisions, which allows for potentially decreased pain, expedited recovery, and avoidance of incisional scar formation, hernias, adhesions, and wound infections.

While the technique was first conceptualized over a decade ago, much research performed in the lab has transitioned to a rapid expansion of this technique into real

H. Wady (✉)
Department of Surgery, Stony Brook Medicine, Stony Brook, NY, USA
e-mail: Heitham.Wady@stonybrookmedicine.edu

S. Docimo Jr
Division of Bariatric, Foregut, and Advanced Gastrointestinal Surgery, Department of Surgery, Stony Brook Medicine, Stony Brook, NY, USA
e-mail: sdocimo@nyit.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_44

applications covering novel solutions to surgical problems. NOTES procedures have been developed and performed throughout the globe with success, and in some cases are slowly replacing traditional surgical techniques as standard of care for surgical pathologies due to their minimal invasive nature. The strides made with regard to NOTES have also left a positive impression on minimally invasive surgery and advanced interventional endoscopic surgery. The focus of this chapter is to discuss the evolution and current status of NOTES.

History

As early as 1994, the basic techniques of NOTES were described by Peter Wilk in a patent filing for the technique, although even prior to this there were unpublished accounts of this approach being studied at the Cleveland Clinic [1]. The first published account of a NOTES procedure occurred in 2004 and involved a peroral transgastric approach to peritoneoscopy in pigs [2]. This group also went on to develop a novel approach to tubal ligation using a transgastric approach in bovine models, which was published in 2005 [3]. This was followed up by an oral presentation at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) conference in 2006 which outlined the transgastric approach to appendectomy in humans [4].

Also in 2006, the Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) working group was formed. The results of this group were published in the first NOTES White Paper in February 2006. The key points of this paper outlined procedural safety for peritoneal access, closure technique for gastrotomy, and prevention of complication strategies. Several barriers were identified with questions posed to help guide research that could answer these questions. The first international meeting on NOTES by the group was held in March 2006 [5]. Subsequently, there was an increase in work performed showing multiple other NOTES

methods being developed and published in literature and presented in conferences [6–8]. Five years from the initial SAGES/American Society for Gastrointestinal Endoscopy (ASGE) NOTES White Paper, the second white paper was published with answers noted to several of the key questions asked—the majority coming with NOSCAR sponsorship. A summary of progress for the key points raised previously is outlined in Table 44.1.

Table 44.1 Key issues raised from first White Paper with progress made to address and resolve these issues

Key issue raised	Progress made
Peritoneal Access	Multiple access routes possible including transvaginal and transgastric routes
Gastric Closure	Multiple commercially available closure devices and techniques established
Infection	Studies clearly show that controlled incision not equivalent to perforation and proper closure decreases infection concerns
Suturing and Anastomotic Devices	Rapid development of devices that are in process for approval
Spatial Orientation/ Navigation	Experience with off-horizon visualization of target anatomy by skilled practitioners with possible image registration or dual cameras being explored
Multitasking Platform	First generation platforms and new promising prototypes of multitasking flexible endoscopes are being developed
Complication/ Hemorrhage Management	Development of instruments for hemostasis, low incidence of hemorrhage partly due to high magnification views, safety net of laparoscopic bailout if required
Training	Postgraduate advanced endoscopic training programs initiated or currently being developed

Much of the appeal of NOTES procedures is with regard to high-risk surgical patients or those with morbid obesity. Multiple potential benefits of a translumenal approach have led to a rapid initiative for advancement of the field in terms of device creation and surgical techniques developed.

Current Status of Procedures

Due to the potential of the NOTES approach, a significant amount of research has been performed, with techniques studied in animal models that utilize approaches to thoracic, abdominal, and pelvic entry into the body. Outlined below are several of the most popular and accepted techniques that use the NOTES approach.

Transesophageal

Sumyiama presented a transesophageal approach to accessing the thorax and mediastinum that involved submucosal tunneling and creation of a mucosal flap, also known as the submucosal endoscopy with mucosal flap (SEMF) technique [9]. By creating a defect in the muscularis propria, the mediastinum could be entered. To minimize contamination, the overlying mucosa would then act as a sealant flap to close the submucosal plane.

In 2007, Pasricha developed the per oral endoscopic myotomy (POEM) using animal models (Fig. 44.1). The technique involved creation of a submucosal tunnel that could be used for endoscopic myotomy in patients with achalasia [10]. It was subsequently popularized by Dr. Haruhiro Inoue's group in Japan as its application transitioned from animal studies to performance on humans [11]. While the traditional approach to surgical management of achalasia had long been via the Heller myotomy, more practitioners are using this minimally invasive approach. The major concern had been the lack of an antireflux procedure performed at the time of the POEM

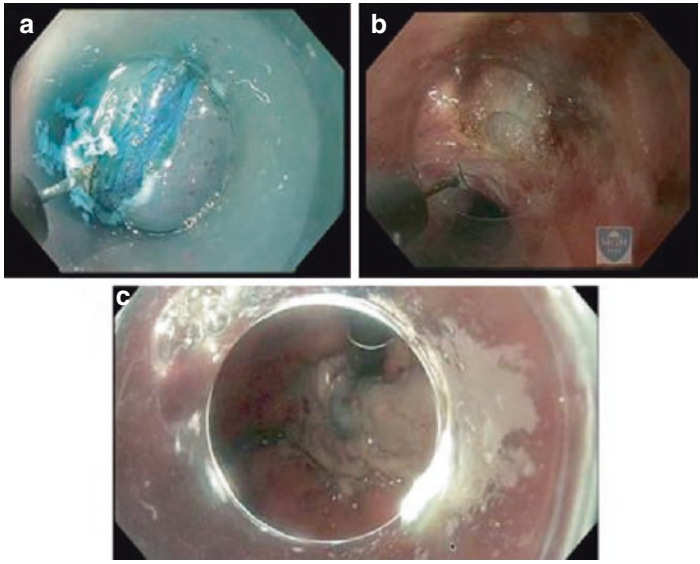

Figure 44.1 Per oral endoscopic myotomy (POEM). (**a**) Incision of the mucosa at the level of the esophagus. (**b**) Dissection and division of the circular muscle fibers of the esophagus within submucosal tunnel. (**c**) Retroflexed view within stomach after completion of myotomy

which was thought to lead to significant GERD. However, studies have shown that severe GERD symptoms did not develop after the POEM procedure [12]. Despite the promising results thus far demonstrated with the POEM technique, long-term prospective randomized control studies comparing the traditional Heller Myotomy with the POEM technique are still lacking.

Endoscopic ultrasound (EUS) can be used to determine safe points of esophageal entry for access to the mediastinum [13]. Its utility was thought to be in avoidance of major vascular structures and orientation with regard to the heart for planned interventions. However, this use of EUS later fell out of favor. A similar approach to the SEMF technique

was published by Willingham and involved use of a flexible laser fiber or mucosectomy device for incision of the esophageal mucosa followed by creation of a submucosal tunnel [14]. By incising the muscular layer, a window to the mediastinum was created. This approach has clinical applications in terms of mediastinal lymphadenectomy, pericardial window, and pleural biopsy [15].

Gastroesophageal reflux (GERD) is a problem ubiquitous in patient populations throughout the world with treatment focused on lifestyle modification and medical therapy. Fundoplication as an antireflux procedure has had great success as a surgical solution to this problem. Since it was first performed in 2005 using the EsophyX device, the transoral incisionless fundoplication (TIF) procedure has now been used in over 17,000 procedures to provide an alternative to traditional surgical techniques for management of GERD [16]. It involves using the EsophyX device by which an endoscope is passed through and retroflexed, followed by the use of a helical retractor to pull back tissue and suction applied for tissue invagination. A >240° fundoplication is then performed using polypropylene fasteners. Multiple studies have subsequently been published demonstrating its effectiveness and superiority to medical therapy in select patient populations with long-term durability for up to 6 years post-procedure [17, 18]. For properly selected patients, this provides an alternative to traditional surgery for management of GERD.

Limitations of the transesophageal approach include the possible risk of an esophageal leak due to failed closure which can lead to mediastinitis or pneumonia and significant morbidity. Additionally, the esophageal lumen provides a relatively confined working space which inherently limits the extent of endoscope flexibility. Capnothorax as a complication of mediastinal access is another potential consequence. Finally, the esophagus is an unsterile field and the use of implants poses a challenge due to concerns of contamination and bacterial seeding.

Transgastric

Some of the earliest iterations of the NOTES method utilized a transgastric approach to accessing the peritoneal cavity for procedures such as appendectomy, cholecystectomy, oophorectomy, and peritoneoscopy. However, risk of transgastric contamination of the peritoneum, iatrogenic injury to the abdominal wall and vessels, and concerns of failed closure of the gastrotomy leading to leakage and infection were major concerns with using this technique [19]. Additionally, performance of the endoscope for visualization and technical manipulation of viscera in the upper abdomen was limited due to the need to steeply retroflex the endoscope. As a result, in-line procedures such as pelvic procedures and appendectomies were more technically feasible procedures that could use this approach.

Interestingly, one of the biggest shifts in treatment paradigm within the last 20 years was in management of necrotizing pancreatitis. Historically, treatment involved aggressive debridement through an open necrosectomy approach which was morbid and associated with poor outcomes [20, 21]. Within recent years, this has largely been replaced by an endoscopic transgastric approach that utilizes a side viewing endoscope to create a gastrotomy followed by removal of devitalized pancreatic tissue [22]. A study published in 2017 showed that for high-risk patients, minimally invasive and endoscopic necrosectomy were associated with reduced death rates when compared with open necrosectomy [23].

For patients with gastroparesis refractory to medical therapy, surgical techniques have evolved to include endoscopic interventions including the peroral pyloromyotomy (POP) (Fig. 44.2) technique to improve gastric emptying. Iterations of the technique involve creating a submucosal tunnel with dissection down to the distal end of the pylorus followed by division of the muscle using a hybrid knife [24]. Mucosal closure can then be performed using clips or endoscopic suturing. Reported outcomes in terms of clinical and technical success rates have shown promise.

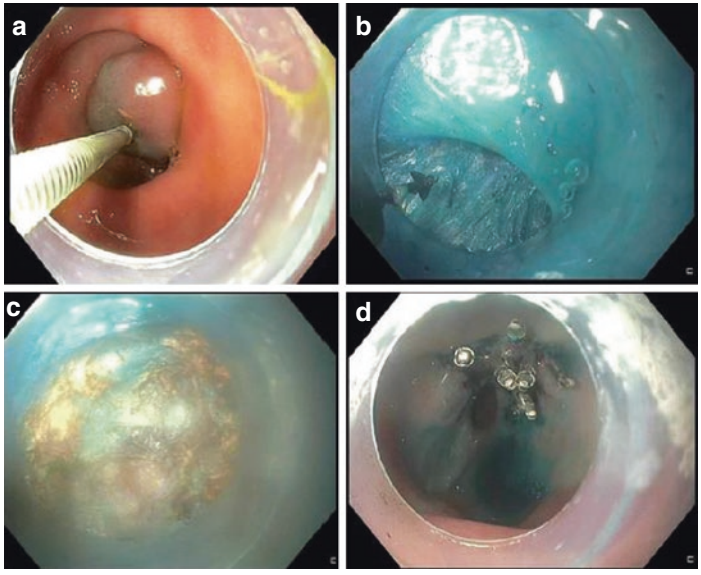

Figure 44.2 (**a**) Submucosal injection just proximal to the pylorus along the lesser curvature. (**b**) View of pylorus muscle within submucosal tunnel. (**c**) Completed myotomy. (**d**) Closure of mucosal incision using clips. (Images adapted from Alleman MT, Strong AT, Haskins IN, et al. How I Do It: Per Oral Pyloromyotomy (POP). Journ Gastrointest Surg. 2017; 21: 1963-1968.)

Early percutaneous endoscopic gastrotomy (PEG) tube dislodgment is a rare occurrence that often prompts urgent surgical intervention due to concerns of gastric contamination of the abdominal cavity. To obviate the need for operative intervention, a transgastric endoscopic technique was developed and used for PEG tube rescue. Through the gastrotomy site, the endoscope is able to evaluate the abdomen for gross contamination, perform necessary irrigation, and replace the PEG tube. A recent study showed the safety and efficacy of this technique as an alternative to surgery with operative times < 2 hours and time to re-initiation of enteral feedings at 48 hours [25].

As outlined in the first NOTES white paper, gastric closure was noted to be one of the challenges that needed to be addressed. Since then, multiple studies have been published outlining that perhaps the once perceived contamination associated with this approach was not as substantial as previously thought and more closely resembled a clean contaminated case [26]. As well, new devices have been created that improve upon gastric closure. Regardless, the transgastric approach remains a feasible alternative to traditional laparoscopic or open procedures for accessing the peritoneum and performing less technically challenging procedures.

Transvaginal

Due to its anatomic location, the transvaginal approach to accessing the peritoneum offers excellent visualization of the viscera in the upper abdomen without the difficulties associated with retroflexion used in the transgastric approach. Additionally, due to extensive experience with transvaginal closures used in the field of gynecology, this method has the added benefit of a reliable and effective technique for closure of the access site. Overall, the transvaginal approach has been performed in cholecystectomy, appendectomy, nephrectomy, and gynecological surgery [27–29].

Among the mentioned procedures, transvaginal NOTES cholecystectomy has become one of the most commonly performed surgeries, with over 4000 cases performed worldwide [6]. It involves a hybrid technique by which abdominal ports are used for stabilization of the bile duct and vasculature. A randomized trial compared this technique with the multi-trocar technique and found improved outcomes in postoperative pain and cosmesis with the transvaginal approach [30].

The field of gynecology has taken advantage of transvaginal surgery and has been using this technique for tubal sterilization, salpingectomy, ovarian tumor enucleation,

hysterectomy, and myomectomy [31–34]. These studies showed that compared with other techniques, such as the transumbilical Single Incision Laparoscopic Surgery (SILS) technique, there was a larger workspace to operate in and decreased collisions between instruments. Transvaginal NOTES appears to be especially effective when used in the appropriate patient population including patients with nulliparity or morbid obesity.

There remain obvious limitations to transvaginal NOTES. Foremost is the fact that this approach is only possible in women. Given the route of access, injury to adjacent structures upon entry (ureters, bladder, rectum) have been reported. Critics of this technique also raise concern about residual sexual and reproductive function after surgery, although studies have shown minimal adverse effects [27].

Transanal

A natural evolution of colorectal surgery as minimally invasive techniques became more prevalent was towards the transanal NOTES approach. Similar to the transgastric approach outlined previously, a flexible endoscope was inserted and a viscerotomy made in order to access the abdomen. However, unlike the transgastric approach, which had concerns for closure, one of the benefits of the transanal approach is in the closure technique. The access incision is often included in the resection specimen for transanal lesions with either a stapled or handsewn colo-anal anastomosis, thus mitigating the concerns for leakage and infection.

Since the 1980s when Professor Buess published his methods for transanal endoscopic microsurgery (TEM) using specialized instruments for an endoscopic platform, advancements in technology have allowed for new approaches towards oncological resection of rectal cancer [35]. A “bottom to top” approach (Fig. 44.3) utilizing well-formed tissue planes for dissection with the possibility of total mesorectal excision during removal of rectal tumors has provided colorectal sur-

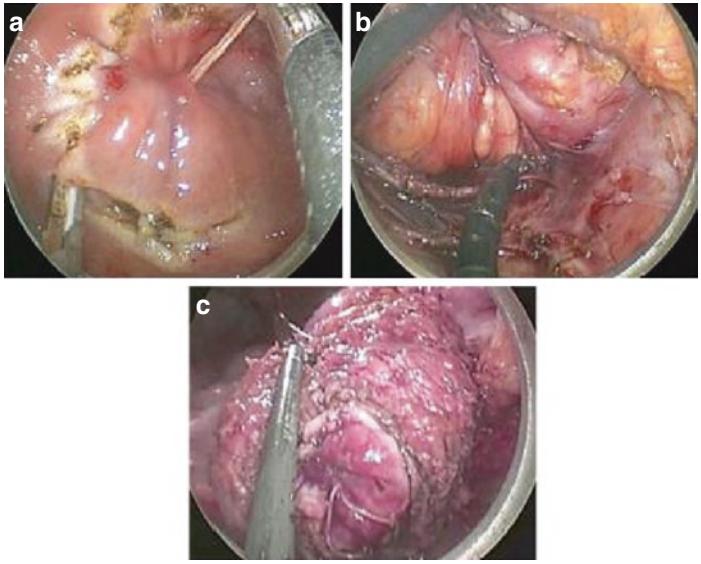

FIGURE 44.3 Transanal NOTES Colectomy. (**a**) Transrectal access via full thickness circumferential division using ultrasonic device. Purse string suture marks distal resection margin. (**b**) "Bottom up" NOTES dissection of presacral space. (**c**) Transanal extraction of specimen

geons an alternative to traditional laparoscopic surgery for removal of low rectal tumors [36]. An added benefit to this technique was easy identification of the distal border of the tumor with excellent distal resection margins.

Commonly employed are hybrid transanal NOTES techniques which add laparoscopic assistance for colonic and rectal resections. New single port devices have been manufactured and can be inserted transanally, allowing for an improved multi-system platform affording the surgeon with more instruments available for dissection.

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have grown in use and popularity as minimally invasive options for removal of colorectal lesions. Studies have shown EMR to be safe, less costly, and

effective with high success rates for removal of complex colon polyps [37]. One of the major disadvantages of EMR is lesion size, with lesions > 15-20mm requiring piecemeal removal, fragmented specimens, and higher recurrence rates [38]. ESD removes lesions by creation of a resection plane that separates the lesion from the underlying muscularis propria. This technique allows for removal of larger lesions in en bloc fashion when compared with EMR. A meta-analysis of 8 studies on colorectal lesions managed with EMR versus ESD showed that tumor size, rate of en bloc, and curative resection were higher and rate of recurrence was lower with ESD [39]. However, ESD was associated with longer procedure times and higher rates of perforation. While both techniques remain viable options, patient selection and lesion characteristics should guide the practitioner as to the ideal approach for proper resection.

For truly oncological resection, dissection down to the vascular pedicles is required, especially for larger size rectal tumors. Thus one limitation of this approach is the need for a laparoscopic port for assistance of colonic mobilization and mesenteric dissection. Nonetheless, transanal NOTES allows for minimally invasive surgery for rectal tumors while preserving adequate lymph node harvests and obtaining appropriate pathological margins [40]. Future studies must assess the standard laparoscopic approach vs transanal NOTES to evaluate long-term oncological outcomes.

Ongoing Challenges

The first NOTES white paper identified challenges inherent to this surgical approach. While some of the problems have been addressed either through studies that assessed infectious risk or via advancements made in technology with device development, there still remain hurdles.

From a safety standpoint, proper placement of incision and of closure remain pressing concerns. Reliably performing a viscerotomy in the proper location without inadvertently injuring intra-abdominal structures while also obtaining a proper view of the surgical field should improve with experience and preoperative imaging. However, viscerotomy closure, particularly the transgastric approach, requires further safety assessment due to risk of leak and device development. Currently, there are several devices on the market that allow for closure, including handsewn techniques and clips. Hybrid techniques employ a combination of the NOTES approach plus laparoscopy to help with visualization and assessment of the closure. In a purely NOTES only approach, techniques for assessing viscerotomy closure are lacking.

Industry development has led to advancements in endoscopic closure techniques, specifically with regard to endoscopic suturing. Additionally, new clips have been developed to help with closure and salvage techniques for patients with leaks. However, many essential surgical instrumentation that can be used for a purely NOTES technique are still inadequate for endoscopic use. These include advanced sealing devices for hemostasis as well as stapling devices and instruments for creating a robust anastomosis. As the field continues to expand and more NOTES procedures performed, improvements on current technology may alleviate these problems.

In addition to safety and technology, the cost to benefit ratio is a concern for practitioners and healthcare systems. As new techniques are developed and new technologies become available to practitioners, there invariably will be an initial cost that may be more expensive than current standard techniques. However, as was the case when initially comparing laparoscopic to open surgical approaches, this cost disparity decreases over time as innovation leads to efficiency and new technologies become more financially viable.

Future Directions

What started initially as a concept for using advanced endoscopic techniques via natural access routes in the body as a means to change the treatment paradigm from open surgical approaches to a more minimally invasive strategy has burgeoned into an enormous field filled with research, technological advancement, and innovations in surgery. Moving forward as practitioners, the goal remains to take ideas created in the lab and formulate and perfect them into approaches that can be used in clinical practice while constantly looking for improvement and actively assessing safety and efficacy.

An exciting potential advancement in the field will be through the development of a robotic platform that can use the NOTES technique for single port and endoscopic surgery. Robotics allows for more degrees of freedom for triangulation and simultaneous use of retraction and dissection devices for increased precision. Several devices are in the works and utilize miniature arms that can perform advanced maneuvers not typically afforded with current endoscopic instrumentation (Fig. 44.4). One such prototype is the K-FLEX flexible robotic platform for endoscopic surgery which has improved payload and articulation capabilities and a design of just 17mm in overall diameter [41]. Many other options are being developed for the purpose of NOTES and include the MASTER, STRAS/Anubiscope, EndoSAMURAI, and Scorpion [42]. A barrier to the use of this technology will likely be the prohibitive costs associated with purchase and maintenance of such technologies.

Establishment of which NOTES approach provides ideal access for intervention remains up for debate, although each approach has its own benefits and limitations. Target anatomy will continue to guide the practitioner when making this decision. As NOTES techniques have been refined and are beginning to be used more widely in practice, the future will see comparisons with NOTES procedures to that of open versus laparoscopic standard of care interventions.

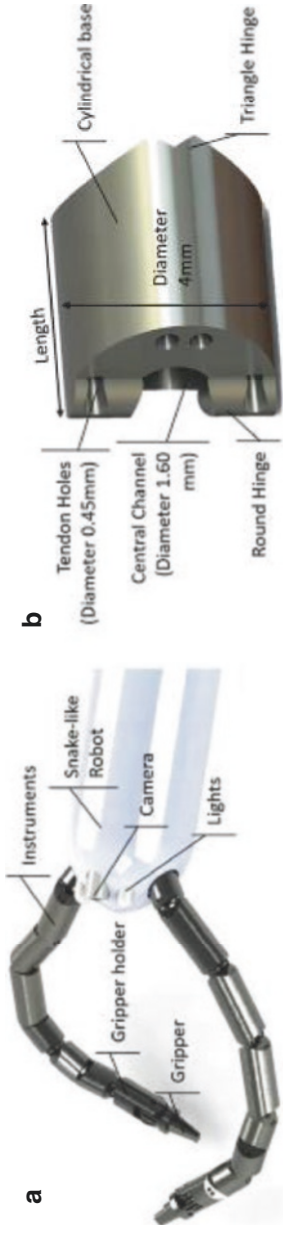

FIGURE 44.4 **(a)** Deployed instruments from head of i^2 Snake platform. **(b)** One of the connectors from which the instruments are built. (Images adapted from Berthet Rayne P, Gras G, Leibrandt K, et al. The i^{2}Snake Robotic Platform for Endoscopic Surgery. Annals Biomed Eng. 2018; 46: 1663-1675)

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Chapter 45
Artificial Intelligence in Endoscopy

Jesse R. Conner, Aman B. Ali, and Nabil Tariq

Introduction

Once the subject of futuristic Sci-Fi movies and books, Artificial Intelligence (AI) has become part of our everyday lives. Algorithms developed by Amazon, Google, and Facebook utilize AI to predict texts, recognize and translate language, suggest purchases, and achieve facial recognition. AI was introduced in 1956 at what is now called the Dartmouth Conference. The conference was organized by John McCarthy, who at the time was an Assistant Professor of Mathematics at Dartmouth. He invited several mathematicians and scientists to gather for summer to perform an intense study of computerized intelligence. He believed that aspects of human intelligence could be precisely described in such a way that a machine could simulate it. He is also credited with coining the term Artificial Intelligence. AI is simply defined as the ability of a computer software system to be able to perform human cognitive functions. Examples of cognitive functions include

J. R. Conner · A. B. Ali · N. Tariq (✉)
Department of Surgery, Houston Methodist Hospital, Houston, TX, USA
e-mail: ABali@houstonmethodist.org; ntariq@houstonmethodist.org

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_45

image recognition, identifying patterns, solving problems, and ultimately learning. The first step in image recognition is that a computer must learn a pattern or part of a pattern. For this, large amounts of data are required. The computer must also make computations, which require massive amounts of computational power [1]. Since the 1950s there was relatively little AI activity as both data and computational power were lacking. As computers have become more affordable and more advanced with increasing processing power, as well as the addition of the internet allowing for access to immense amounts of available data, we are now seeing substantial expansion in AI developments today. As AI makes its way into our daily lives, it also has great potential to aid the clinician in the diagnosis and treatment of diseases.

Definitions and Terminology

The idea of Artificial intelligence (AI) was first described in the 1950s by British mathematician Alan Turing. He defined this intelligent behavior of a computer as its ability to achieve human-level performance in cognitive tasks [2]. He believed that a machine could identify patterns within data and learn from these patterns to perform a specific task that would otherwise require human intelligence. Examples of these tasks include problem-solving, independent pattern recognition, and learning. Essentially all AI today is based on machine learning.

Machine Learning (ML)

Machine Learning (ML) is under the umbrella of AI; however, essentially all AI today uses machine learning. The term ML was first introduced in 1959 by Arthur Samuel from IBM. ML refers to a computer system that can develop the ability to learn by using data without specific programming and can develop predictive algorithms by analyzing input data and recognizing patterns [3]. Computers can be taught

simple tasks when they are given data, and the algorithm can complete every portion of a problem and come to the correct conclusion. In more advanced tasks, this algorithm becomes much more difficult to create. Thus it is easier to let the computer help make the algorithm and then solve the problem. Machine learning essentially uses different approaches to teach computers to accomplish tasks where no satisfactory human-made algorithm exists. There are three main types of learning methodologies: *supervised learning* is when the computer is given human-labeled data and desired outputs, and the computer learns general rules to categorize inputs to determine the desired outputs; *unsupervised learning* is when the computer is given unlabeled data and is tasked with uncovering the hidden pattern within the data to group and further categorize the data until it can differentiate the desired output; *reinforcement learning*, is when the algorithm learns from trial and error scenarios [4, 5].

Deep Learning (DL)

As depicted in Fig. 45.1, Deep Learning (DL) is a specialized form of machine learning and is based on multiple layered

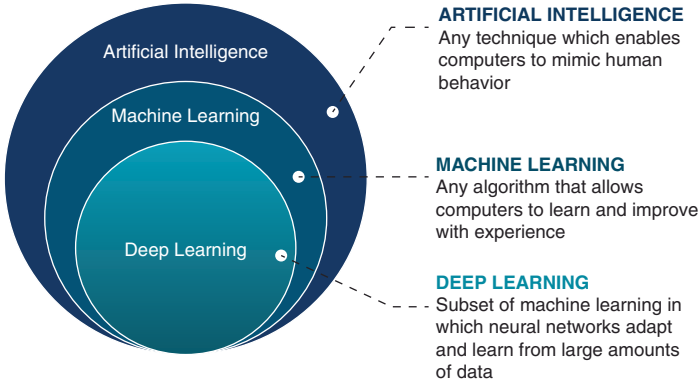

Figure 45.1 Artificial intelligence, machine learning, and deep learning

neural networks. Neural networks are the hidden layers within a machine learning algorithm that identify unseen patterns and are able to group similar data into categories, which can be further categorized by additional hidden layers until the desired output is identified. While ML often consists of 1–2 layers of neural networks, DL contains several, often up to 150 layers. This allows the computer to take unlabeled data and further subcategorize it to be able to make predictions and conclusions about the data. This eliminates the need for manual feature extraction and makes DL models ideal for processing data in the form of images and videos. Once the framework of the neural network has been established with vast quantities of labeled data, or in this instance images, the computer has the ability to extract relevant features straight from the data and make inferences and predictions on raw, unlabeled data. An important feature of DL algorithms is the more data the algorithm has, the better it is able to perform, so as we collect more images and video images over time, the more accurate the predictions should become. This has made DL instrumental in processing images and videos, which has helped in endoscopic detection and diagnoses of diseases [6].

Current Applications of Artificial Intelligence in Endoscopy

As computing power and data storing capacities have improved, so too has the exploration of the application of artificial intelligence (AI) in medicine. The following is a review of the applications of AI in endoscopy that are in use currently.

Evaluation of Barrett's Esophagus

Barrett's Esophagus (BE) poses a difficult diagnostic problem as it is a known risk factor for the development of esophageal adenocarcinoma and may harbor dysplastic

changes that are not readily evident on conventional endoscopy. The current solution to this problem is random biopsies (Seattle protocol); however, this approach is labor-intensive and has a relatively low per-lesion sensitivity of 64% for the detection of dysplasia [7]. The Seattle protocol consists of four-quadrant biopsies every 2 cm of the Barrett's segment. Two centimeters of BE would equate to approximately 14 cm^2 of surface area. A single biopsy samples approximately 0.125 cm^2, so the Seattle protocol would only cover 0.5 cm^2 of the esophageal mucosa, which would only be 3.5% of the Barrett's segment [8]. Recently the American Society of Gastrointestinal Endoscopy (ASGE) has endorsed the use of advanced imaging techniques to aid in targeted biopsies to replace random four-quadrant biopsies. The society determined performance criteria that new technologies should meet in order to be considered effective, including the sensitivity of more than 90%, a specificity of 80%, and a negative predictive value of 98% [9]. Technologies that have been developed include volumetric laser endomicroscopy, wide-area transepithelial sampling, chromoendoscopy, and magnification endoscopy. While these techniques have shown promise in achieving the ASGE criteria, they still are time-consuming and require special expertise, which limits their use. This has led to the investigation of the use of AI to aid the nonexpert endoscopist in diagnosis.

The evaluation of BE with standard white light endoscopy (WLE) and the addition of narrow-band imaging (NBI) is one of the longest-standing techniques. AI algorithms were developed for WLE/NBI images by van der Sommen et al. to detect early neoplastic lesions with BE. The algorithm was based on 100 images from 44 patients with BE to develop specific color and texture filters and machine learning to differential dysplastic from nondysplastic BE [10]. The system achieved a sensitivity and specificity of 86% and 87%, respectively, showing the potential of computer-assisted diagnosis of neoplasia within BE using standard, widely available endoscopic techniques. Hashimoto et al. improved upon this idea, creating an AI algorithm utilizing 916 retrospectively col-

lected images of histology-proven high-grade dysplasia or T1 adenocarcinoma in BE as well as 916 control images [11]. These images were obtained with standard WLE, NBI, as well as Near Focus which is an imaging technique on Olympus™ endoscopes that allows the focus to adjust to objects within 2mm of the endoscope. The system was trained to first identify any neoplastic image within a video and flag it as an image of interest. Once flagged, the image would be analyzed, and the area of neoplasia would be identified with a rectangular box. The algorithm was validated utilizing 458 test images with an overall sensitivity of 96.4%, specificity of 94.2%, and accuracy of 95.4%. Importantly the algorithm is able to make predictions on >40 frames per second, which made real-time evaluation a potential possibility. Ebigbo et al. realized this potential in their computer-aided diagnosis model, which utilized AI and deep learning (DL) to identify early adenocarcinoma in BE [12]. They used a state-of-the-art encoder-decoder to transfer live endoscopic images to their AI system. The AI system can be activated at any time during the endoscopy by the practitioner once the segment of interest has been reached. Once activated, the system randomly analyzes images from the live feed and produces a blue bar that displays the probability of cancer in the given segment, with positivity being considered a probability over 90%. The system underwent validation on real-time images from endoscopic video on 14 patients, which contained 36 images of early AC and 26 of normal BE. The model's predictions were compared to the corresponding pathological examination of resected specimens. The AI system had a sensitivity of 83.7%, specificity of 100%, and an overall accuracy of 89.9% showing its potential for real-time use.

Volumetric laser endomicroscopy (VLE) is a newer endoscopic imaging modality that has been developed to aid in the diagnosis of dysplasia within BE [6]. VLE uses the second-generation optical coherence tomography in a balloon-based system. After endoscopic deployment of the device balloon within the area of BE, an infrared light generates a circumferential scan of 6cm segment of the esophagus. The scan

reaches a penetration depth of 3mm into the tissue with an axial resolution of 7 μm allowing for visualization of esophageal layers and submucosal vascular networks [13]. The scans then must be manually reviewed for concerning features, including surface intensity greater than subsurface intensity, lack of layering, and presence of irregular and dilated glands. Once an area of suspicion is determined, the area is marked between two laser cautery marks for subsequent biopsy with WLE. The technology has shown promise, improving neoplasia diagnostic yield in BE by 55% compared to random biopsies alone in a multicenter US trial. However, it can be burdensome because of the large amount of complex visual data that must be processed [3]. An AI software known as intelligent real-time image segmentation (IRIS) was developed to assist the endoscopist with quickly and accurately identifying areas of suspicion. The system identifies the three established VLE features associated with histologic dysplasia and color codes them, then displays them superimposed over the VLE imaging. Areas on the VLE image that contain all three colors then can be marked for subsequent biopsy. A prospective randomized trial is currently underway comparing the use of VLE with and without IRIS, with primary outcomes being the time of interpretation, biopsy yield, and a number of biopsies (NCT03814824). Results of this study are pending as of January 2022.

Wide-area transepithelial sampling (WATS) is another technique to increase the diagnostic accuracy of random biopsies surveillance for BE. The technique consists of passing a brush through the working endoscopic channel and rotating the brush repeatedly back and forth across BE tissue until pinpoint bleeding is observed. The brush is then removed, and its contents smeared onto two glass slides; the bristles are then cut into a transport medium. The slides and transport medium are transported to a central pathologist that specializes in WATS specimens. The transport medium and slides are then analyzed by a high-speed, computer-assisted neural network that has been optimized for esophageal mucosa—the computer flags all abnormal cells, which

produces a high-resolution image for the pathologist to review. The concept was first validated by a study by Vennalaganti et al., in which 149 BE WATS specimens were reviewed by four pathologists with a very high interobserver agreement (percent agreement calculated at 88.6%) [14]. A multicenter, prospective, randomized trial was then conducted comparing Seattle protocol to Seattle protocol plus WATS. The addition of WATS to biopsy sampling resulted in an additional 23 cases of high-grade dysplasia/esophageal adenocarcinoma, which was a 14% increase. Interestingly, 11 of the 23 additional cases identified by WATS had no evidence of dysplasia on biopsy histology alone. WATS added an average of 4.5 mins to the procedure. [15]

Esophageal Squamous Cell Carcinoma

While AI has shown promise in aiding in the diagnosis of esophageal adenocarcinoma, it has also been applied to the identification of esophageal squamous cell carcinoma (ESCC). Squamous cell carcinoma of the esophagus is more prevalent in Asian populations, which results in less experience in Western communities in the diagnosis and treatment of this relatively rare disease. The current gold standard in screening is Lugol chromoendoscopy, which requires the application of Lugol's solution to the lower esophagus. While this method has a high sensitivity (>90%), it has a relatively low specificity of near 70%, thought to be secondary to overidentification of inflammatory mucosa as neoplastic [7]. In addition to the low specificity, the Lugol's solution can cause GERD-like symptoms, discomfort, as well as allergic reactions. There have been several advancements in endoscopic techniques to try to replace the Lugol chromoendoscopy, including confocal laser endomicroscopy, endocytoscopy, and high-resolution microendoscopy; all are variations of identifying and interpreting microscopic images in order to better target biopsies. Despite these advancements, which have shown good performance on test images, their use remains

quite limited because of the relatively low access. To this end, Horie et al. created a convolutional neural network trained on 8428 retrospectively obtained training images utilizing WLE alone [16]. The program was tested on 1118 test images containing an array of adenocarcinoma, squamous cell carcinoma, and no carcinoma. Esophageal cancer was detected with a sensitivity of 98%. However, there were quite a few false positives with a positive predictive value of only 40%. Most of the false positives were due to shadowing and identification of normal structures as cancerous. The next year, Tokai et al. took the same CNN and used an additional 1751 test images with information about invasion depth to see if the system could accurately predict the depth of invasion of esophageal SCC. The depth of invasion determines the extent of treatment. According to Japanese guidelines, lesions reaching muscular mucosa (T1a) or infiltrating the submucosa up to 200μm (T1b-SM1) have a very low likelihood of nodal metastases and are amendable to endoscopic resection, whereas those infiltrating the submucosa past 200μm (T1b-SM2) are treated with esophagectomy. The system was tested along with 13 expert endoscopists against 291 retrospectively obtained images of ESCC of different invasion depths. The AI system identified 95.5% of ESCC within the test images and was able to accurately predict the invasion depth with a sensitivity of 84.1% and an accuracy of 80.6% [17]. The system accuracy was better than 12 out of the 13 experts, showing its potential diagnostic ability.

Detection of Helicobacter pylori (H. pylori) infection

H. pylori infection is a known risk factor for developing gastric cancer. However, diagnosis on endoscopy can be challenging. Watanabe et al. illustrated this point by testing endoscopists ability to diagnose *H. pylori*. Six endoscopists of varying experience were given a series of retrospectively obtained images of *H. pylori*-infected and uninfected patients.

They found that the diagnostic yield for identifying *H. pylori*-infected patients was 62.1%. They also discovered that the less experienced the endoscopist was, the lower their diagnostic yield was, thus demonstrating the potential for CAD in recognizing *H. pylori-infected* patients [18]. In 2017 Shichijo et al. developed a CNN-based CAD to identify *H. pylori* infections using regular WLE. They retrospectively obtained 32,208 images of *H. pylori*-positive (735 patients) and negative (1015 patients) from which their CNN was constructed. The system, as well 23 endoscopists with varying levels of experience, was asked to classify a separate retrospectively obtained data set of endoscopic images as either *H. pylori*-infected or *H. pylori*-uninfected. The CAD system had a sensitivity, specificity, and accuracy of 88.9%, 87.4%, and 87.7%, respectively. As a whole, the endoscopists obtained sensitivity, specificity, and accuracy of 79%, 83.2%, and 82.4%, with the more experienced endoscopists performing better than less experienced endoscopists [19]. Around the same time, Itoh et al. also created a CNN utilizing 149 prospectively obtained images from a single endoscopist to train the system. The CAD system was then tested on an additional 30 images that had been obtained at the same time but that were not used for the development of the CNN. The system was able to identify *H. pylori*-infected patients with a sensitivity and specificity of 86.7% and 86.7%, which was a slight improvement from previous studies [20]. While these CNN-based CAD systems do show promise in aiding the endoscopist in the endoscopic identification of *H. pylori* infection, they have yet to be used in a real-time, live fashion, which limits their current feasible use.

Colonic Polyp Detection

Colonic polyp detection has also been an area of active AI research. The rate of colonic polyp detection should be consistent within a given population; however, studies have shown the detection rates among endoscopists vary greatly. It

is also estimated that every 1% increase in adenoma detection rate will decrease the adenocarcinoma rate by 3–6% [21], which is why polyp detection is fertile ground for AI utilization. In 2003, Karkanis et al. created a selection algorithm based on feature extraction to identify colonic polyps on colonoscopy images. The system showed the feasibility of computer-aided diagnosis, reaching a specificity of 97% and a sensitivity of 90%. However the system was tested on still images limiting its clinical use [22]. In 2013, Glòria Fernández-Esparrch developed a computer-aided diagnosis model that analyzed colonoscopy videos and produced an overlying energy map correlating with the likelihood of a polyp being present. Tested on 24 videos, the system had a sensitivity of 70.4% and a specificity of 72.4% for polyp detection [23]. Urban et al. aimed to improve upon this performance in 2018, developing a state-of-the-art learning CNN. The system was trained first on millions of labeled natural images contained on the ImageNet learning database. Once this baseline training had been complete, the system was then fine-tuned on 8641 hand-labeled images from screening colonoscopies from over 2000 patients [21]. Testing commenced on 1300 still images, where it achieved an accuracy of 96.4% with an Area Under the Curve (AUC) of 0.974. Not only did the system show good accuracy, but it was also able to analyze 98 images per second, making real-time use feasible. This was tested by running the system over 9 full colonoscopy recordings in which 28 total polyps had been removed at the original colonoscopy. The video of the colonoscopies was first reviewed by three experts, who identified 36 unique polyps. The CNN system was then tested on the videos and was able to identify all 36 polyps as well as an additional nine polyps that were missed by the experts. Of the 9 additional polyps that were identified three of them were deemed high likelihood of being an actual polyp while the other 6 were considered low likelihood. While this system showed promising result, it still was not tested in a live clinical situation. In 2019 Klare et al. performed a prospective study, testing a developed automated polyp detection software utilizing AI which had previ-

ously been validated in ex vivo applications. The software was designed to identify and mark polypoid structures in real-time endoscopy. The system works by utilizing a frame-grabber device to capture the colonoscopy video stream. The images are then cropped by the software neglecting unnecessary image data such as the black frame. A weighted combination of color, structure, textures, and motion information is used to identify regions of interest that may represent a polyp. The system gives feedback to the endoscopist by encircling the area of interest with circles displayed on an HD screen. To test the feasibility of use during real-time colonoscopy, the system was applied to 55 real-time colonoscopies. The endoscopist was unable to see the screen that displayed the computer-aided diagnosis system. A researcher was able to see the real-time unbiased endoscopy screen next to the diagnostic system computer screen. The endoscopist would give vocal cues to when a polyp was identified. The researcher would then correlate this information with the information provided by the system. A total of 73 polyps were identified by the endoscopist, 40 neoplastic, 36 adenomas, and 1 intramucosal carcinoma. The CAD system identified 55 of the 73 polyps (75.3%), and 31 of the 40 neoplastic polyps [24]. The system also indicated an average of 6 false positive images per procedure. No polyps were identified by the system prior to being detected by the endoscopist. On logistic regression analysis the system struggled to identify flat-shaped and small polyps. While the system did not perform as well as the expert endoscopist, this study did show the potential utility of real-time computer-aided diagnosis of colonic polyps, especially with deep learning models that continue to improve their performance over time.

Detection of Inflammatory Conditions

Ulcerative colitis (UC) and Crohn's disease are conditions that can be difficult to diagnose, differentiate from each other, and stratify severity of disease. Ozawa et al. applied AI

to this problem by creating a CNN-based CAD system intended to identify the severity of ulcerative colitis. The motivation for creating the CAD was the amount of interobserver variability that existed among endoscopist when classifying the severity of disease, which was greater among nonexperts. This can affect clinical decisions, such as starting patients on expensive biological medication. They trained their CNN image recognition system using 26,304 colonoscopy images from 841 patients with UC. They then tested the system on a separate set of 3981 images, tasking the system to identify the images as Mayo grades of inflammation. The system was able to correctly classify 73% of the Mayo 0 images, 70% of the Mayo 1 images, and 63% of the Mayo 2–3 images [25]. In 2018 Maeda also developed a machine learning-based CAD utilizing endocytoscopic images to try to predict histological healing of UC. They argued that there is an incremental benefit of achieving histological healing of UC beyond just endoscopic mucosal healing, as ongoing histological inflammation increases the risk of exacerbation and dysplasia. The CAD was trained on 12,900 endocytoscopic images with known, biopsy proven histological grades of healing. It was then validated on 525 retrospectively obtained images, where the histology was also known from biopsy. The system had an overall diagnostic sensitivity, specificity, and accuracy of being able to predict ongoing histologic inflammation of 74%, 97%, and 91% respectively [26]. While the sensitivity is too low to do away with physical biopsies, as systems improve it could reduce the need and cost of several biopsies within each area of UC. Celiac disease is another relatively common inflammatory disorder that is immune-mediated. The gold standard for diagnosis is endoscopy and biopsy; however, there is interobserver variability with this approach as well. Celiac disease is another disease which can be difficult to diagnose by the unexperienced endoscopist. Wimmer et al. strived to create a CNN that would accurately identify celiac disease using CAD. They trained models already in existence that had been previously trained on large image data sets of the natural world. They then fine-tuned them to be able to

identify images of celiac disease using modified immersion technique with traditional WLE as well as under NBI. Modified immersion technique is a technique that consists of closeup views of the wall of the duodenum under clear water to enhance the image of the duodenal villi. The system was able to achieve an accuracy of 90.5% in diagnosing celiac disease from the endoscopic images alone [27]. There has yet to be a computer-aided diagnostic system for celiac or IBD that has been tested in real-time conditions, which limit their applicability to clinical practice.

As we make technological advances in medicine in terms of smaller and more precise equipment, we have also used imaging and navigation with the help of AI for procedural planning and guidance. Though this application is not gastroenterology related, it is one of the new applications of AI in therapeutics, not just diagnostics. Figure 45.2 shows the Auris Bronchoscope to target small lung lesions for biopsy which are not accessible through conventional bronchoscopy. The Auris Bronchoscopy uses an outer sheath and an inner bronchoscope with a 4-way steering control, electromagnetic navigation guidance, and continuous peripheral visualization for procedural navigation and biopsy [29]. The Auris Bronchoscope uses the MONARCH Platform which combines electromagnetic tracking, optical pattern recognition, and robotic kinematic data to help locate the bronchoscope during the procedure and provide positional data for the scope in relation to the target lesion. In 2019, a post-marketing multicenter study using the Monarch Auris robotic platform in 165 patients showed successful navigation to 88.6% of the lung nodules with 70.7% of the nodules located in the outer third of the lung [30].

AI—Limitations and Challenges

Despite the significant advances made in medicine over the last several decades, there continue to be large and increasingly complex problems that arise. This is partly because of

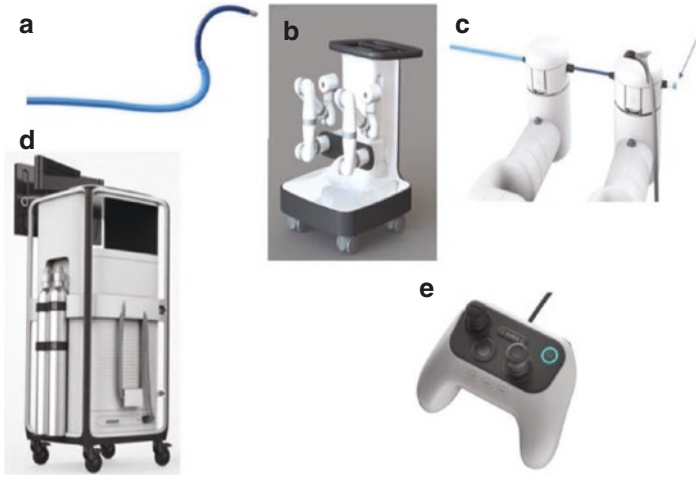

FIGURE 45.2 The Auris Bronchoscope is formed by an inner scope and the outer sheath. (**a**) The bronchoscope includes a camera that provides the operative perspective, an integrated light source in the handle, and a 2.1 mm inner diameter working channel for the passing of manually controlled tools. (**b**) The Auris Cart with the robotic arms. (**c**) Attachment of the bronchoscope to the robotic arms with the proximal valve for saline, air, or instrument insertion (arrow). (**d**) The tower with the monitor for endoscopic and electromagnetic navigation display. (**e**) The controller. From Murgu, S.D. Robotic assisted-bronchoscopy: technical tips and lessons learned from the initial experience with sampling peripheral lung lesions. *BMC Pulm Med* **19**, 89 (2019) [28] http://creativecommons.org/licenses/by/4.0/

the phenomenon of "we did not know what we did not know," as we become aware of more and more layers of complexity in each disease process. What adds to this challenge is the decreasing tolerance (appropriately) of failure and error. With massive amounts of data becoming available, there is an opportunity to use artificial intelligence to make things better for our patients, clinicians, health systems, and society overall.

Recently, the Food and Drug Administration (FDA) approved one of the first AI systems for clinical use in oph-

thalmology for interpretation of diabetic retinopathy funduscopic images [31]. AI can be instrumental in computer-assisted diagnosis (CAD) in multiple fields but especially endoscopy. It can assist in quality control of procedures being performed as well as performance improvement of novice (and even expert) endoscopists. It can help make diagnoses more quickly and potentially more accurately, especially with premalignant lesions [32]. It can also potentially help in disease localization and therapeutics in the future using preoperative image guidance. With the vast and rapid advances in computing power, the role of artificial intelligence in clinical medicine should have been ubiquitous. The fact that it is not is due to several challenges and limitations.

Many of the AI systems used in endoscopy so far have used limited datasets. They rely on high-quality endoscopic images to train the datasets for recognition, excluding lower quality images like those with some mucus or bile on them. This does not always follow real-world conditions, potentially falsely increasing accuracy in the initial single center studies. This could cause overfitting of the models and falsely increase detection accuracy [3]. The artificial intelligence neural network training will need to include live, unprocessed videos to simulate real-world conditions. Just like humans, the more training and feedback the AI gets, the better it can get.

The involvement of AI in diagnostics and clinical medicine will have nonclinical implications as well. These include assumption of responsibility for errors, ethical concerns, and medico-legal risks. There is also the risk of amplification of this error by a faulty algorithm. Instead of a single error by a single physician, the application of the AI broadly could result in a vast number of errors [33]. Currently, there is a relative lack of standards and regulations to evaluate efficacy and safety of AI systems in clinical medicine [34]. These regulatory and legislative issues will need to be addressed by involving all the stakeholders including clinicians, technology experts, industry and regulatory bodies among others. Payors like insurance companies and/or the government will also need to be involved to address reimbursements for the added initial cost that AI incorporation may introduce.

Recently, Watson for Oncology, IBM Watson Health's AI algorithm, was used by several hospitals around the world for treatment recommendations for cancer patients. Some of the recommendations were found to be faulty such as recommending use of bevacizumab in a patient with bleeding, which is a contraindication [33]. The algorithm was based on a small number of theoretical cases with limited input from oncologists [33, 35]. This example highlights potential problems with current algorithms and also provides opportunities for future improvements. This has regulatory implications and significant work has yet to be done on that front. As mentioned earlier, because of the potential for amplification of these errors, the algorithms need to be based on as large a dataset as possible with ongoing machine and deep learning. There needs to be detailed simulation, validation, frequent audit, and periodic prospective evaluation of the algorithm. This would need to go beyond the current FDA requirements for medical algorithm approval [33, 36]. There may also be regulatory need to make algorithms more accessible so they can withstand scientific scrutiny as well, but it can be challenging to balance intellectual property rights with transparency. There also is a need to address data security and privacy. With global teams of hackers already pervasive and involved in data breaches and ransom, significant software security measures will need to be taken to maintain data privacy and also to avoid a malicious hack of algorithms that can result in erroneous or dangerous recommendations from the AI.

Conclusion

Will AI ever replace clinicians? Though there are fields like radiology and pathology that initially seem more at risk, physicians will still be needed to process the information and come up with a treatment plan for the foreseeable future. AI will be used to analyze, process, and find patterns in massive sets of data that observe and detect things that are not humanly possible [33]. It can do so accurately, efficiently, repeatedly, and reliably. What seems difficult to replace is the

advantages of an actual person to communicate with the patient and their family with empathy and sympathy, to read the nonverbal cues of a stressed patient, and to provide the ever-important human touch to comfort the patient [31].

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Chapter 46
Advanced Imaging Through The Endoscope

Reid Sakamoto and Dean J. Mikami

The advent of endoscopy has allowed for both diagnostic and therapeutic assessment of the human gastrointestinal tract. Initially, endoscopy was limited due to the rigid nature of the gastroscope, which caused significant patient discomfort. The advent of fiberoptic technology in the 1960s allowed for improved visual assessment due to the flexibility of the endoscope and enhanced patient comfort. Optical viewing bundles composed of glass fibers carry light to the viewing lens through total internal reflections [1, 2]. Early iterations of this endoscopy came with complaints that it was too flexible, resulting in insufficient control over the distal tip of the scope. Additional criticism was that this endoscope did not maintain focus as well as commercially available gastroscopes. In the 1980s, Welch Allyn incorporated a charge-coupled device into a flexible endoscope, which permitted the digital visualization of images. Individual photocells (pixels) receive light reflected from the mucosa, which is then projected onto a chip. The information on the chip is then reproduced as a video image [1, 3]. Current standard definition endoscopes offer images in

R. Sakamoto · D. J. Mikami (✉)
Department of Surgery, University of Hawaii, Honolulu, Hawaii, USA
e-mail: dmikami2@hawaii.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_46

a 4:3 aspect ratio and can produce an image quality of 100,000 to 400,000 pixels. Alternatively, new high-definition (HD) endoscopes now produce images of 850,000 to 1 million pixels [4].

Several new technologies have been developed that allow for improved acquisition and characterization of mucosal and submucosal abnormalities. HD and zoom endoscopy enable closer characterization of mucosal surfaces with white light. Chromoendoscopy utilizes the application of stains to improve tissue differentiation. Electronic chromoendoscopy modalities include narrow-band imaging (NBI), i-scan, flexible spectral image color enhancement (FICE), and confocal laser endoscopy (CLE), which allow for improved mucosal and submucosal definition. Current improvements in advanced endoscopic techniques have resulted in technology that may be able to more accurately identify metaplasia, dysplasia, and neoplasia earlier in the disease process.

High-Definition Endoscopy

HD endoscopy permits closer examination of mucosal and vascular details with resolution greater than 1 million pixels [5]. With this improved degree of definition, displayed images are superior in quality in comparison to standard definition white light endoscopy. Further, HD endoscopes may be equipped with a zoom function that allows for up to 150-fold magnification of images without loss of resolution [1, 6]. Theoretically, a better definition should result in better detection of intraluminal pathology. However, there are conflicting reports on HD endoscopy's utility in improving lesion detection rates [7, 8]. One meta-analysis demonstrated a small increase in the detection rates of colonic polyps and adenomas using high-definition endoscopy but did not find an improvement in the detection rate of high-risk adenomas [9]. A randomized control trial performed by Rastogi et al. demonstrated that HD endoscopy had an adenoma detection rate of 1.12 per subject in comparison to 0.69 in standard defini-

tion white light. Additionally, HD endoscopy has a comparable detection rate in comparison to chromoendoscopy [10]. HD endoscopy has become a more widely adopted endoscopic technique due to its superior ability to obtain mucosal and vascular detail. Currently, the American College of Gastroenterology recommends using high-definition white light endoscopy for the surveillance of Barrett's esophagus (BE) due to its advantages over white light endoscopy in detecting dysplasia [11].

Chromoendoscopy

Chromoendoscopy involves the topical staining of mucosal surfaces with dyes to improve the characterization of mucosal surfaces using WLE. There are three different types of stains that can be used: absorptive (Lugol's solution, methylene blue), reactive (congo red, phenol red), or contrast (indigo carmine) [5, 12]. The stain is applied evenly throughout the target organ using a spray tip as the endoscope is rotated clockwise and counterclockwise while being withdrawn. For absorptive and reactive stains, the lumen is then rinsed with water. Additional time may then be needed for the staining to be complete. Lugol's solution is especially useful in BE. This solution binds to glycogen contained in the nonkeratinized squamous epithelium and will result in staining normal epithelium brown. Columnar mucosa does not contain as much glycogen and will be pale, allowing for the endoscopist to identify areas of dysplasia. Methylene blue undergoes active uptake by the normal absorptive epithelium of the small intestine and colon. Areas of heterogenous staining patterns or no staining indicate inflammation or dysplasia and should be investigated further [13]. Additionally, methylene blue is taken up by intestinal epithelium, so esophageal metaplasia in the case of BE can be identified. Reactive stains include congo red and phenol red, which undergo color changes when applied to certain cellular components. In the presence of acid (pH <3), congo red will change from red to dark blue/

black. Historically, this has been used to identify gastric mucosa and areas suspicious for gastric neoplasia. Alternatively, phenol red changes color from yellow to red when exposed to an alkaline environment. In the stomach, a color change suggests the presence of *Helicobacter pylori. H. pylori* breaks down urea into ammonia, which in turn causes phenol red to turn red. Indigo carmine is a contrast stain that is used for the evaluation of colonic mucosa. The dye collects in pits and grooves on the mucosal surface. Magnification and zoom endoscopy may be coupled with indigo carmine staining to improve pit and groove characterization. Neoplasia is marked by small, nonstructural, or irregular pits [13, 14]. Chromoendoscopy is a safe, cheap, and easily performed endoscopic technique that helps with identification and characterization of mucosal surfaces. It has shown utility in esophageal neoplasia, gastric neoplasia, colorectal neoplasia, and ulcerative colitis. However, large randomized trials of chromoendoscopy versus other advanced endoscopic techniques are lacking [15, 16].

Virtual Chromoendoscopy

Virtual chromoendoscopy enhances mucosal and superficial vascular definition through optical or post-processing filters. These systems utilize a narrow spectrum of the available light spectrum to enhance images. Currently, there are three available virtual chromoendoscopy systems: Narrow-band imaging (NBI) (Olympus), Flexible spectral image color enhancement (FICE) (Fujifilm), and i-Scan digital contrast (Pentax).

NBI is the first and most widely used virtual chromoendoscopy modality. NBI is activated using a switch on the endoscope, which causes an optical filter to be placed in front of the light source. Blue and green wavelength filters are applied at 415 nm (blue) and 540 nm (green) [17]. Hemoglobin maximally absorbs light at 415 nm. Thus superficial microvasculature will appear black/brown. The green light will penetrate deeper into the mucosa, and because hemoglobin's second

absorption peak is centered around 540 nm, deeper vascular structures will appear cyan. Dysplasia and neoplasia will appear darker in comparison to surrounding mucosa due to their irregular vascular patterns [18]. For BE, NBI is superior to standard definition and HD endoscopy in detecting dysplasia and was comparable to indigo carmine chromoendoscopy in detecting high-grade dysplasia and early esophageal cancer [10, 19, 20]. NBI has not been shown to improve colon adenoma or polyp detection yields. However, it does appear to improve the characterization of neoplastic polyps [21, 22].

Similar to NBI, FICE enhances mucosal and superficial vasculature visualization. FICE utilizes post-processing filters that select a narrow band of wavelengths from white light endoscopy. Images are reconstructed using a single wavelength and assigned to red, green, or blue inputs to display a combined image. FICE has ten available filter settings that can be altered by the endoscopist [23]. Color differences and better tissue contrast allow for differentiation between neoplasia and normal mucosa. FICE improves characterization of colon polyps but does not improve adenoma yield in comparison to white light endoscopy or indigo carmine chromoendoscopy [24, 25]. In addition, there is no significant difference between FICE and chromoendoscopy in the detection of high-grade dysplasia in BE [26].

i-Scan is another form of virtual chromoendoscopy that allows for improved characterization of mucosal surfaces. Like NBI, i-Scan uses post-processing filtering to display images. There are three modes: surface enhancement (SE), contrast enhancement (CE), and tone enhancement (TE). SE and CE modes sharpen the image and darken depressed areas. These are primarily used to improve visualization of mucosal texture and superficial microvasculature. TE improves contrast between mucosa and blood vessels. i-Scan has three factory settings, which combine SE, CE, and TE settings [1, 21, 23]. i-Scan has not been shown to improve colorectal adenoma yield in comparison to HD endoscopy but may better be able to predict histology in comparison to HD white light endoscopy [27, 28].

Virtual chromoendoscopy is a useful technology that can be used much more quickly and easily than dye-based chromoendoscopy. It does not significantly improve adenoma and polyp detection rates, however, it has shown to help discern benign from malignant polyps without the need for histologic diagnosis. In addition, there are significant costs and an operator learning curve associated with using these technologies [21, 23].

Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) creates microscopic images with subcellular resolution up to 250 μm below the mucosa. A laser is focused on a single point. Light from that point is then collected through a pinhole, thus blocking out extraneous light. Fluorescein is injected intravenously to improve the contrast between cellular components [1, 21]. The resulting image is magnified up to 1000 times, thus allowing for real-time microscopic examination of the mucosa during endoscopy [28, 29]. Currently, there are two CLE) systems available: one system is integrated into the tip of an endoscope (iCLE), while a probe-based system (pCLE) can be inserted through the working port of a standard endoscope. pCLE is superior to NBI in predicting histology of colon polyps [30]. One meta-analysis demonstrated that CLE had a pooled 94% sensitivity and 95% specificity for the detection of colorectal neoplasms [31]. CLE has also been shown to benefit in the assessment of BE and associated neoplasia [5]. Despite CLE's promise for accurate histologic diagnoses, there is a significant learning curve associated with becoming proficient in the interpretation of CLE images. Also, CLE's wide adoption is limited by its unknown cost-effectiveness in community and academic practices [32].

A recent Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Technology and Value Assessment Committee (TAVAC) analysis determined CLE

to be a safe endoscopic adjunct to the histological examination of lesions in the gastrointestinal tract. Study evaluations demonstrated the most common adverse events were related to the use of contrast dyes. In regard to efficacy, CLE increased the accuracy and decreased the number of biopsies during surveillance of Barrett's esophagus-associated dysplasia when compared to the Seattle protocol. CLE was also effective in further classifying polyps into adenomatous versus non-adenomatous groups. Furthermore, CLE had a higher dysplasia detection rate in comparison to standard screening [33].

Conclusion

Advanced endoscopic techniques have allowed for improved mucosal, submucosal, and cellular assessment. HD endoscopy has already been shown to offer clear advantages over standard definition endoscopy. Neither chromoendoscopy, virtual chromoendoscopy, nor confocal laser microscopy is superior to HD endoscopy in community practice. Chromoendoscopy is limited by longer procedural times, while virtual chromoendoscopy and CLE have significant learning curves and are associated with high costs. Further randomized control trials are needed to evaluate the diagnostic utility of virtual chromoendoscopy and CLE before these technologies can become more widely adopted.

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Chapter 47
Robotics in Endoscopy/ Tele-Endoscopy

Omobolanle Oyefule and Barham K. Abu Dayyeh

History

The development and application of robotic technology in laparo-endoscopy has come a long way from the initial purpose of providing means of performing remote battlefield trauma surgery. Today's commercially available robots have become a standalone mode of providing minimally invasive care separate from but complementary to traditional laparoscopy and endoscopy. Robotic technology allows for technically precise and reproducible results while improving ergonomics for proceduralists. Contemporary robotic technology offers technical advantages to endoscopists by way of sensitized haptic feedback, improved visualization with three- and four-dimensional spatial imaging, and increased degrees of freedom,

O. Oyefule
Department of Surgery, Mayo Clinic, Rochester, MN, USA
e-mail: mobola.oyefule@emory.edu

B. K. A. Dayyeh (✉)
Department of Gastroenterology and Advanced Endoscopy, Mayo Clinic, Rochester, MN, USA

Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA
e-mail: AbuDayyeh.Barham@mayo.edu

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_47

allowing for complex movements. With telemedicine, robotic technology has the ability to bridge gaps in access as endoscopists may be even remote in relation to the patient's location [1]. This chapter provides a review of the history of robotic-assisted laparo-endoscopy technology and outlines current and future developments in robotic endoscopic surgery.

This first prototype of a robotic system, developed by Green, Rosen, and Satava at Stanford Research Institute (SRI) in the late 1980s for open surgery, was the "Telepresence Surgery System" developed for military use in battlefield surgery. It comprised of: (1) a telepresence surgeon workstation (TSW) with handles of actual surgical instruments and stereoscopic monitor akin to a surgeon console, (2) a remote surgical unit (RSU) akin to the patient cart [1]. The surgeon's hand movements were transmitted to the RSU by cables with end effectors that could be coupled to exchangeable instruments. While ergonomically comfortable for the surgeon and able to provide haptic feedback, this technology provided limited motion and visualization compared to today's technology with motion in four degrees of freedom, 120-degree view of the operating room field space, and the need for the surgeon to don passive polarized glasses for the three-dimensional stereoscopic image. To adapt this system further for battlefield use, transmission from the TSW to the RSU was conducted by bidirectional microwave technology. By the early 1990s, the Telepresence Surgery System featured exchangeable manipulator handles with motion in six degrees of freedom, the ability to perform surgery over distances up to three miles with video latency of 50 ms. The application of this telesurgery system, however, was limited to military use [2].

Private sector application of robotic technology was soon to follow in the mid-1990s. Computer Motion®, developed AESOP, the first FDA-approved surgical robot in 1992, and Zeus™, a complete robotic system in 1996 for use in cardiothoracic and later urological surgery [3].

In 1995, building on development initiated at Stanford, Moll, Freund, and Younge founded Intuitive®. An earlier robotic system developed by Intuitive (Mona™) was used by Himpens, who performed the first tele-cholecystectomy on a patient located in New York City, the USA, from Brussels, Belgium, in 1997 with Leman stateside driving the endo-

scopic camera [4]. By 2000, Intuitive's Da Vinci™ system became FDA approved for commercial use in general laparoscopic surgery [5]. Two decades and four generations later, the Da Vinci™ robot, Intuitive's most popular product, has become the most recognizable stand-alone mode of delivering minimally invasive endo-surgery, complementary to but distinctively separate from traditional laparo-endoscopy [6]

Employing the principles of robotic technology in complex endoscopy, current platforms aim to provide solutions to the needs of endoscopists—stable working platforms in a limited but dynamic endoluminal working space, multiple instruments that can be used with increasing degrees of freedom, improved visualization with magnification, precision, target triangulation allowing for tissue retraction, and safety. The real and potential benefits to the patient include quicker recovery time, lack of external incisions, less need for sedation/anesthesia, easier resumption of diet, and no wound care issues [7].

This chapter reviews current commercially available robotic endoscopy systems and spotlights key future applications which are in development. We specifically focus on technology with true robotic design, which Eubank et al. [8] define as platforms with a computer interface that allow transmission of hand motion to the end effectors.

Current Robotic Endoscopy Systems

Invendoscope E200™ System (Invendo Medical, GmBH Germany)

FDA approved in 2015, the *Invendoscope E200*™ system is a robotically assisted single-use colonoscope controlled by a hand-held controller. Its most recent iteration features a 210 cm scope with a tip that can be deflected 180° in all directions and a 3.2 cm working channel that admits standard endoscopic working instruments [9]. The scope design features an outer double-walled sleeve over an advanceable inner flexible shaft that reduces the amount of pressure applied on the colonic wall when compared to traditional colonoscopy. The detachable *ScopeController* features a joystick that allows the proceduralist

to advance, withdraw, torque, and perform interventions with very minimal trauma when compared to traditional endoscopy. In clinical trials, 95.1% of colonoscopies were able to be completed without sedation with a 98.4% cecal intubation rate and average patient-reported discomfort scores of 2.3/6 [10].

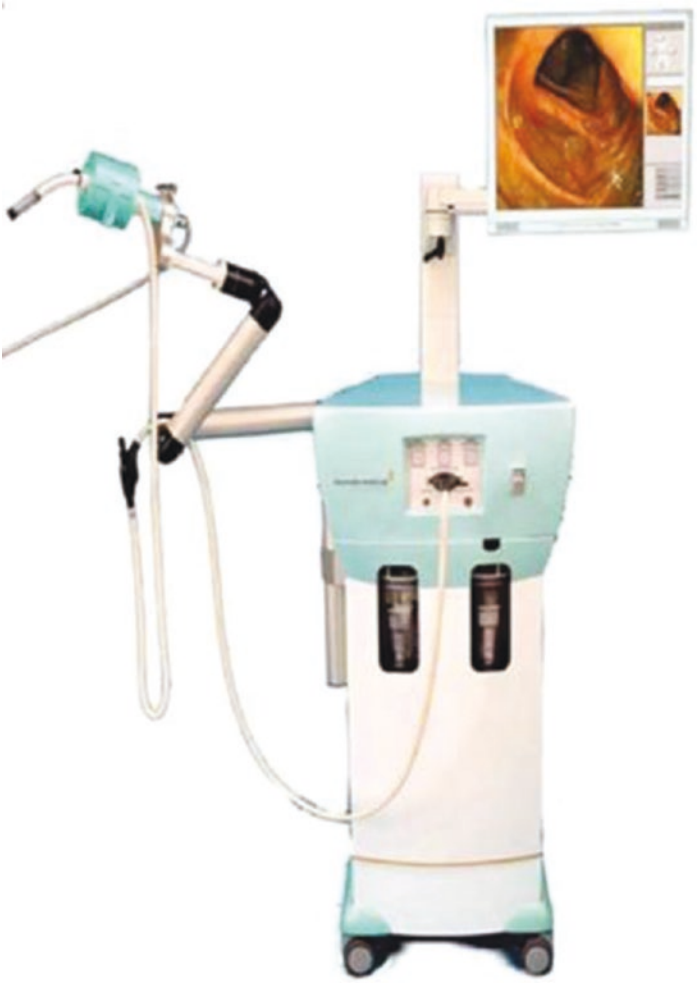


Image Source: Peters BS, Armijo PR, Krause C, Choudhury SA, Oleynikov D. Review of emerging surgical robotic technology. Surg Endosc. 2018 Apr;32(4):1636–1655. doi: 10.1007/s00464-018-6079-2

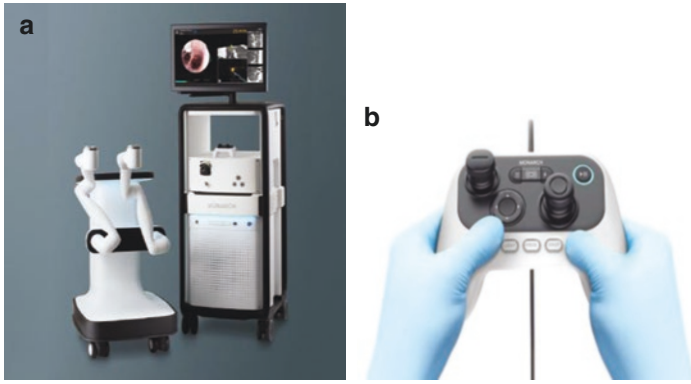
Flex® Robotic System (Medrobotics Corp., Raynham MA)

Originally used in transoral otolaryngology procedures, the Flex® robotic system is an FDA-approved single-port robotic endoscope approved for colorectal endoluminal procedures [11]. The disposable HD endoscope is coupled onto a reusable base that is mounted to the patient table. The scope possesses an advanceable, steerable outer mechanism that provides a stable working base while charting a path for the inner tube. Working instruments are inserted into channels that flank the endoscope bilaterally. 2D images are projected to the console screen from a scope tip camera able to move in three axes (vertical, horizontal, in/out). This inner-outer tube system provides a stable platform for hard-to-reach, dynamic anatomical areas with limited working space. Flex instruments available on the market include various needle drivers, forceps, graspers, and dissectors, all of which can be coupled to energy sources [12].

Monarch® Robotic Platform

Developed by Auris Healthcare, *Monarch*® is a robotic-assisted bronchoscopy platform approved for FDA use in 2016 [13]. The platform consists of a robotic tower with an attached monitor and a remote unit with robotic arms to which the bronchoscope is attached. The bronchoscope is housed in an outer sheath. Both scope and sheath can be advanced towards target lesions independently or as a unit. Once a target is localized, a biopsy instrument is introduced into the working channel of the scope, and multiple passes through the tissue can be made to achieve satisfactory diagnostic yield. The monitor provides a 3D navigation model in addition to the real-time visualization obtained from the scope camera. The proceduralist is able to drive the sheath, scope, and working instruments using a controller akin to a video game controller pad, completely detached from the patient tower. A recent multicenter feasibility study demon-

strated a 96.2% lesion localization success rate with <4% complication rate, although the diagnostic yield was reported at 74.1% [14].



Monarch Platform including tower Controller pad

Image source: www.aurishealth.com (permission pending) (**a**) Monarch platform including tower. (**b**) Controller pad

Ion™ Robotic Platform

The Ion™ System is a robotic-assisted endoluminal platform for bronchoscopic biopsy created by Intuitive® [15]. The system features a pre-procedure software planner, *PlanPoint,* that reconstructs patients' CT imaging into 3D airway models, with consideration given to instrument navigation around critical anatomic structures. A fiber-optic catheter capable of 180-degree articulation serves as the working sheath for a vision probe and possesses a working channel for instrument insertion. Once target tissue acquisition is confirmed, multiple passes can be performed to increase pathological yield with the catheter locked in place to provide a stable working platform. The *BiopsyMarker*™ feature allows the interventionalist to track biopsy trajectories when multiple biopsies

are taken. The diagnostic yield for Ion™ has been estimated to be about 98% in preliminary studies [16].

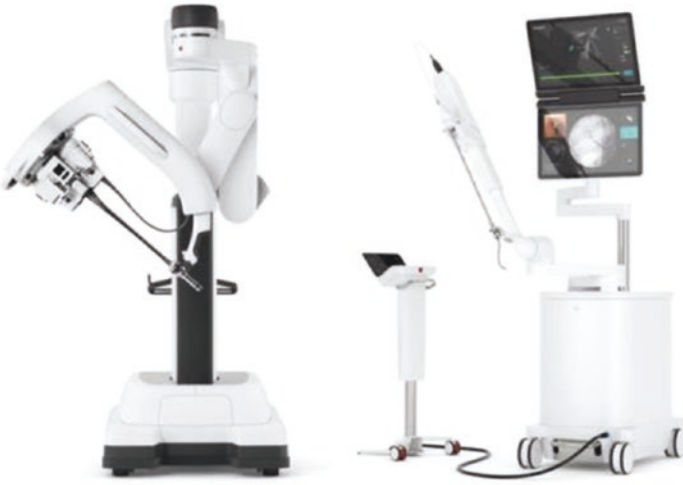


Image source: www.intuitive.com (permission pending)

Products in Development

EndoMaster EASE (Endoluminal Access Surgical Efficacy) System

Previously known as MASTER (Master and Slave Transluminal Endoscopic Robot), this flexible robotic endoscopy system developed in Singapore comprises of true surgeon console-remote patient cart system that operates akin to the traditional surgical robot [17]. At the patient side, a specialized endoscope that possesses a pair of miniature working instruments that fit through two working channels is introduced into the patient by an endoscopist. The instru-

ments are similar in design to transabdominal robotic instruments. They have nine degrees of freedom and are controlled by the proceduralist who operates at a console. Clinical trials are underway for this device, and this device is yet to be approved for clinical use. Preliminary reports from 2020 with EASE used to perform endoscopic submucosal resection of early-stage colon cancer have had positive results with fast recovery and no reported patient complications or safety concerns [18].

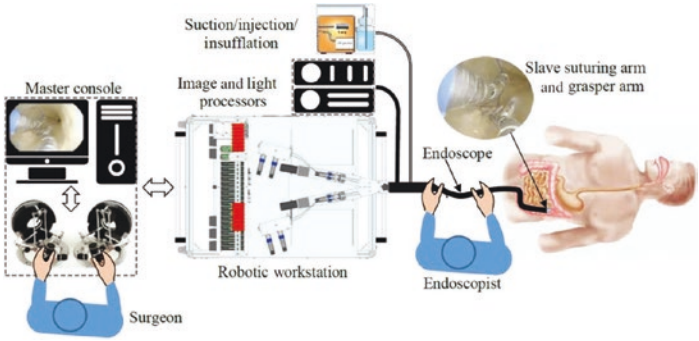


Image source: Kaan HL, Ho KY. Clinical adoption of robotics in endoscopy: Challenges and solutions. JGH Open. 2020 Sep 9;4(5):790-794. doi: 10.1002/jgh3.12412

ISIS-Scope/STRAS System

This robotic platform is a product of conjunctive efforts between Karl Storz (Tuttlingen, Germany) and IRCAD (Strasbourg, France). To our knowledge, this is the first platform that can be completely teleoperated by the surgeon/endoscopist from the operating console, although a bedside assistant can be employed. After manual scope insertion, the endoscope is attached to a cradle attached to the patient's bed. The proceduralist then sits at a console from which they can maneuver the scope using joystick controls with instrument motion in ten degrees of freedom. The scope features two

robotic working channels that are parallel to its scope shaft in addition to one standard endoscope working channel. These working channels permit the use of hollow robotic instruments with interchangeable tips such as forceps, hooks, and graspers. Nonhuman clinical trials completed in porcine models demonstrated successful completion of ESD procedures. Clinical application of this device is currently pending [19].

Summary and Future Directions

Robotic endoscopy continues to be a field with several tested applications and even more potential frontiers for development. The incorporation of artificial intelligence mechanisms in robotic platforms (currently under development) and self-propelling robots are some areas of likely progress in the next decade.

Conflict of Interest BKA is consultant for Boston Scientific and Medtronics. He received research support from USGI, Apollo Endosurgery, and Medrobotics. He is a speaker for Johnson and Johnson and Olympus.

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Chapter 48
Future Horizons in Flexible Endoscopy

Lee L. Swanström and Margherita Pizzicannella

Introduction

Since the invention of the fiberoptic endoscope in 1957, flexible endoscopy has grown exponentially both in technology and in its field of application. Initially developed only as a diagnostic tool, over time flexible endoscopy has become more and more a therapeutic tool. Surgeons and gastroenterologists have both pioneered the progress and evolution of this tool, pushing the boundaries and creating new endoscopic interventions, and in some instances replacing traditional surgery in the management of some diseases [1].

It has been the innovative drive of surgery that has opened the frontiers for this endoscopic revolution. With the advent of laparoscopy, robotic and digital technologies, surgery has progressively changed its focus, embracing the concept of minimally invasive, organ-sparing and patient-tailored interventions. The aging populations of developed countries, along with their increasing digital awareness and increasing chronic comorbidities, have created a demand for early diagnosis and minimally invasive treatments with fewer side effects or

L. L. Swanström (✉) · M. Pizzicannella
IHU-Strasbourg, Strasbourg, France

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0_48

effects on lifestyle. Current new developments in surgery have therefore focused on expediting and making the management of surgical diseases easier, targeting the therapy, sparing normal tissues, leaving little or no scars, preferably in a same-day facility, with minimal morbidity and rare mortality.

In this era of extraordinary surgical transformation, flexible endoscopy has gained recognition as an important tool for delivery of such patient-centered care. Evolving from its traditional role as a simple diagnostic tool, over the last few decades it has become increasingly the preferred platform for several incisionless therapies. This development was supercharged by the concept of Natural Orifice Transluminal Endoscopic Surgery (NOTES) in the mid-2000s, which perhaps represents a pivotal moment in the history of flexible endoscopy (Fig. 48.1). NOTES was conceived as an evolution

FIGURE 48.1 Natural orifice endoluminal surgery was to some extent the spark that ignited modern interventional endoscopy—rather like lap chole did in 1988 for laparoscopic surgery (SAGES/ASGE NOSCAR group of 2007)

of laparoscopic surgery, providing the benefits of minimally invasive approaches to diseases with even less invasiveness for patients. Indications were broadened even further by the intermediate step of hybrid therapies that combined laparoscopy with flexible endoscopy [2, 3]. NOTES presented the prospect of truly operating with an endoscope, gaining luminal access and then passing through the wall of the stomach or other hollow organ to perform an intraperitoneal or intrathoracic procedure [4]. When the first NOTES cases were described it was clear that to obtain satisfactory results the current design of the endoscope had to be changed [5, 6].

The execution of NOTES procedures was complicated by the limitations of standard flexible endoscopes which deprived the surgeon of the triangulation and stability they were accustomed to, making tissue manipulation, dissection, and apposition significantly more difficult. NOTES was a revolutionary vision but was ultimately unable to establish itself in the mainstream of clinical application, and its vision of a replacement for laparoscopic cholecystectomy as well as other procedures slowly faded away. Notably, there are still centers that offer transvaginal cholecystectomy to patients with success [5]. NOTES was the spark that ignited the reformulation of operative endoscopy. The NOTES experience showed that breaching the GI tract with nonsterile endoscopes had minimal consequence, that full-thickness closures of GI defects was possible and generally effective, and that new endoscopic technologies could surgically alter patient anatomy through a different pathway. The past decade has seen efforts to develop new equipment to facilitate this vision, including robotic and suturing platforms, better energy tools, advanced stents, and other devices that have allowed the growth of new endoluminal, intramural surgical, and extramural surgical procedures. The NOTES experiment has had multiple positive benefits: it has led to the fields of third-space endoscopy, endoscopic full-thickness resections, and EUS-guided interventional procedures, among others. And now with the implementation of digital innovation, artificial intelligence (AI), and optical imaging, a second critical revolution in operative endoscopy is taking place.

Tomorrow's endoscopy will likely be able to make accurate diagnosis without the need for histological sampling. These changes will continue to replace surgical approaches in an increasing number of procedures, offering safe and effective patient treatments in a less invasive way and opening the door to increased use of endoscopy as a definitive or hybrid therapeutic tool to both surgeons and gastroenterologists. So let's explore the developments in flexible endoscopy that are happening or may come, which will continue this revolutionary shift in surgery.

Flexible Robotic Endoscopy

Robotic technology has been one of the most impactful breakthroughs in laparoscopic surgery. This is in spite of the maturity of laparoscopic surgeries that are now well taught, safe, effective, and low cost. This has led some to argue that the current laparoscopic robots are an expensive answer to a nonexistent need [7]. Flexible endoscopy may be different however. Current endoscopes were designed in the 60s for diagnostic use and are nonergonomic, inefficient, and, compared to modern laparoscopic technologies, primitive. This is compounded even more as additional tools such as suturing, echography, etc. are added on. This has led to the need for prolonged education and practice to master this complex tool which limits its use to only a select group of users. It may be that the answer to "democratizing" flexible endoscopy so it can be a tool for anyone may be robotics. As they are also tied to the other advantages of computer interfaces, robots will probably change the concept of endoscopy itself [8, 9]. In this era of routine endoscopic screening, the demand for endoluminal resection of submucosal tumors or early cancers is steadily increasing. Performing such advanced procedures through the scope with current flexible platforms present multiple challenges including time to perform the procedures, as well as complication rates, and therefore is restricted to a few experienced operators. There have been and are many

academic and commercial efforts worldwide to develop a flexible robotic platform to hybridize the basic principles of surgery (namely magnified view, triangulation, stability, traction–countertraction, tissue apposition, and suturing) with the current flexible endoscope which is optimized for access and patient tolerance. If it is doable, this may open the door to expanded fields of application and increasing the number of operators able to perform them.

Many systems have been tested on preclinical trials and a few have been granted CE Mark or FDA approval. These include the Flex Robotic™ system (Medrobotics Corp, USA) and the Endoluminal Surgical System-ELS™ (ColubrisMX, USA) [10]. Promising preclinical platforms include the Endoluminal Assistant for Surgical Endoscopy™ (EASE) (KARL STORZ/IRCAD, Strasbourg, France) (Fig. 48.2) and the Endomaster™ EASE System (Endomaster Pte Ltd, Singapore). The importance of such platforms is highlighted by reports showing that novice endoluminal surgeons could

FIGURE 48.2 The endoluminal assistant for endoscopic surgery (Karl Strorz)

obtain equal or better results compared to endoluminal surgery experts [ref Legner, dallemagne et al]. We are clearly only in the early stages of this evolution. Current platforms have only been tested in clinical trials for rectal lesions and in order to be attractive in the marketplace, flexible robotic platforms should enable at least resection of right colon and cecal lesions, and of the stomach and duodenum.

To be competitive, endoscopic robotic systems should be versatile. A robot which is dedicated solely to recto-sigmoid procedures is limited and probably not justifiable. There will also be pressure to miniaturize the endoscope. The smaller and more flexible the robotic scope is, the easier it can access remote areas or traverse strictures, increasing its usefulness and justifying its cost. The Endomaster™ platform, for which a prospective, single arm trial for the treatment of colorectal neoplasms is currently ongoing, has another drawback: it requires two operators, one at the console and one driving the endoscope [11]. This is a major limitation that has to be overcome, as coordination of two operators is difficult to achieve and reduces precision.

The ColubrisMX Endoluminal Surgical (ELS) System™ is one of the latest systems to reach the market [12]. ELS attempts to solve all the limitations of the other existing endoscopic robotic platforms. It is the first completely robotic endoluminal surgical platform, with 7 degrees of freedom. This endoscopic robot with its noncumbersome structure is designed to perform procedures for both the upper and lower gastrointestinal tract. The field of view is not hampered by the robotic arms that incorporate a spectrum of surgical devices (needle driver, forceps, monopolar cautery, monopolar scissors). Furthermore, performance of surgical suturing has been demonstrated. The company has announced that its next-generation system will be implemented with haptic feedback, computer-assisted navigation, and AI.

In the near future we can expect that endoluminal robots will be equipped with increasingly sophisticated technology, will be miniaturized, and will be usable for a broad range of operative procedures in the upper and lower GI tract. This

instrumentation may give endoscopists the tools to perform surgical-like procedures outside the operating room, expanding the field of endo-surgery. A final barrier to be overcome will be adequate reimbursement. All robotic platforms will add substantial cost to procedures. Unless *endoluminal* procedures become recognized as beneficial *surgical* procedures, and become reimbursed as surgeries, this technological evolution may be blocked to the detriment of patients.

AI and Deep Learning

The use of AI in endoscopy is growing rapidly and will play a crucial role in the practice of endoscopy going forward. By means of deep learning (DL) algorithms and convolutional neural networks (CNNs), computers are trained to recognize specific features using as ground truth massive datasets of images or videos annotated by experts with the required relevant clinical information and corresponding histology [9]. AI models are able to learn and recognize lesions without the need for human supervision. Digestive endoscopy is a discipline that relies on images and videos. With the improvement in optical imaging technology and virtual chromoendoscopy, endoscopists currently have better means to predict lesion histopathology during optical evaluation. For example, during colonoscopy the operator has the potential to recognize which polyp should be resected and which one should be left in place. However, these skills are achieved only after prolonged training and extensive experience in order to achieve a high expertise in optical evaluation [13]. For this reason, there is growing interest in applying AI to endoscopy in order to improve the precision and performance of the procedures, reducing human error, and shortening learning curves. AI systems applied to endoscopy have been designed for detection (computer-aided detection: CADe) or characterization (computer-aided diagnosis: CADx) of lesions. CADe algorithms are programmed to identify abnormal findings during endoscopic exams while CADx systems help in the real-time

characterization of the suspected region of interest offering a probable diagnosis, the depth of invasion of a tumor, or other features (Figs. 48.3 and 48.4).

Although this is a relatively new development, preliminary clinical data for AI in endoscopy are encouraging and several

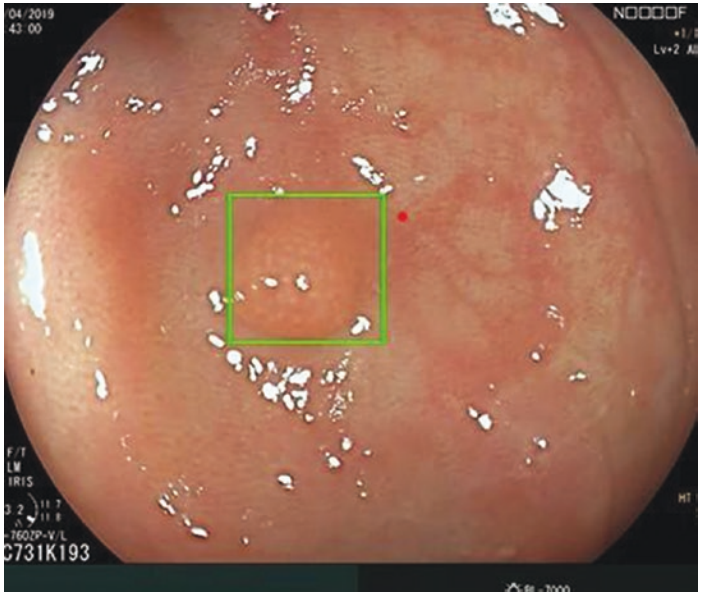

Figure 48.3 Artificial intelligence as an aid to feature recognition

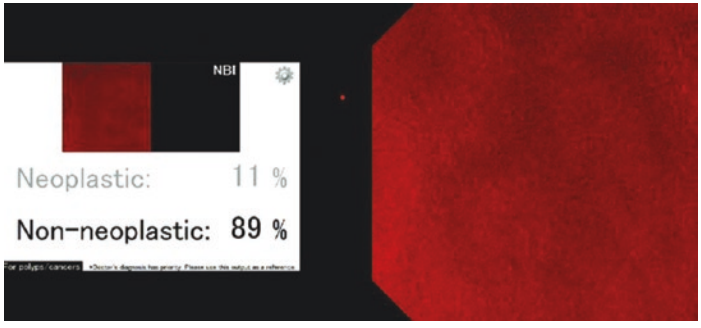

Figure 48.4 Artificial intelligence as an aid to tissue determination

systems are coming to the market. Currently, four DL-based systems for conventional white-light colonoscopy have been approved as medical devices for clinical use by regulatory authorities (PMDA, EMA, and FDA) as of mid-2020 [14, 15]. All of them exhibit CADe functionality and one also has CADx functions. Current systems have been approved only for colorectal applications to date but CAD systems will be soon incorporated in the WCE (Pillcam, Gi-Genius Medtronic) for small intestine examination and other indications for gastric and esophageal pathologies are expected to be approved soon. The rapid evolution of AI systems opens the door to a number of additional future applications of this technology to digestive endoscopy. In particular, several groups are working on the use of DL to provide intelligent systems for endoscopic ultrasound examinations [16, 17]. Over time, AI will likely be able to predict how fast a particular adenoma or lesion could degenerate into invasive carcinoma, for example, or could be able to personalize surveillance intervals, merging image data with clinical metadata.

Robotic Endoscopic Capsules

The greatest goal in diagnostic endoscopy would be to perform precise and accurate examinations in the GI tract without introducing an endoscope into the patient. This would potentially avoid sedation, lessen patient discomfort, and decrease societal cost, which in turn may make population screenings for certain disease economically justifiable (e.g., Barrett's, pancreatic cancer, etc.). One could also expect increased compliance with screening examinations which might lead to earlier diagnosis and overall improved survival. Wireless capsule endoscopy (WCE) may have the potential to advance this goal in the near future.

Since its introduction in 2000, WCE has established itself as a first-line investigation for small bowel disorders [18]. The primary indications are obscure bleeding, small bowel Crohn's, screening in polyposis syndromes, celiac disease, and small intestine cancer [19–21]. The procedure is safe, painless, and well tolerated by the patient who has only to swallow the

capsule and wear a monitor. High patient acceptability due to noninvasiveness has encouraged the development of future capsules for the exploration of the entire gastrointestinal tract including the esophagus, stomach, and colon [22–24]. In particular, second-generation colon WCE has shown high sensitivity and specificity for the detection of polyps greater than 10 mm (87.4% and 95.3% respectively) and greater than 6 mm (86% and 88% respectively) [25] (Fig. 48.5). Even though it has become an essential tool for endoscopy, WCE has several major limitations, including a time-consuming and tedious reading process, a lack of active locomotion or guidance, an inability to obtain biopsies and to perform therapeutic interventions such as, for example, drug delivery.

In order to overcome these disadvantages, several research groups and companies are working to implement WCE with

Figure 48.5 Modern wireless capsule endoscopy

novel technologies [26]. Currently however, full digital integration remains challenging due to size constraints and limited onboard power. Currently, research groups are creating models of WCE with active locomotion which can be either self-propelled or externally directed by magnetic fields [27]. Such ability to externally direct capsule endoscopy may lead to enhanced mucosal visualization and inspection, and challenge the current paradigm of flexible endoscopy. Truly intelligent WCE would be capable of performing forceps biopsy or fine needle aspiration (FNA) of target lesions or to release specific target therapies, but these are as-yet still future directions. A solution that is nearer at hand is the application of AI, using deep learning, to WCE interpretation, which would be potentially time and financially beneficial to the current rather laborious process of reading WCE studies [26]. An advantage of WCE in this age of COVID-19 is its ability to be performed remotely. Medtronic™ has recently announced a partnership with Amazon™ to deliver its new WCE integrated with an AI system (Pillcam Genius™), directly to patients. The patient has just to ingest the pill and then mail the recorder back to the company for evaluation.

Therapeutic Endoscopic Ultrasound

Endoscopic ultrasound (EUS) has evolved from a purely diagnostic to a therapeutic procedure provoking a paradigm shift in the management of several pathologies that used to be in the surgical or percutaneous domain. The development of linear transducer technology, increasing sizes of the working channels, and innovation in accessory devices have opened the door for further EUS-guided interventions. Over the last few years, we have therefore seen its field of application expanded . Procedures such as EUS-guided trans-gastric or trans-duodenal internal drainage (i.e. hepatico-gastrostomy, choledocho-duodenostomy,

cholecysto-gastrostomy, Wirsung-gastrostomy, cysto-gastrostomy, necrosectomy of walled-off pancreatic necrosis) using plastic or metal stents are currently becoming established treatment alternatives to conventional approaches [28–30]. As the potential of this technology has been recognized and consolidated, more and more aggressive interventions have been attempted [31]. EUS has started to be used to create endoscopic anastomoses. For example, gastrojejunostomy has been described for cases of gastric outlet obstruction and creation of a gastro-gastrostomy in patients needing ERCP biliary drainage after Roux-en-Y gastric bypass is now fairly routine [32–34]. This has been made possible thanks to the introduction of lumen apposing metal stent (LAMS) technologies and, in particular, cautery-assisted LAMS (Fig. 48.6). Many research groups are currently studying the possibility of EUS-guided targeted ablation of tumors or other lesions. The most-accrued experience with EUS-guided device ablation so far has been radiofrequency ablation (RFA) of pancreatic endocrine tumors (PETs) with promising results to date [35].

Looking at this rapid spread and evolution of EUS-guided therapies, we strongly believe that the technique is still in its infancy and will likely expand its applications in the future as we see development of new smart devices and technologies. Further development is needed to shorten the time needed to master EUS and improve consistency in image interpretation. This may come through the integration of navigation into the system and potentially the addition of AI-assisted tools for image interpretation or needle placement. Advances in flexible EUS systems will parallel those of external ultrasound systems and we can expect to see real-time 3D ultrasound imaging and enhanced navigation capabilities based on real-time co-registration with segmented CT images [36].

FIGURE 48.6 Electrocautery enabled lumen apposing stents for endoscopic anastomoses

Augmented Imaging and Navigation

Flexible endoscopy always seems to lag behind laparoscopy in terms of technology development. One area this is particularly true is in advanced imaging capabilities. Imaging in laparoscopy that we rather take for granted—video recording,

4-K resolution, 3-D imaging, near infrared—is only just now starting to make an appearance in flexible endoscopy. There is really only one area in this field where flexible endoscopy has excelled and that is in the area of digital chromoendoscopy [37]. 3-D laparoscopy has been demonstrated to have some clinical benefit particularly for novices. Very recently there have been systems introduced in the European and Asian markets that use software to convert 2-D flexible endoscopic video into real-time 3-D images [38]. Preliminary experimental evidence seems to show some benefits with procedure time and accuracy, but the true test will be via large multicenter prospective trials. Fluorescent imaging in laparoscopy is another currently popular topic and modern laparoscopic cameras are increasingly equipped with near infrared (NIR) capabilities for either injectable or topical photophores or autofluorescence. Because some mucosal-based metaplasia demonstrates differences in fluorescent characteristics from normal tissues, there has been interest in developing similar technology for endoluminal application. Early experiences with these prototype flexible scopes show the ability to discriminate between tissue types and cancers and to better highlight microvascular details. These findings may also be augmented with AI-driven computer assistance and be the next generation beyond simple filtering such as Narrow Band Imaging [39].

Navigation is another important computer-assisted tool for rigid endoscopy, currently in spine and neurologic applications but increasingly being used for laparoscopy as well. Considering the lack of horizon and established landmarks in flexible endoscopy, it seems that navigation, directed targeting, spatial presentation and recording, and needle direction could have an even more important role on an endoscopic platform. A very basic example is the use of electromagnetic colonoscope tracking to help novices with loop management in colonoscopy. A more advanced example of the potential of endoluminal navigation is the ability to automatically return to a spot in the GI tract that had been previously of interest. Take for example a case where an endoscopist removes a

polyp and the pathology suggests malignancy. It would be advantageous to have software that directs the endoscope back to the same site based on image recognition [40]. One can imagine even more advanced scenarios where a robotized endoscope is directed to go automatically to a lesion that was identified on preprocedural imaging.

Conclusion: New Role for NOTES?

Advanced interventional endoscopy has evolved rapidly in the last few years in large part due to the availability of smart tools and the development of new endoscopic procedures. Looking at the increase of innovative endolumenal interventions, it seems to be just the beginning of a new promising era. Endoscopic anastomosis, EUS-guided procedures, minimally invasive treatment for neoplastic lesions, full-thickness resection, third space endoscopy, and many other interventions are already a reality in the daily practice.

The next phase is nearly ripe and will mark a momentous change. The first clinical trials on high-tech robotic platforms are underway. AI systems are evolving and spreading. Future WEC will enable noninvasive diagnosis optimizing time, increasing patient's compliance and early diagnosis. The increased proficiency achievable with robotic-assisted endoscopy definitely will shorten the learning curve and democratize the techniques, enabling more surgeons and gastroenterologists to perform endoluminal and transluminal organ-sparing new therapies.

Once this digital technology becomes more widespread, the barriers which limited the spread of NOTES™ some years ago may be overcome. A new hybrid of endoscopy and surgery will become a reality. Miniaturized fully robotic platforms will further enhance the capabilities, performance, and safety of NOTES™ procedures. Future robotic machines, fitted with image navigation guidance, suturing platforms, AI systems, and EUS assistance are expected to become a surgeon's extended hands, eyes, and even mind in delivering the best patient-targeted therapy.

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Index

M. Kroh et al. (eds.), *The SAGES Manual Operating Through the Endoscope*, https://doi.org/10.1007/978-3-031-21044-0

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