Innovative Endoscopic and Surgical Technology in the GI Tract

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Preface

In the past decades we have witnessed a revolutionary change in medical and surgical treatment concepts due to an exciting development of innovative technology in endoscopy and surgery. Fortunately, this process is continuing, and new technology is emerging every year. Minimal invasive surgery has not only changed surgical techniques and procedures, but the entire surgical management of patients and hospitals. Interventional endoscopy has done the same thing. Thus, innovative endoscopic and surgical techniques are both being nourished by new technology and may benefit from unconventional new ideas, which need to be explored and driven to thorough evaluations. Today, in a few institutions around the world, surgeons, gastroenterologists, engineers, and computer scientists work together and exchange their ideas to find synergisms and areas in which collaboration may be fruitful for future concepts to further minimize the trauma of therapy for the benefit of patients.

We, at the Center for the Future of Surgery at the University of California San Diego, have focused on these subjects in our institution, as we are excited about new endoscopic and surgical techniques and keen to explore and test new innovative technologies. We are happy to gather authors and scientists from around the world with their specific focus and specialties to create this manual in order to provide an overview and insight in some of the innovative ideas around gastro-intestinal surgery and endoscopy to stimulate further activities.

We want to thank the authors and co-authors for their excellent contributions to make this manual possible. We also want to express our gratitude to all involved at Springer publishing company for their help and professionalism through the publishing process.

La Jolla, CA, USA — Santiago Horgan
La Jolla, CA, USA — Karl-Hermann Fuchs

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Overview of Current Robotic Technology

1

Alice Race and Santiago Horgan

1.1 Introduction

Ubiquitous in modern life and work, robotic technology is used across the globe in industries including manufacturing, service, and healthcare. Technological advancements have enabled great potential for innovation within healthcare. The field of surgery has moved toward less invasive procedures, with more operations completed via laparoscopy or robotic surgery. While laparoscopic surgery has allowed for smaller incisions and shorter hospital stays, there are many limitations that preclude universal uptake and utility. Robotic surgery platforms attempt to minimize such limitations by improving visualization, enabling advanced fine motor control, and reducing technique-specific learning barriers.

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1.2 History

The foundation of modern robotics began in Ancient Greece in the third century BC. The earliest form of the self-operating machine or automata was created for the amusement of the wealthy by Ctesibius and Philon of Byzantium [1]. Status quo remained until the sixteenth and seventeenth centuries, when the Industrial Revolution expanded the use of machinery to perform labor. Following World War II, an explosion of technology led to Raymond Goertz designing the first teleoperated articulated arm to manipulate hazardous radioactive materials for the Atomic Energy Commission [2]. George Devol and Joseph Engelberger later developed the first programmable manufacturing robot, the "Unimate." Unimate saw commercial implementation by General Motors in 1962, advancing ability and improving safety of heated die-casting [3]. In the nearly six decades that have followed, an unprecedented pace of innovation and globalization has spurred ever-expanding utilization of robotic technology across numerous industries.

Devol and Engelberger's company, Unimation, developed the first "robot surgeon" that was used on a human patient. The programmable universal machine for assembly (PUMA) 200 was used in 1985 for neurosurgical biopsies (Fig. 1.1). This concept was used in urological surgery by the surgeon-assistant robot for prostatectomy (SARP) and the prostate robot (PROBOT) [4].

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Fig. 1.1 The programmable universal machine for assembly (PUMA) 200 [6]

Fig. 1.2 AESOP®, a voice-controlled robotic endoscopic positioning system, provides an absolutely steady picture during minimally invasive surgeries [11]

Those robots required fixed anatomic landmarks and could not be used in dynamic subjects [5].

1.2.1 Robotic Telesurgery

Robotic telesurgery was initially conceptualized in the early 1970s, aiming to provide surgical care for astronauts while in space. Several medical events at National Aeronautics and Space Administration (NASA) between 1981 and 1998 reinforced the need for a novel technology capable of such a feat. NASA investigators developed the head-mounted display (HMD), providing a stereotactic display with 3D vision. Giving astronauts access to real-time data, the HMD combined with an instrument telemanipulation operating system provided the tools to theoretically enable telesurgery [7]. Telerobotic space surgery was ultimately not feasible; however, the Pentagon's Defense Advanced Research Projects Agency (DARPA) co-opted the concept to investigate remote battlefield surgery. DARPA investigators developed a functional prototype mounted to an armored vehicle that could take the surgeon virtually to the field [8].

1.2.2 AESOP

Born via DARPA efforts, Computer Motion, Inc. (acquired in 2003 by Intuitive Surgical) developed a robotic arm for endoscopic camera control, the Automated Endoscopic System for Optimal Positioning (AESOP) [9]. AESOP (Fig. 1.2) was intended as a voice-activated system for endoscope control to replace surgical assistants and minimize tremor, fatigue, and human error. In 1993, a laparoscopic cholecystectomy was performed using AESOP and it gained FDA approval a month later [1]. Necessitating affixation to the operating table, AESOP was impractically immobile. However, the platform laid the foundation for integrating robotic devices into surgical practice [10].

1.2.3 ZEUS

Computer Motion, Inc., sought additional minimally invasive solutions with a robot capable of movement translation in response to commands of a surgeon. In 1995, three modified AESOP arms were combined to form the ZEUS platform. Collectively, ZEUS provided a steady camera platform, 3D video, improved ergonomics, and six degree-of-freedom manipulation [12]. ZEUS was used in 1998 in the University Hospital Munich-Grosshadern in Germany for the world's first robot-assisted endoscopic coronary artery bypass procedure [13]. The world's first transatlantic telerobotic surgical procedure was the laparoscopic cholecystectomy performed in Strasburg by Jacques Masescaux in New York [14]. ZEUS has since been used in digestive, urologic, gynecologic, and cardiac surgeries [15]. In 1995, Computer Motion, Inc., merged with Intuitive Surgical, Inc., and future generations of robotic platforms were born [16].

1.3 Current Robotic Platforms

In recent decades, operating room robotics has made rapid progress with advancements benefiting patients and surgeons alike. Patients experience decreased length of stay, smaller incisions, and less pain. Surgeons note improved ergonomics (sitting while operating), visualization (3D glasses with magnified views), and intra-operative dexterity/control (joysticks with wristed articulation and tremor reduction). Collectively, technological improvements have enabled increased operative precision and development of novel surgical approaches. See Table 1.1 for a comprehensive list of current robotic platforms. A common limitation of current platforms is a lack of haptic feedback. New platforms in development use torque and force sensor-enable instrumentation to relay tactile information from tissue to the hands of the surgeon.

1.3.1 Da Vinci©

In 1995, Intuitive Surgical, with licensed technology from NASA, Stanford Research International (SRI), International Business Machines (IBM), and Massachusetts Institute of Technology (MIT), developed a platform with the goal to provide better 3D visualization using a novel binocular endoscope, articulating instruments, and improved ergonomics [9]. By 1997, "Lenny" became the first animal trial prototype, and later that year "Mona" was created for the first human trials involving vascular and gynecological procedures at Sain-Blasius Hospital in Belgium [8]. The first market-ready version of the robot named after the great inventor, da Vinci, began clinical testing in 1999. The 200-patient randomized clinical trial demonstrated the safety and efficacy of the platform for cholecystectomy and Nissen fundoplication [17]. This led to United States Food and Drug Administration (FDA) approval by July 2000 [18]. This system used upgraded control and improved ergonomics in the field of general laparoscopic surgeries including gallbladder, gastroesophageal reflux, and gynecologic surgeries.

The goal of the da Vinci platform included three specifications: (1) a software system with intuitive control of a suite of seven degree-of-freedom laparoscopic instruments; (2) a stereoscopic vision system displayed in an immersive format with stereo separation and resolution necessary for complex abdominal surgery and microvascular procedures in the chest; and (3) a system architecture composed of redundant sensors providing maximum safety by verifying the position of the instrument every 750 microseconds to eliminate erroneous movements [19].

The fourth-generation da Vinci surgical systems (Fig. 1.3) are currently utilized in a variety of minimally invasive surgical procedures. The components of the platform include the surgeon's console, equipped with two cameras combining to provide a 10x 3D-HD view of the surgical field. The master console also includes several adjustable components including finger-loop telemanipulators, variable intraocular distance, and cable-driven joints allowing instrument motion. The four-boomed mounted robotic arms are each capable of three degrees of freedom (DOF) while the EndoWrist instrument provides an additional seven DOF [21].

Table 1.1 Overview of current robotic surgical platforms

Company	System	Applicability	FDA status	Additional features
Intuitive Surgical Inc.	da Vinci surgical system	General, urologic, gynecologic, abdominal, thoracoscopic, cardiac surgeries	Approved	Tremor filtration, 10x 3D-HD vision, 4 robot arms with 3 DOF + 7 per wrist
TransEnterix	Senhance® surgical system	Laparoscopic gynecological surgery, colorectal surgery, cholecystectomy, and inguinal hernia repair	Approved	Haptic feedback, standard reusable laparoscopic instruments, eye-tracking camera with 3D-HD
Medtronic	Hugo	Robot-assisted, laparoscopic and open bariatric, thoracic, colorectal, urologic, and general surgery	Pending	Modular independent robotic arms adaptable to open, laparoscopic, and robotic surgeries
Cambridge Medical Robotics	Versius® robotic system	Upper GI, colorectal, gynecology, and urology	Pending, CE marked 2019	Modular independent arms with 4-axis wrists, 5-mm articulating instruments with 7 DOF, haptic feedback, 3D-HD vision
Virtual Incision	Miniaturized in vivo robotic assistant (MIRA)	Single-port colorectal surgery	Pending	Single-incision portable platform, articulating camera
DLR (German Aerospace Center)	MiroSurge	General abdomen and thorax	Commercially available in Germany	Variable table-mounted arms with 3 DOF, haptic feedback, impedance-controlled mode
Titan Medical Inc.	SPORT™ surgical system	Single-port abdominal surgery	Pending	Console-based, single-armed 25 mm platform with multiple articulating arms with disposable tips, 3D-HD vision
Intuitive Surgical Inc. (formerly NeoGuide systems Inc.)	NeoGuide endoscopy system	Colonoscopy	Approved	Computer-aided segmental articulating colonoscope with 3D mapping for decreased colonic wall force
Ambu	Invendoscopy E210 system	Colonoscopy	Approved	Single-use endoscope with self-propulsion controlled by joystick, HD vision with 180 degree rotation, flexible 3 mm instruments
Medrobotics Corp.	Flex® robotic system	Single-port transoral, colorectal, and gynecologic surgeries	Approved	Single-port steerable telescoping inner and outer mechanism controlled by joystick, 3D-HD vision with 180 degree rotation, 2 working channels for flexible 3 mm instruments
iCUBE control, vision and Robotics laboratory	STRAS	Single-port endoscopic surgery	Pending	Single-port modular flexible endoscope with 3 working channels and steerable distal end

The modern da Vinci system overcomes some limitations of laparoscopic surgery through improved visualization, tremor filtration, motion scaling to 5:1, and a comfortable user interface. Its array of tangible benefits led the da Vinci to become the most widely adopted robotic surgical

Fig. 1.3 The three basic components of the da Vinci telerobotic system – the surgeon's console, video cart, and four-armed patient cart [20]

Fig. 1.4 The da Vinci SP surgical system [20]

system with over 5582 systems globally and over 7.2 million procedures performed as of 2019. The da Vinci has been increasingly utilized for a variety of procedures including colectomies, cholecystectomies, ventral, incisional and inguinal hernia repairs, and bariatric surgeries. In contrast to urologic surgeons, most general surgeons performing robotic surgery were already experienced in laparoscopy, whereas in urology, many of the procedures were converted directly from open to robotic without a laparoscopic intermediary [22]. Studies demonstrate that da Vinci operations are less expensive than open surgeries, which can be attributed to decreased length of stay. While it appears based on published data that outcomes between laparoscopic and robotic surgeries are comparable, the costs of the robot, lack of haptic feedback, the bulky nature of the system, and the need for trained personnel present itself as limitations over traditional laparoscopy [23].

As the use of minimally invasive procedures has become more widespread, Intuitive, Inc., has developed specialized platforms. In 2014, the FDA cleared the company for a fourth-generation single-port surgical system called the da Vinci SP (Fig. 1.4). This system was developed for deep, narrow access surgery. Use of a single 2.5-cm cannula with three fully wristed, elbowed instruments and a wristed endoscope enables reaching depths up to 24 cm with 360° rotation around the boom [24, 25]. The da Vinci SP is currently FDA approved for urologic, lateral oropharyngectomy, and tongue base resection procedures [26].

In the past year, Intuitive gained FDA clearance for its first internally developed robotic generator called E-100 for the da Vinci Xi and X platforms. It is accompanied by the SynchroSeal, which uses advanced bipolar energy with wristed articulation, one pass seal, and cut with rapid cooling to facilitate tissue and vessel transection [28]. The da Vinci system also incorporates advanced imaging technology in addition to the magnified 3D-HD vision and depth perception. An anatomical visualization system that creates a 3D model from a preloaded CT scan (named "Iris") is available intraoperatively on the surgeon's console using TilePro. Further, the da Vinci endoscope is capable of Firefly fluorescence near-infrared imaging which can be used intraoperatively to assess vessels, bile ducts, and relative tissue perfusion [29, 30].

In 2019, Intuitive was also granted FDA clearance for Ion™, a robotic endoluminal lung biopsy system for safer bronchoscopic lung nodule sampling (Fig. 1.5). The Ion™ uses a 3.5-mm catheter with a 2-mm working channel that is passed through the airway to reach nodules in any airway segment. The working channel accommodates the flexible biopsy needle, as well as other biopsy tools such as brushes and forceps. This system has the ability to integrate with existing imaging technology such as fluoroscopy, radial-endobronchial ultrasound, and cone-beam CT [31]. The system is currently undergoing a multicenter, 300-patient trial to prospectively evaluate its use [32].

Fig. 1.5 The da Vinci Ion system for robotic lung biopsy [27]

1.3.2 Senhance®

Senhance® (TransEnterix) was initially introduced in a dry lab in 2012 as a novel value-driven robot-assisted digital laparoscopy system. The system gained CE trademark in Europe and FDA approval in October 2017 for general surgery, gynecology, urology, and thoracic surgeries. The Senhance system (Fig. 1.6) is an enhanced digitized interface between the surgeon and the patient and functions as an intermediate between traditional laparoscopy and robotic surgery. Sitting at the ergonomic open-platform console, the surgeon controls each of the individually mounted arms with laparoscopic style handles with 7 DOF. The system uniquely incorporates zoom-enabled, eye-tracking visualization which centers the image where the surgeon is looking. The enhanced 1:1 haptic feedback system was designed to minimize tissue trauma and provides direct feedback to surgeons' hands through the distal end of the instruments. The reusable laparoscopic instruments are attached via magnets, easily replaceable, and are compatible with 3-mm microinstruments. The robotic component of Senhance allows for precision, tremor-free instrument control with the ability to visualize anatomically tight spaces using 3D cameras with polarizing glasses [34].

Senhance has been successfully used in a variety of surgeries including gynecological, colorectal, foregut, bariatric, and inguinal hernia repairs, but it has yet to find commercial success within the United States [35–37]. The surgical system has been adopted in 15 countries globally with

Fig. 1.6 Senhance® (TransEnterix, Morrisville, NC) surgical system with digital laparoscopy [33]

the Japanese government reimbursing healthcare providers for Senhance procedures [38]. The majority of published literature has been European likely due to the articulating instrumentation and four manipulator arm configurations' exclusive availability in European and Japanese markets. By the end of 2020, Senhance aims to launch the 5-mm articulating instruments as well as obtain general surgery and bariatric indications within the United States [39].

Senhance is awaiting FDA approval for a personal digital assistant for surgeons during abdominal procedures. Intelligent Surgical Unit is marketed as an add-on which will aim to augment the surgeon's control of the camera by a combination of operator commands, eye-tracking, and recognition of certain objects and locations in the field of view. The software also includes scene cognition and surgical image analytics [40]. Overall, Senhance aims to overcome the limitations of traditional laparoscopy with a cost-effective solution enabling hospitals to leverage existing laparoscopic technology/instruments with expanded utility in a robotic system.

1.3.3 Hugo

Medtronic launched a robot-assisted spinal surgical platform in the United States featuring computerized surgical planning, 3D assessment of spinal anatomy, robotic guidance, and live navigation feedback to perform precise spine surgeries called the Mazor X Stealth. Medtronic acquired Mazor Robotic's Mazor X platform in 2018 and combined it with Medtronic's Stealth software to use real-time intraoperative imaging feedback [42]. The system won FDA clearance in November 2018 and is indicated for use in precise positioning of surgical instruments or spinal implants in open, minimally invasive, or percutaneous procedures [43, 44].

The company unveiled a soft-tissue robot-assisted surgical platform in September 2019 called the Hugo (Fig. 1.7), which is marketed as a more flexible, cost-effective system. The Hugo system features an open surgeon console to facilitate communication and independent mobile carts for the robotic arms and surgical instruments. The system's arms and other components are modular, allowing them to be split for different procedures and flexibility in placement. The tower, visualization system, generator, and endoscope can support minimally invasive and open applications. The FT10 generator in the robotic system is the same type which powers laparoscopic and open surgery devices. Hugo further benefits from the large intellectual property and expertise of the existing Medtronic surgical portfolio, providing familiarity for the surgeon [45]. Each component can be individually upgraded without a need to purchase an entire system.

Fig. 1.7 Medtronic's Hugo robot-assisted surgery platform [41]

Medtronic aims for both European CE marking and FDA filing in 2021 [46, 47].

1.3.4 Versius® Surgical System

The Versius Surgical Robotic System from Cambridge Medical Robotics (CMR) aims to provide an accessible, versatile experience with a modular system that is portable and cost-effective. The platform (Fig. 1.8) utilizes individually cart-mounted arms with four-axis wrists, allowing for 270 degrees of rotation of the distal arm [49]. The fully-articulating 5-mm instruments with seven DOF further enable adaptable port placement control from the open console, where the surgeon may choose to sit or stand. Additional features include 3D-HD glasses for improved visualization and advanced joystick controllers with haptic feedback from the instrument tips. The system aims to be more intuitive to train with surgeons learning to complete procedures and suturing in only half an hour [50, 51].

Versius gained European CE mark in 2019 after completing cadaveric and human clinical trials. The first 30 laparoscopic gynecologic and upper GI surgeries were successfully completed at Mangeshkar Hospital & Research Center in India with no adverse events and no 30-day complications [52]. The Versius platform has been used in over 600 clinical cases in gynecology, upper GI, urology, and colorectal surgeries. The system has now been installed in the United Kingdom, India, Italy, and France and is looking to expand to Asia and the Middle East. Versius has completed the US-based training programs and is currently awaiting FDA approval [53].

1.3.5 Miniaturized in Vivo Robotic Assistant (MIRA)

Virtual Incision and Center for Advanced Surgical Technology (CAST) developed the MIRA, a miniature robotic surgical platform for use in general surgery. The MIRA (Fig. 1.9) is an investigational robot developed to be portable and lightweight, weighing only two pounds, and able to be taken into any hospital without the need for a "mainframe." The miniature single incision platform has a removable, articulated endoscopic camera, a multi-use robotic base link, and interchangeable surgical tools at its tip [22, 55, 56].

Several feasibility studies with an early prototype, the miniature in vivo robot (MIVR), have been successful, including a robot-assisted porcine single-incision colectomy [57]. In 2016, the first human feasibility and safety trial demonstrated MIVR safety for right and left colectomies. The ability of the robot to perform dissection, ligation, and suturing is increasingly well documented in the surgical literature [58, 59]. Virtual Incision has filed for Investigational Device Exemption (IDE) with the FDA, with initial aims to complete confirmatory clinical studies in colorectal surgery [60].

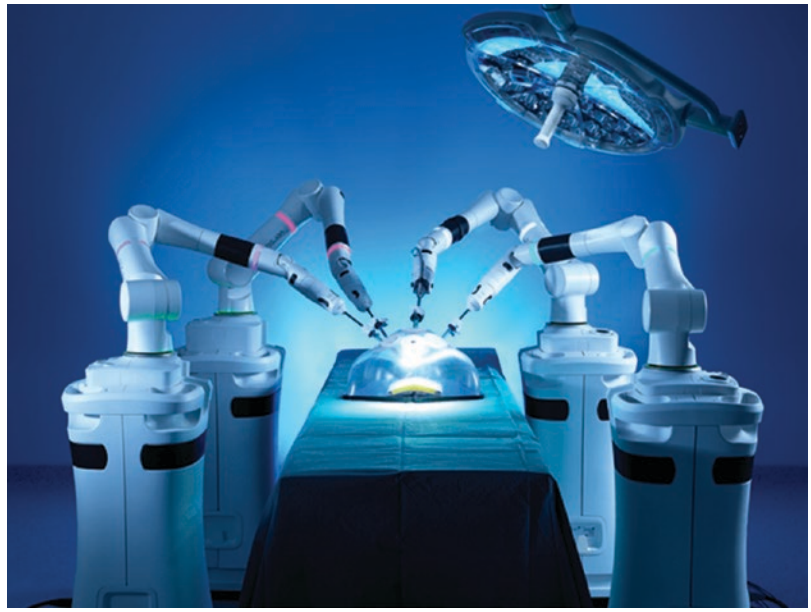

Fig. 1.8 CMR's Versius Surgical System with modular independent arms [48]

1.3.6 MiroSurge

MiroSurge (Fig. 1.10) (DLR, German Aerospace Center) is a research platform for teleoperation in minimally invasive robotic surgery. The system consists of a surgeon console, which includes a 3D display with two haptic input devices which control the versatile, lightweight robotic arms (MIRO). Due to the kinematic redundancy achieved with seven fully torque-controlled joints, each MIRO arm is amenable to a flexible operation room setup. The joint units' ability to integrate both position and torque sensors allow for precise manipulation [62]. The MICA instrument attached to the MIRO arm comprises a task-independent drive unit and a task-specific tool. Variable exchangeable tools targeted at differing surgical applications can be used with the MICA drive unit. An additional MIRO arm carries the Wolf stereo endoscope [63]. The MiroSurge system enhances precision with its ability to prevent instrument collision and permit rapid instrument changes. The ability of the MiroSurge system to implement impedance control allows for sensitive interaction dynamics [51, 64]. The license for the MIRO medical robot developed by DLR was sold to Medtronic. The world's largest medical technology company is developing the technologies of the DLR system further for a medical robot that will soon be available in the operating room [65].

1.3.7 SPORT™ Surgical System

Titan Medical, Inc., developed the Single Port Orifice Robotic Technology (SPORT) Surgical system as a console-based platform for single-port abdominal surgery. SPORT is composed of an ergonomic open workstation (Fig. 1.11) that allows the surgeon to interact via hand controllers, foot pedals, and a high-definition touch-screen with 3D-HD endoscopic view. It was designed to provide a small operating room footprint and to be a cost-efficient solution that would allow access in underserved market segments, such as ambulatory surgery centers. The design uses a collapsible system inserted through a 25-mm incision with multi-articulating instruments bearing disposable tips [67]. Mobility and efficiency are enhanced via the single-arm mobile patient cart due to the single-port nature of the device [68]. Preclinical studies demonstrated feasibility in porcine models undergoing cholecystectomy, splenectomy, Nissen fundoplication, and hepatic pedicle dissection [69]. After suspending development due to funding in 2019, the following year, Titan Medical, Inc., announced develop-

Fig. 1.9 Virtual Incision Corporation's MIRA ("miniaturized in vivo robotic assistant") [54]

ment and licensing agreements with Medtronic. Following preclinical trials, in July 2020, the company completed design enhancements of its instruments and is working toward submission to the FDA and European regulatory bodies [70].

1.4 Robotic Endoscopic Systems

1.4.1 NeoGuide Endoscopy

The NeoGuide endoscopy system is a computer-aided colonoscope (Fig. 1.12) that was developed to prevent looping during the procedure to reduce patient discomfort. The colonoscope works fundamentally differently to the conventional endoscopic systems by utilizing real-time 3D computerized mapping to travel along the natural curves of the colon. The colonoscope uses 16 equally-sized electromechanically-controlled segments, each manipulated by an actuation controller to maneuver through the colon. This results in decreased force applied to the colonic walls, decreased looping, and the potential to eliminate procedural sedation. The system also includes a programmable overtube that prevents reformation of colonic loops once they are reduced. As the scope is advanced, the articulating segments replicate the shape of the distal tip which can be guided in a combination of directions. The two modes of the system can be used in either passive mode, which allows for therapies and biopsies, or the active mode, where the scope relays information from the user's commands to the actuation controller [22, 71]. In an in vitro evaluation of colonic wall force, the colonoscope was found to have significantly decreased levels compared to the traditional colonoscope. The same authors completed a feasibility and efficacy trial which demonstrated successful endoscopic reduction of loops and no adverse effects in all 11 patients who underwent a colonoscopy [72]. The NeoGuide endoscopy system received FDA 510(k) clearance in 2006 and the company was acquired by Intuitive Surgical in 2009 [73].

1.4.2 Invendoscopy E210 System

The Invendoscopy E210 system is a colonoscope that aims to address concerns of contamination while reducing pain and discomfort for patients. The single-use, flexible colonoscope is capable of self-propelling through the colon while avoiding excessive stretching of the bowel. The unit is composed of a detachable and reusable handheld controller (Fig. 1.13) with a lightweight joystick that allows for single-handed 180° tip deflection, insufflation, suction and image capture. This controller is attached to the single-use colonoscope (Invendoscope SC210) with an insertion length of 170 cm and a 35-mm bending radius that allows for retroflexion and visualization of the colon. The standard flexible instruments are compatible with the 3.2-mm working channel. The vision system is equipped with three white-light LEDs

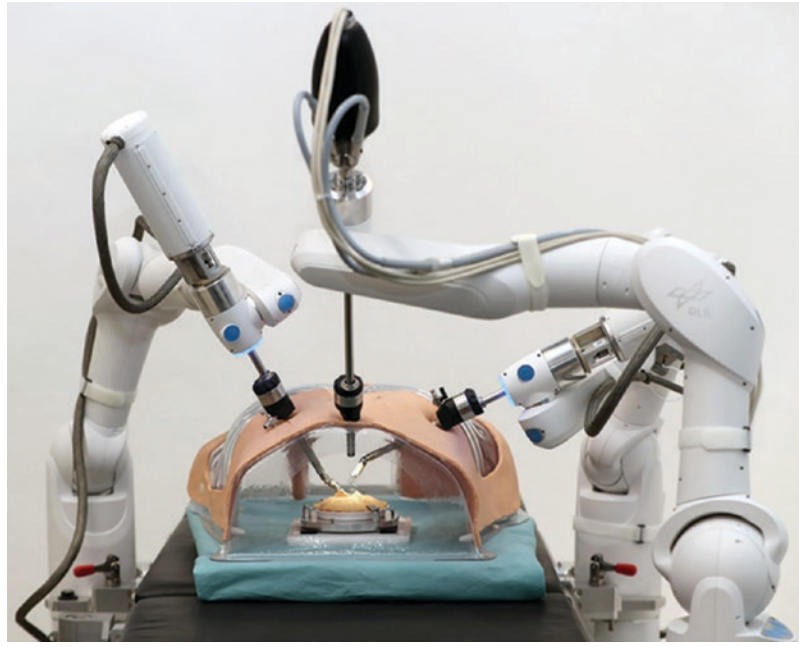

Fig. 1.10 MiroSurge telemanipulated minimally invasive robotic surgery (MIRS) system [61]

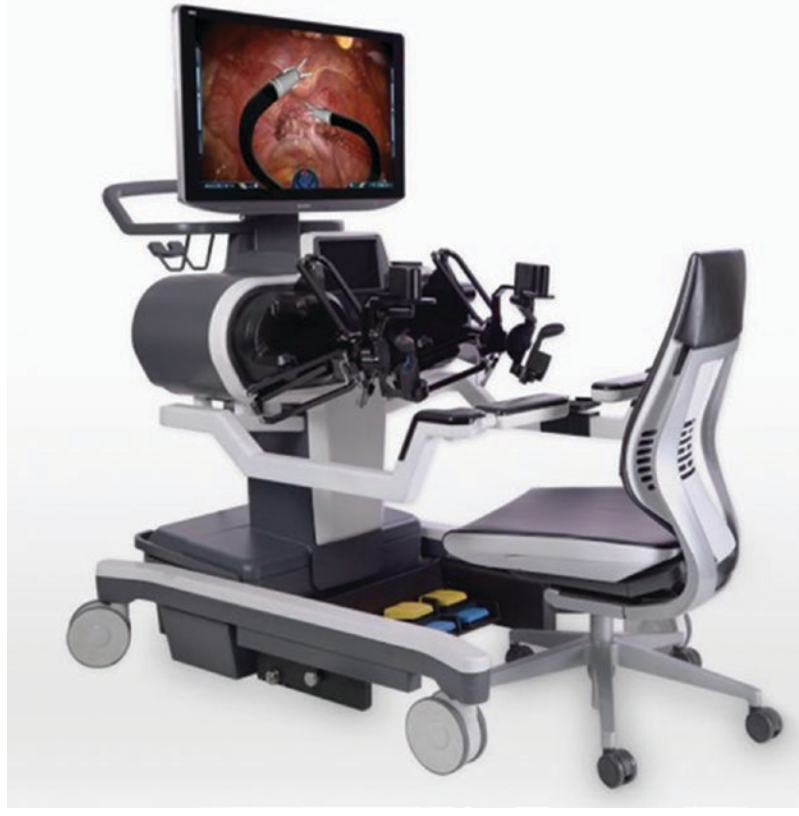

Fig. 1.11 The workstation of the SPORT robot-assisted surgery system [66]

Fig. 1.12 NeoGuide Endoscopy System for computer-aided colonoscopy [22]

Fig. 1.13 The Invendoscope handheld propulsion unit with single-use insertion endoscope [74]

and an advanced complementary metal oxide semiconductor imaging chip. The outermost layer of the colonoscope is composed of a double-layer, inverted sleeve which provides propulsion [75].

The Invendoscopy E210 system aims to improve the safety of colonoscopies by reducing collateral tissue damage in difficult areas, thereby eliminating the need for sedation. A 2011 feasibility study in 61 healthy volunteers demonstrated a cecal intubation rate of 98.4% with 95.1% sedation-free completion. A limitation noted in study was the increased time for the procedure with an average of 16.4 minutes to cecal intubation and a similar withdrawal time [76]. Invendoscope E210 acquired CE marking in 2016 and gained FDA approval in 2018. The company was recently

Fig. 1.14 The Flex robotic system with patient cart and single-port control [78]

acquired by Ambu in October 2017 [77]. Due to the enhanced visualization, improved safety features, and ease of use, the Invendoscopy system could provide a foundation for robot-assisted natural orifice applications in the future.

1.4.3 Flex® Robotic System

The Flex® robotic system from Medrobotics Corp. is a single-port flexible, steerable platform (Fig. 1.14) created for robot-assisted surgery using an integrated 3D-HD vision system. The dual-lumen endoscope's design of adjacent segments of cables allow for variable states of semi-rigidity or flexibility depending on the required function. The camera, with six light-emitting diodes, is able to articulate nearly 180° with the camera rotating horizontally, vertically, or on its own axis. The single-port endoscope is controlled with a joystick which steers the robotic outer mechanism, through which the inner mechanism follows. The endoscope has two flexible guide tubes – the External Accessory Channels (EAC) which allow for the utilization of compatible flexible 3-mm instruments such as scissors, needle driver, grasper, and dissector [79].

After FDA approval for transoral use in 2015, Flex has been safely and successfully used globally in surgeries of the oropharynx, hypopharynx, and larynx and was demonstrated to overcome the disadvantages of standard rigid instruments [80, 81]. Based on those promising outcomes, it gained FDA approval for colorectal and gynecologic applications in 2018 and has been used in endoscopic transanal resection of colorectal lesions [82].

1.4.4 STRAS

STRAS (iCUBE, Strasbourg, France) is a modular flexible endoscopic system developed for single-port intraluminal surgery. The system consists of a main 55-cm endoscope which acts as an overtube and provides three working channels for insertion of 3–4 mm surgical instruments. STRAS has a flexible passive shaft with a steerable distal end which is controlled using tendons. The three modules (Fig. 1.15) consist of the endoscope (drives four directions of scope tip deflection), instrument modules (enable two-way deflection), and translation rotation modules (instrument articulation). The modules, held in place by table-mounted positioning arms, collectively allow for 10 DOF. The telemanipulated open master console controls the axes of motion via a joystick. The endoscope is also capable of the standard features of scopes, including an

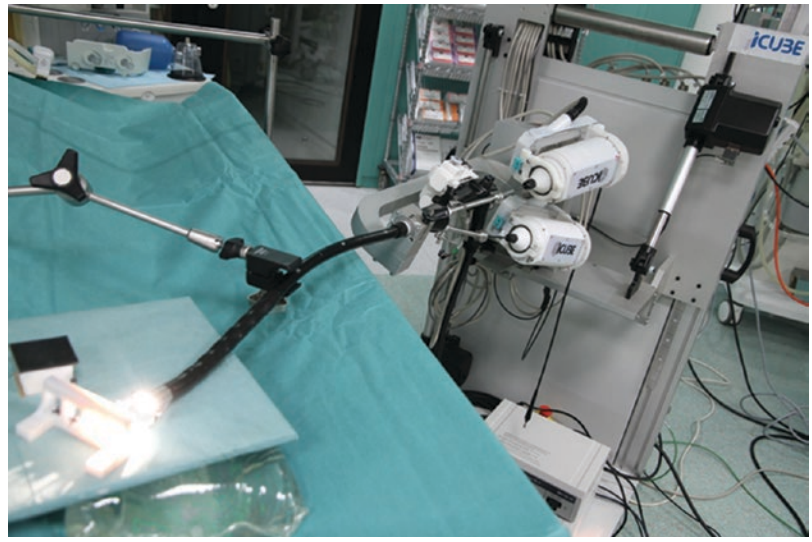

Fig. 1.15 STRAS flexible endoscope [83]

internal channel for fluids and lighting. STRAS seeks to overcome the limitations of traditional scopes with its improved stability, triangulation, working channels, and flexibility [84].

While STRAS remains in pre-clinical development, the platform has been successfully used for endoscopic submucosal dissection (ESD) in porcine-modeled large lesion removals [84, 85]. The system has also been successfully tested for appendectomy, cholecystectomy, and dissection of the gastro-esophageal junction. System benefits include its ease of setup, small size, and practicality. However, significant limitations arise in the maneuverability of the instruments secondary to the lack of control in the cable-driven systems and lack of compatible flexible instruments [86]. As there are no current commercial platforms which allow completely robotic intraluminal surgery, STRAS aims to fill this void.

1.5 Conclusion

Drawing upon historical lessons from the evolution of robotic automation, the integration of technology and focus on patient outcomes have led toward an exciting and fluid landscape in surgical robotics. Current advances in robotic surgical technology have been driven by the desire for less invasive interventions while maintaining greater visualization and control. Rapid advances in technology have enabled integration of modern robotics in everyday medicine to the benefit of both patients and physicians. A limited number of robotic platforms are currently utilized in practice, but emerging platforms seek to overcome the limitations of traditional laparoscopy and expand the utility of robotic surgery platforms. In parallel, new systems show promise for improved safety, efficiency, and usability both over traditional laparoscopy and current robotic platforms. Ongoing advancements and technological developments will push modern-day platforms toward an era of single-port and even incisionless robotic surgery.

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2 Challenges in Robotic and Minimally Invasive Pancreatic Surgery in the Year 2020

Florian Gebauer, Christiane J. Bruns, and Hans Friedrich Fuchs

2.1 Background

Robotic pancreatic surgery (RPS) is increasing in recent years [1]. No randomized controlled trial has demonstrated superiority when comparing robotic to laparoscopic pancreatic surgery (LPS).

Nevertheless, robotic technology may have an edge when performing complex, gastrointestinal, minimally invasive reconstructive tasks in narrow anatomical regions, such as minimally invasive esophagectomy, pancreatoduodenectomy, and deep rectal cancer surgery. Other advantages of RPS include extended triangulation possibilities and a 3D view of the operative field [1].

This chapter highlights the status of laparoscopic or robotic surgery for pancreatic cancer today. The specific data available for pancreatoduodenectomy for pancreatic head carcinoma and for distal pancreatectomy or pancreatic left resection for pancreatic carcinoma located on the left side of the mesenteric-portal axis will be taken into account. The indication for RPS should be identical to LPS. As RPS and LPS are a rather evolving procedures, the current experience of experts should be taken into account and modular approaches as well as well-selected cases should be chosen [2].

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2.2 Review of the Current Literature

2.2.1 Distal Pancreatic Resections

The clinical outcome quality of minimally invasive distal pancreatectomy was recently evaluated in a multicenter, randomized controlled clinical trial in the Netherlands [3]. This patient-blinded study, which was conducted in 14 national centers from 2015 to 2017, compared the time to functional recovery of patients who received either minimally invasive (n = 51) or open (n = 56) distal pancreatectomy (LEOPARD; NTR5689) without vascular involvement in a tumor confined to the left side of the pancreas. The primary endpoint, time to functional recovery, was significantly shorter with 4 days for minimally invasive versus 6 days for open pancreatectomy. The conversion rate was 8%. The overall complication rated as Clavien-Dindo

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≥ III was not significantly different, but there was less gastric emptying disorder and a better quality of life without increasing costs for minimally invasive distal pancreatectomy. Surgical quality control was performed prior to patient enrollment in the study, since only surgeons who had undergone >50 complex minimally invasive GI procedures, >20 distal pancreatectomy, and >5 minimally invasive distal pancreatectomies were accepted as surgeons within the clinical trial [4].

The results of the LEOPARD study (Dutch Pancreatic Cancer Group data, 17 centers; 2005–2016) were compared with the database of the American College of Surgeons' National Quality Improvement Program (ACS-NSQIP) (88 centers; 2014–2016). In this international cohort study, severe 30-day morbidity including mortality was evaluated according to the surgical procedure – either minimally invasive or open distal pancreatectomy. Of the 2921 ACS-NSQIP patients, 1562 (53%) received a minimally invasive distal pancreatectomy with 18% conversion rate and 1359 (47%) received an open distal pancreatectomy. The minimally invasive surgical technique was associated as an independent factor with reduced severe 30-day morbidity including mortality for distal pancreatectomy. [5]

In a retrospective analysis of the prospective database of the American College of Surgeons-National Surgical Quality Improvement Program, morbidity and mortality following minimally invasive (n = 166; 33.1%) versus open (n = 335; 66.9%) distal pancreatectomy in 501 patients with pancreatic ductal adenocarcinoma (PDAC) and distal pancreatectomy were investigated with preoperatively comparable comorbidity and pathological staging. Overall morbidity, transfusion administration, pneumonia rate, surgical wound infections, sepsis, and hospitalization time were lower with minimally invasive distal pancreatectomy. Mortality, pancreatic fistulas, and gastric emptying disorders were comparable. Accordingly, the short-term postoperative outcome from this large multi-institutional database for minimally invasive distal pancreatectomy in pancreatic cancer appears to be improved [6].

A further study, in the sense of a population-based retrospective cohort study, investigated perioperative factors with regard to differences between minimally invasive and open surgery. A total of 8575 open surgery procedures were compared to 382 minimally invasive distal pancreatectomies. This analysis revealed a low incidence of general perioperative complications (39.0% vs. 30.1%, $P < 0.001$) and less frequent postoperative bleeding events (20.6% vs. 13.6%, $P < 0.001$). Hospital length of stay was shorter in the minimally invasive group, so the authors conclude that minimally invasive distal pancreatectomy is associated with a more favorable complication profile and therefore minimally invasive distal pancreatectomy can be used as an alternative to open surgery [7].

In a retrospective, monocentric analysis of a high-volume center (n = 422 distal pancreatectomies from 2005 to 2014), the oncological outcome in 79 comparable patients with PDAC after laparoscopic (n = 33) or open (n = 46) distal pancreatectomy was investigated. Intraoperative and pathological variables were comparable, such as surgery time, duct size, glandular texture, tumor size, type of pancreatic closure, number of lymph nodes removed, tumor stage, and R0 status at the removal site. The 1-, 3- and 5-year survival and local recurrence and distant metastasis rates were comparable in both groups. Laparoscopic distal pancreatectomy was judged by the authors to be comparable to the open surgical technique in terms of oncological criteria [8].

Furthermore, the question arises to what extent the robot-assisted surgical technique offers advantages in the quality of results compared to laparoscopic distal pancreatectomy. Huang B. et al. have compared robot-assisted and laparoscopic distal pancreatectomy in adult patients with malignant, borderline malignant, and also benign disease. Primary endpoints were conversions to open surgery, transfusion rate, spleen preservation, surgery time, complications (pancreatic fistula), and length of hospital stay. A total of nine studies with a total population of 1167 patients were evaluated, including 929 patients undergoing laparoscopic and 238 patients under-

going robotic distal pancreatic left resection. Overall, there was no significant difference between laparoscopic and robotic pancreatic left pancreatic resection for any of these endpoints. However, despite the small number of robotic pancreatic left resections, the authors evaluated them as safe and effective compared to laparoscopic pancreatic left resection [9].

A retrospective analysis compared the quality of results between laparoscopic and robotic distal pancreatectomy. A total of 247 procedures were identified in a database analysis at a center in the USA (135 laparoscopic, 108 robot-assisted operations). It was shown that the surgery time was shorter in the laparoscopic group, but the proportion of spleen preservation was higher in the robotic group. There were no significant differences in the incidence of clinically relevant B/C fistulas, conversion rate (4.3% and 1.8%), and oncological 2-year outcome [10].

To summarize this paragraph, perioperative complications seem to be lower in minimally invasive distal pancreatic resected patients.

2.2.2 Complications in Minimal-Invasive Pancreatic Surgery

In a recent systematic review from 2020 with meta-analysis, the perioperative outcome quality of laparoscopic versus open elective pancreaticoduodenectomy for patients with benign or malignant pancreatic diseases was compared from three randomized controlled clinical trials with a total of 224 patients. Primary endpoints were 90-day mortality, complication rated as Clavien-Dindo $\geq$ III, and length of hospital stay. Secondary endpoints were pancreatic-specific outcome parameters such as postoperative pancreatic fistula, gastric emptying disorder, biliary fistulas, blood loss, re-operation, hospitalization, oncological outcome (R0-resection, number of removed lymph nodes), and surgery time. The meta-analysis showed only a significant difference in surgery time in favor of open pancreatoduodenectomy and less blood loss with the laparoscopic surgical technique. All other primary and secondary outcome parameters were not significantly different with overall moderate to low evidence levels. Based on these results, laparoscopic pancreaticoduodenectomy currently has no advantage over open surgery. In the future, the learning curve in the respective medical technology and the increasing implementation of robotic surgery must be taken into account when evaluating the quality of perioperative outcome. [11]

A retrospective monocentric analysis examined the perioperative outcome quality as well as pathological and oncological outcome parameters in a total of 1623 minimally invasive pancreaticoduodenectomies (1458 laparoscopic, 165 robot-assisted operations). It could be shown that robot-assisted surgery is more likely to be performed at high-volume and university facilities. There was no difference between laparoscopic and robotic surgery with regard to the investigated target parameters. Only the conversion rate was lower in the robot-assisted group (17.0% vs. 27.6%, $P = 0.003$). There was no statistically significant difference in resection status (R0/R1), number of lymph nodes examined, hospitalization time, 90-day mortality, and median overall survival (laparoscopic 20.7 months vs. robot assisted 22.7 months; log-rank $P = 0.445$) [12].

In a Dutch multicenter randomized study (LEOPARD-2), the safety profile of laparoscopic pancreatic head resection in periampullary carcinomas was investigated in a prospective setting [13]. The study design was a two-stage concept so that a phase II/III design could be run in parallel. The study initially focused on the description of a detailed safety profile of periampullary carcinoma resection. Interestingly, the primary endpoint of the phase II part was the postoperative elevation of the cytokine interleukin-6. Surgical complications (POPF, hemorrhage, etc.) were only considered as secondary endpoints.

As a result, the study was presented by the Data and Safety Monitoring Board and terminated with five deaths in the group of minimally invasive surgery in the 90-day postoperative period (10%).

Regarding the primary endpoints, the study cannot provide discriminatory results, as the total number of patients enrolled is too low. The authors conclude that the number of perioperative complications was worryingly high and unexpected, especially considering that only centers and surgeons with high expertise in both open and minimally invasive pancreatic surgery were included. As a result, the program for minimally invasive pancreatic head resections has been suspended at national level in the Netherlands. The authors speculate that the required qualifications of the surgeons may not have been sufficient and that an even longer training period is necessary to perform this type of surgery with a comparable quality of outcome as is currently possible with open surgery.

With regard to the development of clinically relevant fistulas, McMillan et al. have analyzed robot-assisted pancreatic head resections in comparison to the open procedure in a propensity matched analysis. A total of 152 open procedures were compared with the same number of robot-assisted operations. It was shown that the incidence of clinically relevant pancreatic fistulas (POPF grade B/C) was lower in the robot-assisted group than in open surgery (OR, 0.4 [95%CI, 0.2–0.7]; $P = 0.002$). In all other secondary endpoints, robotic procedures and open surgery were comparable and did not show significant differences (total complication rate (73.7%vs 66.4%; $P = 0.21$), median hospital stay (8 vs 8.5 days; $P = 0.31$), 30-day recovery (22.4% vs 21.7%; $P > 0.99$), 90-day mortality (3.3% vs 1.3%; $P = 0.38$)) [14].

Identical results could be shown by a likewise monocentric retrospective database analysis of the National Cancer Database (NCDB) from the USA. There was no difference in perioperative outcome parameters in the study, only the conversion rate was higher in the laparoscopic group than in the robot-assisted group (27% vs. 10%, $P < 0.001$) [15].

To summarize this paragraph, robotic surgery seems to lower conversion rates of minimally invasive pancreatoduodenectomies without any other quality differences when compared to open or laparoscopic surgery.

2.2.3 Oncological Outcomes

A propensity score-matched analysis investigated oncological overall survival in comparison between open and laparoscopic procedures in a monocentric retrospective analysis. A total of 1947 patients were identified, 605 of whom underwent laparoscopic surgery. A balanced group formation with 563 patients was achieved. In the 3-year survival rate, there was no difference between open and laparoscopic procedures (41.6% vs. 36.0%; hazard ratio 0.93, 95% confidence interval 0.77–1.12; $P = 0.457$). The time from surgery to the start of the first adjuvant chemotherapy was identical in both groups with 50 days, as well as the number of resected lymph nodes (median 12 lymph nodes in both groups). Furthermore, there was no difference in the 30-day and 90-day mortality rates. Therefore, the authors conclude that a minimally invasive procedure is an acceptable alternative to open surgery in terms of oncological outcome [16].

A prospective randomized study compared the open versus robotic pancreatic corpus resection with the primary target criterion of hospitalization time. A total of 107 patients were randomized and 50 vs. 50 patients were evaluated in the intention-to-treat analysis. Hospital stay in the minimally invasive group was shorter (15.6 vs. 21.7 days, $P = 0.002$), surgery time was shorter, blood loss was less, and the occurrence of clinically relevant pancreatic fistulas was less frequent. The authors conclude that the robot-assisted technique is superior to open surgery in all primary and secondary endpoints [17].

In a meta-analysis of all studies published by the end of 2017, the clinical outcome quality after robotic pancreatoduodenectomy and distal pancreatectomy was examined in comparison to the respective open surgical technique. A total of 15 non-randomized, controlled studies with 3690 patients (11 studies on robot-assisted vs. open pancreatoduodenectomy, 4 studies on robot-assisted vs. open pancreatic left resection) were included in the analysis. There was no significant difference between robot-assisted vs. open pancreatic ductectomy in terms of lymph node status, postoperative complications (pancreatic

fistula, p.o. voiding disorder), re-operation rate, hospitalization time, and mortality. Robot-assisted pancreatoduodenectomy required significantly longer surgery time, while blood loss, wound infections, and R1 status at the weaning margin were significantly lower than with open surgery.

Compared to open distal pancreatectomy, the robot-assisted procedure resulted in a lower overall complication rate, less blood loss, shorter hospital stay, and also a lower number of removed lymph nodes. There was no significant difference in spleen preservation, R1 status, mortality, and especially pancreatic fistulas.

The authors evaluate robot-assisted pancreatic surgery as a safe and possible alternative to open surgery in terms of perioperative, clinical outcome quality, subject to the lack of randomized controlled trials [18].

Comparable results (12 studies; a total of 2186 patients, 705 of them with minimally invasive and 1481 pancreatoduodenectomy) provided a systematic review with meta-analysis of minimally invasive (robot-assisted or laparoscopic) pancreatoduodenectomy compared to the open surgical method [19].

In a systematic review of published papers in the period 2000–2016, total robotic pancreaticoduodenectomy is compared to open pancreaticoduodenectomy in different diseases. A total of 13 non-randomized controlled studies with 692 robotic pancreatoduodenectomies were included in this review. The incidence of complications (biliary fistula, pancreatic fistula, postoperative bleeding), reoperations as well as mortality were comparable, but especially for complications due to missing data from large series, the results were not considered representative. The number of conversions (6.5–7.8% on average) to open surgery as well as surgery time decreased over time as the number of robotic pancreaticoduodenectomies increased. Lymph node status was comparable, but the number of R1 resections was shifted in favor of robotic pancreatoduodenectomy, most likely a selection bias. The authors conclude that robotic pancreatoduodenectomy is safely feasible in high-volume centers, but no data on long-term oncological survival and cost-effectiveness of this surgical technique are available [20].

In a retrospective non-inferiority propensity scored-matched analysis, the influence of the surgical method on the R-status after pancreatic head resections was investigated. A total of 20 robot-assisted procedures were compared to 24 open surgery procedures. In the robotically operated group, the R1 rate was 55.0% compared to 41.7% in the open surgery group ($P = 0.38$), and no difference was found in the secondary endpoints (number of lymph nodes examined, number of blood transfusions, adjuvant chemotherapy, overall survival, disease-free survival). With regard to the R0/R1 rate, the robot-assisted technique does not appear to be inferior to open surgery [21].

To summarize this paragraph, the evidence of minimally invasive pancreatoduodenectomy is still limited. When performed in high-volume centers, the procedure seems to safely achieve comparable long-time oncological outcomes.

2.3 Conclusions

The indication for RPS should be identical to LPS. As RPS and LPS are still rather evolving procedures, experiences of experts should be taken into account and modular approaches as well as well-selected cases should be chosen to safely perform the procedures without quality compromises.

If an RPS or LPS of a pancreatic carcinoma is performed, it should be reported to national and international registries such as the laparoscopic pancreatic surgery register of the German Society of General and Visceral Surgery (http://www.dgav.de/studoq/weitere-register.html).

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3 Challenges in Robotic Liver Surgery

Alberto Mangano, Valentina Valle, and Pier Cristoforo Giulianotti

3.1 Introduction

Over the course of the last 20 years, **minimally invasive liver surgery (MILS)** has been gaining increasingly widespread acceptance. MILS is currently considered, by multiple lines of evidence, a valuable alternative for the more traditional open surgery [1–11]. According to numerous experiences, **laparoscopic liver resection (LLR)** is deemed to be an effective approach, for example if performed for anterior segments (S II-S IV) or in case of left lateral segmentectomy [1, 3–11]. In the literature data, there is a growing body of evidence, showing that MILR has better perioperative results when compared to laparotomic strategies: shorter hospitalization, decreased blood loss and morbidity, as well as improved cosmetic results [1, 3–13]. Notably, there is evidence that LLR provides results similar to open surgery in terms of oncological outcomes (e.g., local recurrence and resection margins *status*) [3, 8, 12–17].

MILS can avert the need for big sub-costal surgical access providing inferior incisional hernia occurrence rate, less intraperitoneal adhesions, less ascites in case of cirrhotic liver (better venous drainage), decreased postoperative pain, and pulmonary complications [1, 16].

Regardless of the numerous improved outcomes, MILS did not yet reach the apex of its popularity. MILS application in routine clinical setting has been fairly restricted mainly to major institutions. The reasons for this delay in MILS routine adoption are to be found in several obstacles posed by the laparoscopic technology itself. These limitations of laparoscopy have been manifested since its inception (i.e., in the mid-80s, when Dr. Erich Mühe carried out the first laparoscopic cholecystectomy): poor ergonomics (with faster fatigability of the team and possible decrease in performance over time), limited degrees of freedom of the instruments (hindering dexterity and operational maneuverability), and 2D unstable vision not directly controlled by the surgeon (variable vision quality dependent upon the skills of the assistant surgeon) [1]. The use of LLR has been limited also by international consensus conferences (e.g., in Morioka and previously in Louisville in 2008) [5, 18] in particular when major resections of the liver or when biliary reconstructions are needed.

Robotic liver resections (LLR), with its technological and operative advantages, have solved some of the LLR limitations.

In this chapter, the present challenges in RLR will be described, and also we will give our additional remarks on the possible future trends.

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3.2 Challenges in Robotic Liver Surgery

3.2.1 Increasing the Penetrance of Robotic Liver Resections (RLR)

The robotic platform has been conceptualized by design, developed, and evolved stemming from the inherent numerous setbacks of the laparoscopic technology [1, 19–21].

Since its pioneering beginnings, starting with the first ever robotic procedure (cholecystectomy) performed by Cadiere and Himpens in the late 1990s [22], the robotic approach has solved several of the limitations of traditional laparoscopy. The robotic platform provides superior ergonomics, three-dimensional and stable view (controlled directly by the console surgeon), tremor suppressing algorithms, instruments with seven degree of liberty, and globally enhanced dexterity. Notwithstanding these advancements, there has been some friction against the standard adoption of the robot into the clinical practice [19, 23]. Notably, the robotic penetrance has been progressively and steadily increasing, and in recent years, this trend accelerated its pace [1].

The quantitative analysis of the scientific articles published in a given timeframe provides a good insight into these trends of increased interest toward MILS applications. Considering a time window from the year 2000 to August 2020, it is manifested how there is a progressively increasing interest of the scientific community. These data can be *de visu* and numerically appreciated in Fig. 3.1 ("Laparoscopic Liver Resections Publications"), Fig. 3.2 ("MILR Surgery Publications"), and Fig. 3.3 ("RLR Publications"). Specifically, as it has been recently shown by our group, regarding robotic surgery, the number of PubMed-indexed MILR publications per year has doubled from 2014 to 2019 [1].

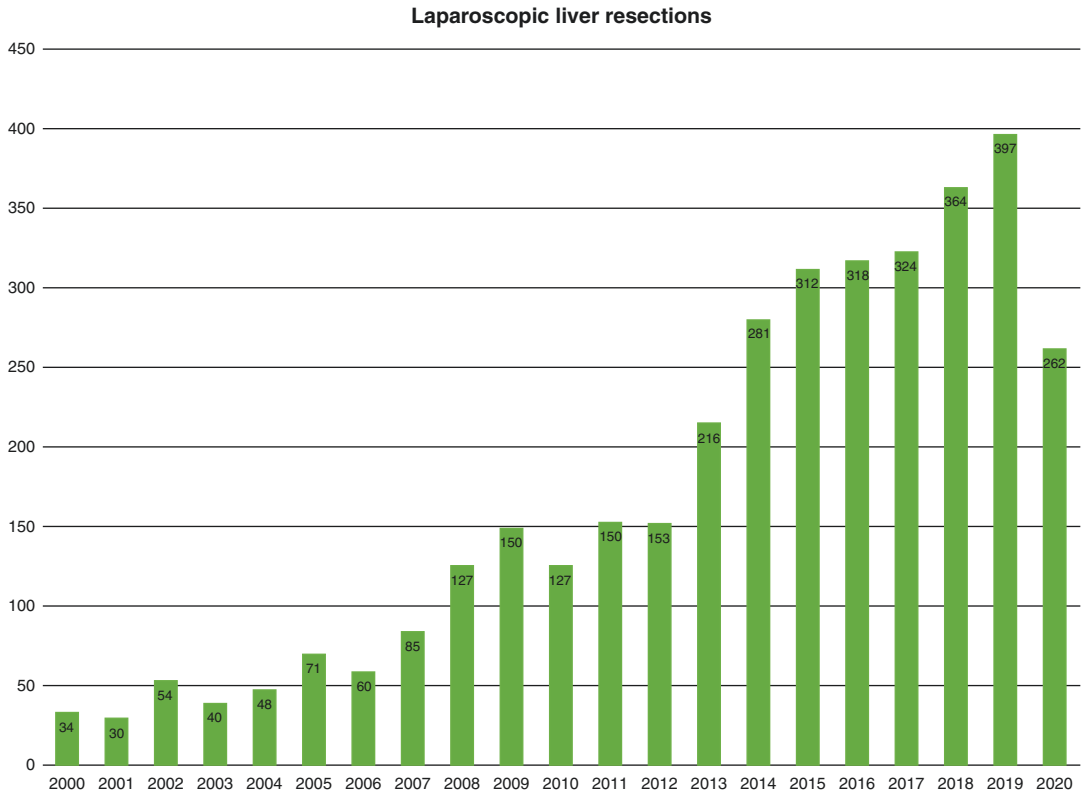

Fig. 3.1 "LLR Publications" in PubMed. (Time window: from the year 2000 to August 2020)

Giulianotti et al. [24] contributed to the literature with one of the first ever published robotic experiences in general surgery. This included 207 miscellaneous (vascular, thoracic, and abdominal) robotic cases, presenting the first worldwide robotic pancreatoduodenectomy and the first hepatic segmentectomies [24].

In liver surgery, the robot offers important advantages which are most notably evident during lymph node dissection, biliary reconstruction, dissection of the hepatic hilum, hemostasis, and management of very narrow surgical fields [1, 25].

In Figs. 3.4, 3.5, 3.6, 3.7, 3.8, and 3.9, we do present some surgical steps carried out during major liver resections where it is evident the accuracy of the bloodless dissection obtainable with the robotic approach, and some technological applications which are maximized by and perfectly integrated into the robotic platform (e.g., near infrared indocyanine green (ICG) enhance fluorescence for hepatic anatomy assessment, or intraoperative ultrasound (US)).

An increasingly more vast *corpus* of scientific data and clinical experiences have been proving RLR to be both safe/feasible [1, 19, 27–33].

These multiple lines of evidences, up to the meta-analytical level [26], show good results for RLR. Some of these reports seem to show that the robot has the ability to improve the rate of operations performed with MIS technique, extending the MIS approach also to more complex cases such as biliary reconstructions, difficult segmentectomy (posterior-superior segments), and major resections [1, 31].

3.2.2 Reducing the Surgical Contraindications

Our surgical department has an extensive expertise in minimally invasive robotic procedures,

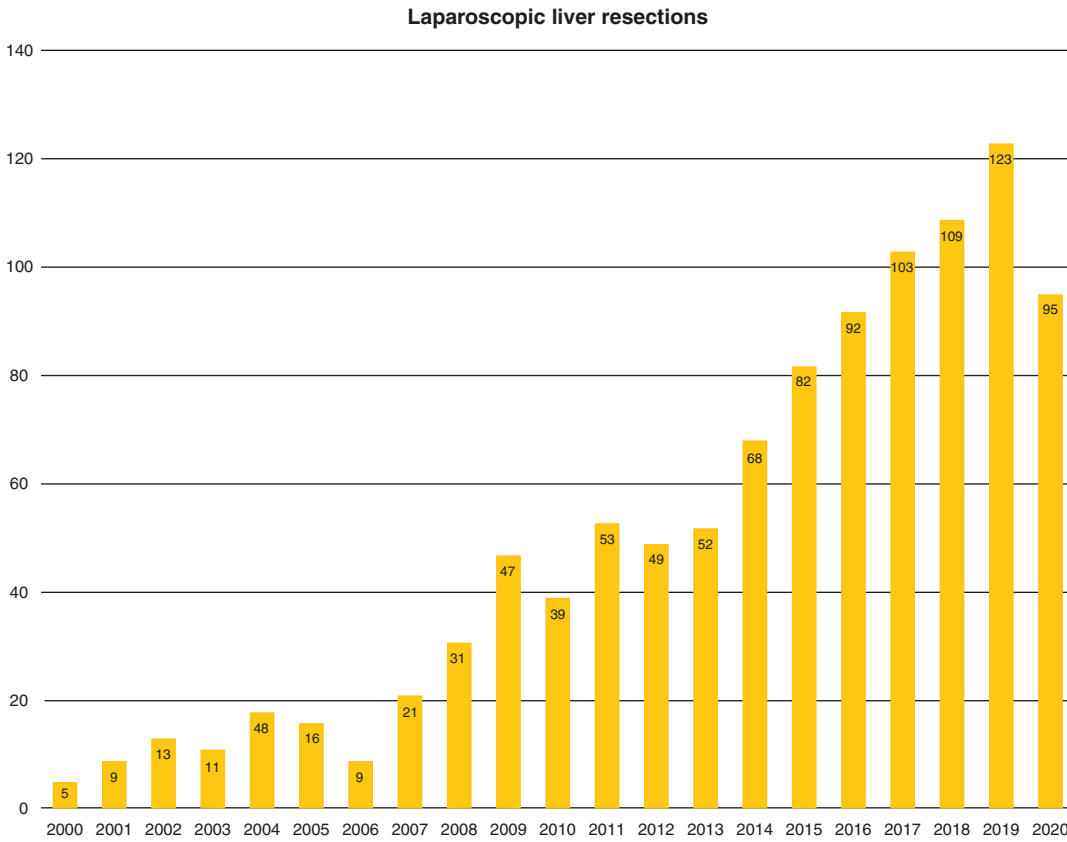

Fig. 3.2 "MILR Publications" in PubMed. (Time window: from the year 2000 to August 2020)

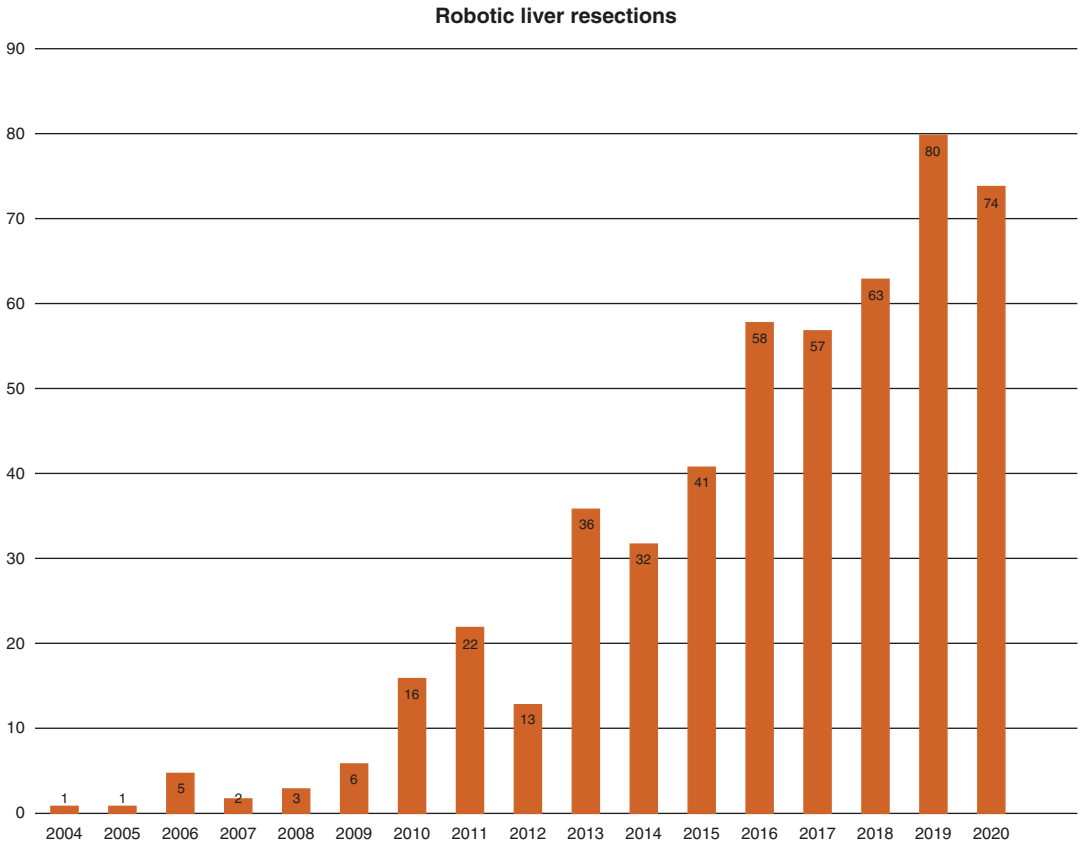

Fig. 3.3 "RLR Publications" in PubMed. (Time window: from August 2000 to August 2020)

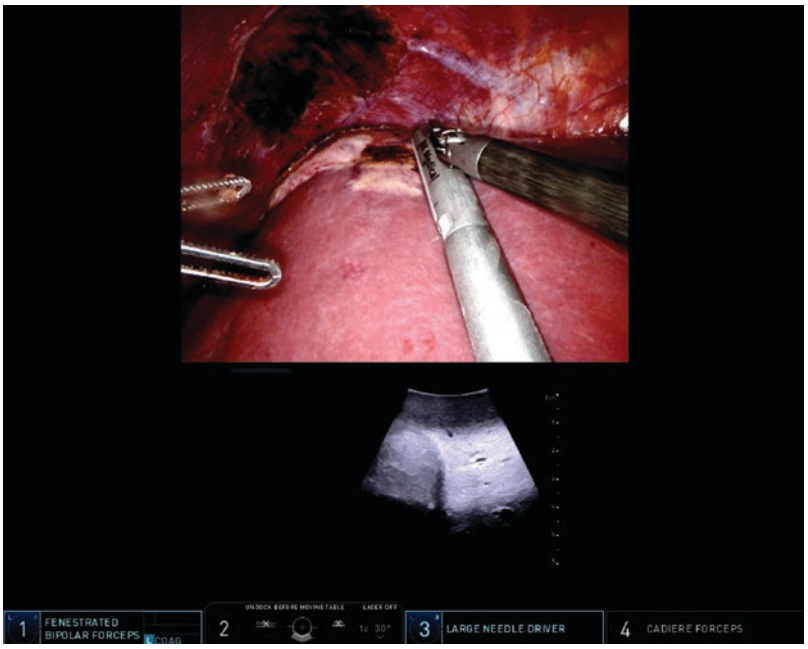

Fig. 3.4 Intraoperative ultrasound. The advantage, if robotic US is used, is that the assessment can be conducted directly by the console surgeon

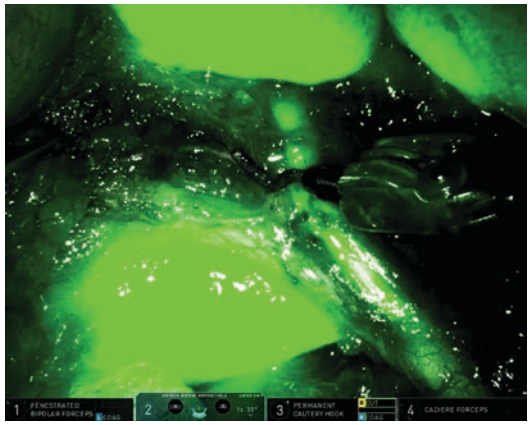

Fig. 3.5 (**a** and **b**) Near-infrared indocyanine green assessment of the anatomy. The ICG technology is maximized by the enhanced 3D stereotactic vision provided by the robotic platform

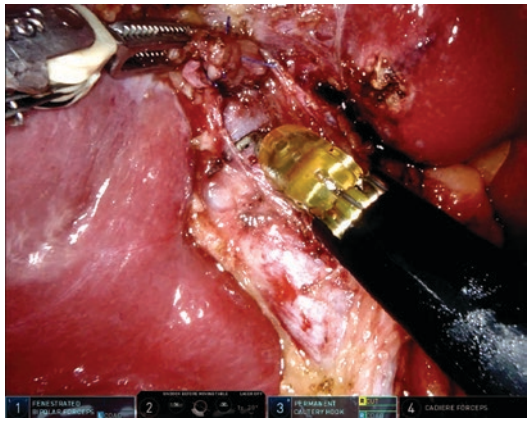

Fig. 3.6 The hook is the ideal tool for the dissection of vascular structure. (The hepatic artery dissection is shown in this picture)

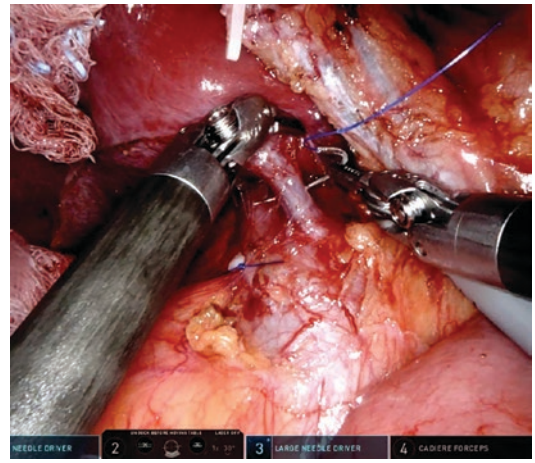

Fig. 3.7 Hepato-caval dissection: short vessels can be accurately controlled; the vision is "microscope"-like and directly managed by the console surgeon

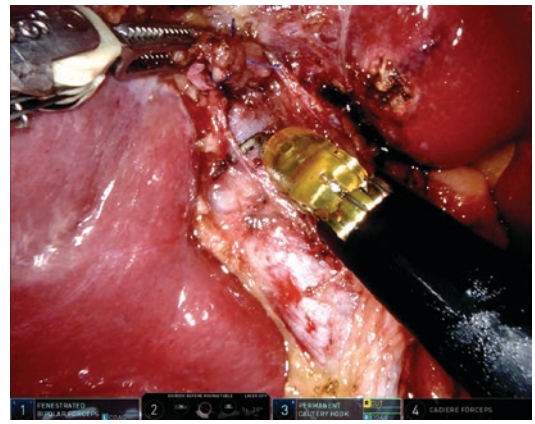

Fig. 3.8 Right portal vein dissection

which takes advantage from a robotic program started by Prof P.C. Giulianotti in the late 1990s [24]. Based on this ground, the clinical evidence shows that every hepatic segment can be resected using a robotic approach. If there is a solid experience in robotic liver surgery, there are no absolute contraindications to RLR [1, 4, 34]. In other words, the boundaries of RLR are predicated upon the peculiar surgical expertise of the institution/surgeon. As it is valid for any other areas of surgical expertise, it is essential to properly select the patients.

Some scenarios may potentially contraindicate (or make more complex) the robotic approach. In particular, additional care should be taken in assessing the risk/benefit ratio of MIS, should some of the following circumstances arise:

1. The dimensions of the lesions are not a contraindication *per se*. However, very bulky lesions, in particular with diaphragmatic involvement in its posterior portion (i.e., near the vena cava), may be difficult to approach in an MIS way [1, 34].

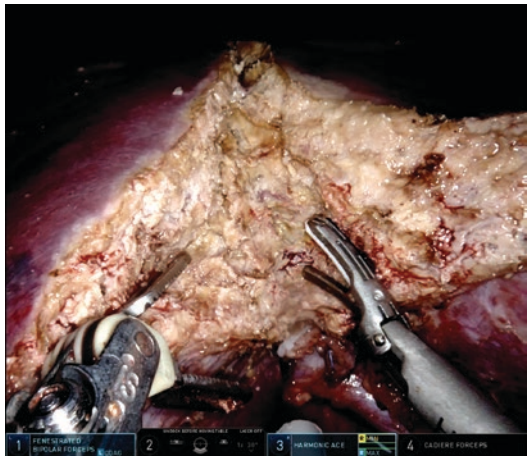

Fig. 3.9 Parenchymal transection

2. Neoplasia invading major vessels. In these circumstances, the MIS procedure may be still possible, but it entails extremely high level of operative skills, and it should be attempted only by very experienced surgeons [1, 34].
3. Preexisting medical conditions. For example, severe cardiac or respiratory diseases making the patient unfit for open surgery are also contraindication to MIS liver surgery [1, 34].
4. Multiple lesions requiring hybrid resection techniques. Open surgery may be more appropriate in the event of multiple parenchymal sparing resections combined with multiple RFAs across the liver. An exception may be voluminous hemangiomas: these have considerable volume reduction after the arterial supply is discontinued. The robotic platform can be extremely useful in making some resections of the superior/posterior segments less complex [35–37]; however, even with the usage of robot, some technical challenges may be not easy to overcome [1, 34].

Age is not an absolute contraindication by itself. Tee MC et al. [38] presented a retrospective analysis conducted in an initial sample of approximately 16,000 patients from the Hepatectomy Targeted Procedure Participant Use File of the ACS (American College of Surgeons) National Surgical Quality Improvement Program. From this sample, they extracted almost 1800 patients over the age of 75 years. They found that MILR provides a reduction in the risk of liver failure, bile leaks, major morbidity, prolonged LOS, and discharge in a place different from home. However, they did not conclude that MIS is a protective factor against postoperative mortality in patients over 75 years old.

In >70% of the cases, the hepatic robotic surgical procedures are carried out for malignant neoplasia, with a prevalence of colorectal liver metastasis and hepatocellular carcinomas. Approximately, 30% of the indications are for benign lesions [1, 3]. In the series reported in the literature, minor hepatic resections are the procedures most frequently performed [1, 3, 39].

Our surgical department has recently published a systematic review pertaining to the causes for conversion during RLR [40]. In this assessment, data derived from a single surgeon (Prof. PCG) experience with a sample of 139 robotic liver procedures (at the time the paper was written) were considered. In the pooled analysis, the conversion rate was 5%: such results are better than the laparoscopic conversion rate in the literature. A relevant conclusion has been that adhesions were not a cause for conversion to open surgery. From this systematic review, it is manifested that additional prospective experiences are required to better clarify the role of robotic techniques in averting/reducing the indications for conversion [40].

3.2.3 Improved Postoperative Outcomes and Postoperative Management

An increasingly more vast body of evidence is available about robotic minor hepatic resections [1, 41–45]. As the robotic platform shows perioperative outcomes comparable (or superior in some cases) to traditional laparoscopy, it can be an additional tool for the approach of superior-posterior segments, for parenchyma-sparing procedures, and in general for any complex case [1]. Also the short-term oncological results are promising [3, 46].

The literature data indicate that robotic major hepatic resections are carried out less often vs

minor robotic liver resections [1, 3, 39]. These surgeries are technically complex and they require a deep surgical/operative knowledge, along with full operative mastery.

An in-depth analysis of the most notable reports, subdivided into major [10, 11, 25, 28, 47–49] and minor hepatectomies [11, 31, 42, 44, 45], has been previously described in our recent review of the literature [1]. It is progressively more evident that RLR is safe and feasible, with perioperative outcomes equivalent/superior to laparoscopy and open surgery. An increasingly vast and solid body of evidence is forming. Despite this data, most of the authors agree that further studies (ideally multi-institutional, prospective, and well powered) are required to further substantiate these promising results [1].

Recent additional evidence come from robust metanalytical lines of evidence [26]: Paschalis Gavriilidis et al. [26] published an interesting and well-composed meta-analysis. The authors, from an initial group of over 1000 research articles, chose 79 manuscripts with a sample size of 25,210 patients. Their main results can be summarized as follows:

1. **Major morbidity** and **LOS** (length of hospital stay): statically significant better results for LLR and RLR were reported in comparison to open surgery [26].
2. **Operative time (OT)**: OT was less in the RLR group by 56 minutes in comparison to traditional laparoscopy and shorter by 69 minutes in comparison to open approach (statistically significant data). When detracting the docking time, the difference becomes not significant. In the literature, the docking time has heterogeneous values. In our experience, the docking time is massively diminished as the team robotic experience increases (in our division, it is <15 minutes) [26].
3. **EBL (estimated blood loss)**: RLR had significantly less EBL by a margin of 170 ml when compared to open surgery. LLR showed reduced EBL by 145 ml. The comparison between LLR and open surgery did not meet statistical significance [26]. The transfusion need is inversely related to some oncological outcomes (e.g., rate of recurrence) [50, 51]. Hence, it is paramount to reduce the EBL as much as it is feasible and the robot is ideal to obtain these results [1].
4. **Five-year overall survival (5-year OS)**: MILS (robotic and laparoscopic) had better 5-year OS when compared to open surgery (indirect evidence-based data for RLR). These estimations did not reach statistical significance in the comparison between RLR and LLR [1].

Given these aforementioned improved outcomes, some authors, such as Warner and Fong et al. [52], suggest an early post-discharge by implementing enhanced recovery pathways (ERPs). This is an interesting take on the matter. However, at the moment, in most cases the system is not yet completely designed for such an early discharge, and some delayed post-op complications can still occur even when a proper MIS technique and ERP protocol have been applied. Additional studies will probably shed light on this aspect.

3.2.4 Developing Better Robotic Surgical Instruments

The **robotic hook** is a very suitable tool during the dissection of the hepatic hilum. The 7 degree of freedom provided by the robotic technology allows a high level of versatility around fragile anatomical structures of the hilum. Lifting the tissue before the application of energy averts thermal lateral spread damages. The safety that this instrument provides is also connected to the small volumes of tissue that can be manipulated in every surgical maneuver [34].

The **harmonic scalpel** is composed of a vibrating blade and a "sealing" one. The combined action of these two components allows a penetration into the tissues coupled with a concomitant hemostasis. For the hepatic parenchyma, this vibrating blade is the ideal instrument which avoids vascular structures' damage (in a cavitronic ultrasonic surgical aspirator (CUSA)-like fashion). Additionally,

once inside the hepatic tissue, the sealing blade has a hemostatic effect while performing the transection of the parenchyma. The harmonic scalpel, if used with proper technique, provides transections without excessive bleeding. A drawback is that, the harmonic scalpel, because it is not endo-wristed, it has to be positioned parallel to the line of dissection. To that end, in a telescopic way, an operative 8-mm robotic port can be positioned in the 12-mm assistant, and it can be utilized for the harmonic scalpel. In order to achieve an optimal hemostasis, the instrument has to encounter vascular structures at an angle of 90°, encompassing the whole vessel while the energy is applied. If the sealing effect is not complete, bleeding may occur [34]. The effect of the harmonic is also dependent upon the hepatic microscopic architecture; for example, fibrosis, cirrhosis, and steatosis reduce the efficacy. If the harmonic is used in a not-fibrotic/cirrhotic/steatotic hepatic parenchyma, it works best if it is set at energy level 5. In other cases, it may work better with a lower energy setting [34].

Another potential negative occurrence, which may happen if the energy is applied in a continuous fashion, is the over-heating of the blades. This causes thermal damages to the plastic coverage of the tool with related reduced sealing performance. Saline irrigation, at regular times, may avert this event extending instrument performance [34].

The **vessel sealer** can seal a larger amount of parenchyma, is highly hemostatic, and is endo-wristed. However, it is not endowed with a vibrating blade, and when introduced into the hepatic parenchyma, it may induce bleeding before achieving a hemostatic effect [34].

The **CUSA (cavitronic ultrasonic surgical aspirator)** is a dedicated liver parenchymal instrument. The cavitron features make it very delicate on vascular structures. However, there is no robotic adaptation available, and it has to be controlled by an assistant surgeon [34].

At this stage of technological development, the perfect robotic tool for liver surgery has yet to be designed. However, the robotic platform is the perfect place to manage, test, utilize, and improve innovative surgical tools in the best integrated fashion [34].

3.2.5 Shortening the Learning Curve

The learning curve (LC) is an essential element to be considered and assessed in order to foster the rapid, safe, and widespread adoption of MIS techniques in liver surgery.

Despite having all the advantages of a MIS technique, laparoscopy has multiple limitations that partly explain the slow adoption of LLR as a routine procedure. One of the hurdles that characterize the laparoscopic techniques is its technical complexity: this is in part related to the limitations of the laparoscopic tools. This high level of operative complexity may translate into longer operative times and extended LC. In particular, the LC is slowed down by the difficulty in gaining mastery of the laparoscopic tools, e.g., during liver mobilization, hilum dissection, or parenchymal transection. Other elements are occurrence of hemorrhages (which can be difficult to control in laparoscopy) and also the scarcity of operative standardization described in the literature [53]. Over the course of the last 10 years, the role of LLR has been discussed in multiple consensus conferences in Louisville, Morioka, and Seoul [5, 54]. The need for standardization and safety in MIS liver surgery was emphasized by most experts [5]. The surgical skills have to be acquired in a safe way: mastering the LC reduces morbidity and conversion rate. To that end, the Southampton Guidelines have elaborated to provide clinical practice strategies specifically conceptualized to increase safety during LLR [55].

Despite these efforts, the LC in LLR is still very steep. In the literature, there is wide disagreement regarding the precise number of surgeries required to meet satisfactory results in the LC of LLR. However, most authors seem to agree that the LC in LLR has to be progressive (procedure of increasing complexity over time), and the whole process takes a considerable amount of procedures to be completed. Simulation training plays an important role in

easing the LC, and it has been shown to reduce the number of complications [56, 57].

Guilbaud et al. report that competency in minor LLR is reached after performing around 60 cases. Moreover, after a surgeon becomes proficient in minor LLR, reaching proficiency levels in major LLR requires up to 50 additional major procedures [53]. Similarly, according to Lai et al., the LC in LLR may be up to 64 cases for minor LLR, and up to 75 for major LLC [58]. A major limitation of the literature data regarding the LC in LLR is that the majority of the studies are retrospective in nature and based on single surgeon experiences.

The improved surgical dexterity allowed by the robotic platform may translate into shorter LC for RLR in comparison to traditional LLR [58].

In the literature, there is no clear consensus regarding standardized training protocols in robotic liver surgery. Most of the robotic hepatic surgical programs use mainly their specific institutional training protocols [58]. The data available show that RLR perioperative outcomes improve concurrently with the progress of LC [10, 58]. We do need more research to obtain a standardized credentialing training [59].

Despite this not-optimal level of evidence pertaining to LC in RLR, some authors suggest that the technical advantages of the robotic technology may produce a faster LC in comparison to LLR [58, 60]. According to Magistri P et al., a fully trained/experienced surgeon in high-volume centers, and with previous experience in HPB, can improve short-term perioperative outcomes after around 30 robotic procedures [59].

3.2.6 The Robotic Platform: A Tool for Integrating Multiple Evolving Technologies

The robotic platform is a formidable tool, with several aforementioned technological advantages. This can be of great benefit during liver surgery. On top of its inherent technological superiority, the platform is also the ideal place for intercommunication of additional technologies, which can operate at their best in an integrated fashion, e.g., near-infrared indocyanine green (ICG) fluorescence, augmented reality, image-guided surgery, and artificial intelligence (AI) algorithms. The potential of the robotic platform in integrating innovative technology is already a reality for the use of near-infrared ICG fluorescence; it is clinically evident that the benefit of the ICG technology is maximized by the improved robotic 3D stereotactic vision.

The robotic platforms currently available are powerful tools, but they could have their effectiveness even more enhanced by a higher level of integration with personalized image-guided surgery, for instance, by having integrated/superimposed on the intraoperative vision system some anatomical information/3D reconstructions derived from CT scan.

AI is another technology that may expand the potential of robotic surgery. The development of AI algorithms integrated into the robot itself would be very useful to recognize the intraoperative image of unclear anatomical structures, assess the viability of the tissue (e.g., after an anastomosis), and also give some aid in performing surgical maneuvers.

3.2.7 Costs/Benefit Ratio

One of the main concerns often claimed by the detractors of the robotic technology is its supposedly superior costs compared to laparoscopy or open surgery. A cost/benefit analysis is a very complex element to be completely and rigorously carried out. In fact, multiple confounding factors may be involved in this process. In other words, the real cost of a procedure should include not only the procedure per se, but also other additional costs related to intra- or post-operative complications, or to the LOS. These factors are not fully considered in all the literature available. The literature evidences indicate the superiority of the robotic approach in several peri-operative outcomes. Hence, the robot may reduce the occurrence of complications and avert the associated increased financial burden.

In our estimation, another element to be taken into account is that the cost of a product in the

marketplace is not a fixed element set in stone. Conceivably, with a wider penetrance of robotic technology, the associated cost of the equipment may decrease in time.

Paschalis Gavriilidis et al., in their meta-analysis, assessed short- and long-term results of open, robotic, and laparoscopic hepatectomies. They also conducted an interesting analysis regarding the costs. The data showed that the results regarding the costs of robotic surgery failed to meet statistical significance in most cases. Hence, most of the conclusions regarding cost are not backed up by statistically significant data. Besides the lack of statistical significance, the magnitude of the claimed (not statistically significant) cost savings with open and laparoscopic approaches is not staggering. More specifically, in a not-statistically significant way, the open approach was less expensive by $1197 and LLR was less costly by $759. Similarly, with not-statistically significant results, the open surgery was less costly by $426 when compared with LLR. In essence, when a meta-analytical assessment is carried out, the available data pertaining to costs are mostly not statistically significant, and there are multiple confounding factors to be considered.

According to some authors, the inferior robotic postop morbidity and conversion rate may overcome the initial cost of starting a robotic program [61, 62].

In general, most of the articles published about robotic liver surgery are retrospective, single-center experiences: in the meta-analysis by Paschalis Gavriilidis et al., only one single RCT was included in the assessment [26]. This situation is related to the complexity of the prospective enrollment of patients up to the amount required to meet the criteria for a well-powered sample size. A possible solution to attain further high-quality data will probably be the usage of prospective registry data, combined with multi-institutional national and international efforts.

Additionally, even if the use of robotic technology is increasing, its penetrance in liver surgery is still confined in a relatively small group. The financial variables and results to be included in this analysis are not static elements, and they most likely will decrease as the robotic technology will become more prevalent.

3.3 Conclusions and Future Perspectives

During the last 20 years, the popularity of MILR has been slowly increasing. This process speeded up in the most recent years. The robotic approach is now considered a valid alternative to open and laparoscopic techniques, also to treat lesion in the anterior and left/lateral hepatic segments [1, 3]. In clinical practice, MILR is now routinely used to perform major hepatic resection mainly in high-volume hyper-specialized institutions [58]. Even if it has all the advantages of MIS surgery, LLR is not considered by most authors to be routinely applicable for major or extended hepatectomies, or in scenarios with high risk for bleeding [1, 3]. Since its pioneering beginnings, robotic surgery was designed to overcome the inherent laparoscopic setbacks and limitations [58], with the aim of expanding the penetrance of the minimally invasive approach also in complex cases.

In the current body of evidences, heterogenous kinds of hepatic resections have been reported: major resections, extended right and left hepatectomy, posterior segment resections, and living donor hepatectomies [1, 3, 11, 39, 45, 47, 63–65]. Despite these data, most of the cases described so far are minor liver resections, whereas major hepatectomies account only for a small but increasing portion [3]. In North America, according to the analysis of Fagenson AM et al., in more than 3000 MIS hepatectomies (in the 2014–2017 ACS-NSQIP hepatectomy targeted database), 86% were partial [39], and less than 15% were major. In 92% of the MIS cases, the technique used was still traditional laparoscopy, with RLR accounting for only 8% of the total. Similarly, according to Stiles ZE et al. [66], among all the hepatectomies performed in the USA, the MILR were less than 18%, with RLR representing only 5.3% of the MILR performed [66].

Despite some limits in the present level of evidence (mostly retrospective single institution experiences and heterogeneity in the literature),

multiple lines of clinical data seem to converge and be concordant about the safety, feasibility, and non-inferiority or superiority of perioperative outcomes of RLR when compared to traditional LLR or to open surgery. Additionally, in terms of oncological outcomes, RLR has promising results [1, 67, 68].

From a technical perspective, the robotic technology is an evolution compared to traditional laparoscopy, and it facilitates multiple surgical maneuvers, allowing an extension of MIS procedure to complex scenarios (e.g., massive adhesions, very bulky neoplasm, extended liver resections). The robotic platform is perfectly well matched to carry out some specific hepatic surgical maneuvers: biliary reconstruction for iatrogenic biliary injuries [68], hepato-caval dissection, dissection of the hepatic hilum, mobilization of liver attachments, and hemostasis during parenchymal transection [1, 3].

Despite the availability of this technological tool, surgical decision-making, accurate patient selection with proper indications, and conducting these procedures in high expertise institutions are still paramount [68] elements.

The ideal robotic instrument for liver surgery is yet to come, but the robotic platform is the perfect space for integrating, controlling, coordinating, and developing surgical innovations (including surgical instruments).

In the last analysis, despite a growing body of evidences about the safety, efficacy, good outcomes, and the clinical significance of this technology, the vast preponderance of the studies available is retrospective in nature and more well-powered RCT are needed [69].

The best way to achieve a data-driven validation of any new technology introduced into the clinical context is its comparison to the previous gold standard. To that end, well-powered randomized controlled multicenter studies, followed by a meta-analytical rigorous assessment, are the best pathway to follow [70]. When considering surgical techniques or technologies, another additional element to be included is describing and following a step-by step standardized surgical procedure. In doing so, there is a reduction of the interpersonal technical variability/heterogeneity, and multiple sets of data can be more easily and rigorously compared. Enrolling enough patients to obtain a well-powered study may be a challenging endeavor. For this reason, multicenter efforts or the use of prospective registry data may be conceivable solutions [1].

Despite some of these current limitations in the level of evidence (which probably will be improved by the increasing *corpus* of scientific literature), there is a very strong clinical significance based upon a longstanding and vast surgical expertise in support of robotic liver surgery.

The robotic platform is, by design, the most suitable tool to effectively actualize the cooperative and synergistic interaction among several technologies, such as near-infrared indocyanine green-enhanced fluorescence, augmented reality, artificial intelligence algorithms, image-guided surgery [1], and any other conceivable device/technology in the future.

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Robotic Esophageal Surgery

4

David J. Straus IV

4.1 Introduction

With the advent of robot-assisted surgery at the turn of the century, robotic esophageal surgery took off in the early 2000s. Early adopters recognized this efficacy, publishing the first robot-assisted transhiatal esophagectomy in 2003 [1]. Since this landmark, robot-assisted surgery has increased in incidence due to a multitude of factors. As general surgery undergoes a minimally invasive renaissance, the robot follows this trend.

Although laparoscopy has undeniably revolutionized the field of general surgery, it is bounded by the linear nature of the instruments. The robot adopts the concept of wrist movement with multiple degrees of freedom. This is fully utilized in the confined space of the hiatus, where small precise movements are integral. Moreover, the high definition, binocular vision of the robotic laparoscope elucidates the anatomy of the mediastinum. Structures such as the anterior and posterior vagus nerves, aorta, azygous vein, and inferior vena cava (IVC) are readily seen in three dimensions. The robot is a platform that pairs well with many other adjuncts. For instance, indocyanine green (ICG) has helped in the areas of biliary delineation and in the assessment of vascular supply.

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It is a tool for modern surgery with ideal application to the foregut and esophagus.

4.2 Robot-Assisted Esophagectomy

The most common indication for esophagectomy continues to be cancer of the esophagus. As chemoradiation regimens become less toxic and more effective, the referral for a minimally invasive esophagectomy becomes more routine. Two schools of thought exist for the preferred method for esophagectomy, but both camps are seeking a safe and curative procedure, maximizing the patient's quality of life.

4.2.1 Robot-Assisted Transhiatal Esophagectomy

Our service currently employs a transhiatal approach mirroring the classical description by Orringer [2]. We use a multi-disciplinary team with separate minimally invasive and surgical oncology services. The minimally invasive surgical team prepares the conduit and dissects the hiatus via the abdomen, whereas the surgical oncologist performs the neck dissection and anastomosis. With this streamlined care, our service has become a high-volume referral center for esophageal cancer with excellent results.

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4.2.1.1 Technique

The esophagectomy begins with a thorough surveillance. A diagnostic and therapeutic esophagogastroduodenoscopy (EGD) is performed. The area of malignancy is inspected and the extent of invasion is grossly observed. Moreover, the stomach mucosa is closely examined in order to ensure that there is no evidence of erosive or ulcerative disease before proceeding. This is to maximize the viability of the gastric conduit and the resulting anastomosis. The pylorus is injected with a total of 200 units of botulin toxin (Botox) in four quadrants to ensure appropriate gastric emptying. This takes the place of the classical pyloromyotomy (or dilation), keeping with a theme of a minimally invasive approach.

Optimal patient positioning enlists the use of a split leg table. This allows for multiple assistants to be involved with the procedure. Moreover, it optimizes the ergonomics of the primary surgeon. The patient's head is rotated to the right, exposing the left neck. The suprasternal notch and the anterior border of the sternocleidomastoid are marked to guide the neck incision.

Abdominal access is obtained and pneumoperitoneum is established. Our service prefers optical access. Ports are placed under direct vision (Fig. 4.1). Of note, the ports need to be placed deeper than normal into the abdominal wall. This will be important for maximum reach during the proximal esophageal dissection.

A judicious surveillance of the abdominal cavity occurs. Special care is taken to assess the liver and peritoneum for any stigmata of metastasis. A liver retractor is then placed for full access to the hiatus.

Although it is classically taught to begin with a wide Kocherization of the duodenum, our experience is that this is rarely needed. While preparing the gastric conduit, dissection is begun at the greater curvature. Gentle traction is employed by a fenestrated bipolar forceps in the left hand, whereas a vessel sealer (or SynchroSeal) is employed for the right. The right gastroepiploic artery and arcade are identified and protected. Our service has found great utility in the use of intravenously administered indocyanine green. In coordination with fluorescent imaging, the vasculature of the greater curvature is delineated. This aids the dissection and ensures the viability of the future conduit and anastomosis.

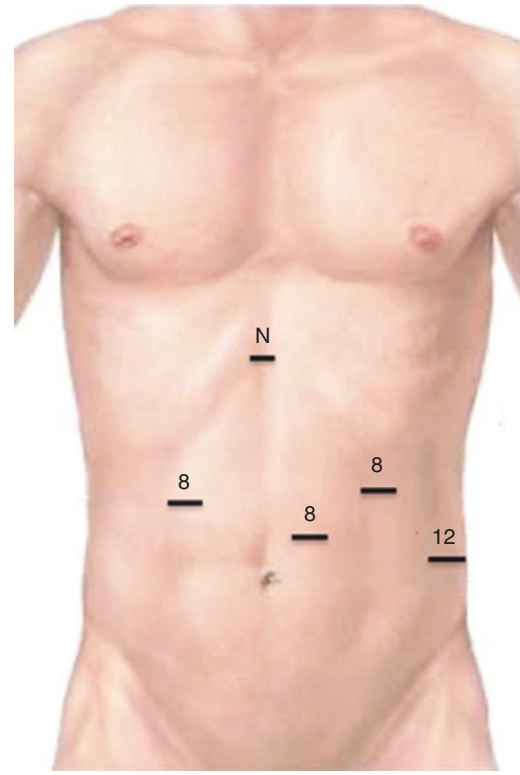

Fig. 4.1 An approximation of port placements for robotic foregut surgery. Three 8-mm ports for the working robotic arms and camera. A lateral 12-mm accessory port. A Nathanson liver retractor

To ensure full mobilization of the conduit, the posterior attachments of the stomach are taken down. The left gastric artery and vein are ligated with a linear cutting stapler. The phrenic membrane is then violated and the left and right crura are fully exposed. As one proceeds with the hiatal dissection, it is paramount to identify the aorta and IVC. The spongy tissue around the esophagus is primarily taken down using blunt dissection with occasional electrocautery. A Penrose drain is used to gently manipulate the esophagus, a key step for counter-traction.

This is the point where the robot reaches maximum utility. The binocular vision has exceptional visualization deep within the mediastinum.

Structures are readily viewed in three dimensions. Vital structures are able to be identified and protected during proximal dissection of the esophagus. To reiterate, if the ports are placed fully within the abdomen, a surprising amount of proximal mediastinal dissection can occur. A zero-degree scope (non-angled scope) is most effective for this dissection.

After maximal esophageal dissection, a linear cutting stapler is used to transect the proximal stomach and prepare the conduit (Fig. 4.2). Interrupted sutures are used to "reconnect" the staple lines so that the conduit will traverse the mediastinum with gentle traction on the proximal esophagus (from the cervical incision). ICG and fluorescent imaging can be used at any time to assess the overall health of the conduit (Fig. 4.2).

At this point, a standard cervical anastomosis is created using a stapled anastomosis (Orringer's technique). Special care is taken not to injure the left recurrent laryngeal nerve. A drain is left in place to bulb suction.

4.2.1.2 Perioperative Care

For direct preoperative care, deep venous thrombosis (DVT) prophylaxis is administered. ICG and Botox are on hand before the patient is intubated. Preoperative antibiotics are administered. A type and screen is performed.

The first night of recovery is spent in the ICU setting with close monitoring of cardiac rhythm, urine output, and pulmonary status. Postoperative day one, the patient is ambulatory with a strict incentive spirometry routine. A multimodal pain regimen is employed in an attempt to minimize opioid use. If the patient is progressing well, they are transferred to an intermediate care setting. Post-operative day three, a swallow study is performed. If no leak is appreciated, the patient starts on a clear liquid diet. Normally, the patient is discharged about postoperative day five to seven on a tailored soft-mechanical diet. The neck drain is removed before discharge.

Perioperative care of esophagectomy patients can be a complicated process, but there are

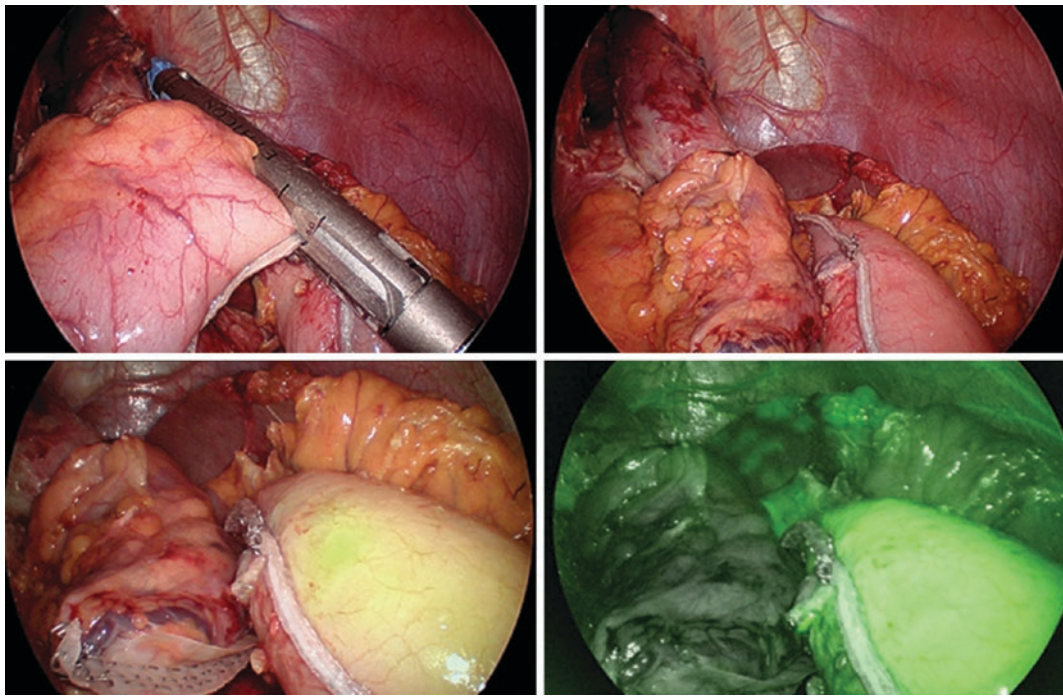

Fig. 4.2 Preparation of the esophageal conduit with a linear cutting stapler via the lateral accessory port. Assessment of the conduit with ICG

detailed resources to ensure optimal short-term results, i.e., ERAS society [3].

4.2.2 Robot-Assisted Transthoracic (Ivor Lewis) Esophagectomy

A major boon for our service is the versatility to offer robotic transhiatal and transthoracic esophagectomy. Although cases are meticulously worked up and discussed beforehand, it is not uncommon for an intra-operative change in surgical modality. Whether it is related to post-radiation changes or the hypothetical location of a tension-free anastomosis, it is a true luxury to be able to count on the thoracic surgical team when a transhiatal esophagectomy is not feasible.

The debate of transthoracic versus transhiatal esophagectomy is not new. There appears to be little difference in operative morbidity and mortality between the two routes [4]. Proponents of the transhiatal modality advocate that anastomotic leaks at the cervical anastomosis tend to run a more benign course. Thus, it is better tolerated by patients. Proponents of the transthoracic modality tout it as a superior oncological operation due to better lymphatic clearance. This appears especially true for patients with stage 2 and stage 3 disease [5]. Ideally, the cooperating services should individualize care to perform the procedure that is best suited for the patient.

Our service begins a transthoracic approach in the same manner as the transhiatal. An EGD is performed for gross examination and Botox injection of the pylorus. Laparoscopy is performed to assess for metastatic disease. The patient is prepped and draped in a supine position. The robot is docked and the gastric conduit is created. At this point, the thoracic surgical team is called in for re-positioning.

Ideal setup for the transthoracic modality begins with anesthesia. Intubation with a double-lumen endotracheal tube is preferred allowing for single lung isolation. The patient is prepped and draped in a left lateral decubitus position. Ventilation to the right lung is stopped. Access to the right chest is gained via blunt insertion of an 8-mm robotic port at the eighth intercostal space (ICS). This incision is made posterior to the posterior axillary line and anterior to the inferior angle of the scapula. Insufflation is started at 10 mmHg. After inspection of the chest**,** 8-mm and 12-mm robotic ports are placed in the fifth and 11th ICSs, respectively.

Another 12-mm Airseal port is placed at an anterior position at the 11th ICS, just above the diaphragm. This serves as an accessory port. The robot is then brought to the field and docked. The left-hand instrument is a fenestrated bipolar forceps and the right hand a monopolar spatula.

The right lung is retracted anteriorly and the inferior pulmonary ligament is taken down sharply. The esophagus should be dissected free at the level of the crura. Circumferential dissection of the esophagus begins at the inferior pulmonary vein. The esophagus is retracted anteriorly and posterior attachments are taken sharply using cautery. The azygous vein is divided with a 45-mm robotic white (vascular) load. Dissection should be carried up to the level of the thoracic inlet for a tension-free anastomosis. As stated previously, lymph node harvesting is crucial for a superior oncologic procedure. All grossly visible lymph nodes at stations 7 and 8 are dissected *en-bloc* (subcarinal and paraesophageal). An ideal number of harvested lymph nodes is 23, which has pointed to increased survival [6].

Once a complete esophageal dissection occurs, the specimen is delivered into the chest. The esophagus is transected at the level of the azygous vein using 45-mm green stapler loads. The conduit is completed using multiple 45-mm green loads, tubularizing the conduit.

Knowing that there are many variations in technique, our service currently uses a linear cutting stapler and running suture for the anastomosis. Cautery is used to make an enterotomy 4 cm from the tip of the conduit, 1 cm above the staple line. A green load robotic stapler is used to create a side-to-side anastomosis between the gastric conduit and proximal esophagus. The common defect is then closed with a mucosa-to-mucosa, running suture from each end. A 3–0, monofilament, barbed suture (i.e., V-loc) is used. These

are then tied in the middle. This layer is then reinforced with a running 2–0 silk. If there is redundancy to the conduit (i.e., a "candy cane"), it can be resected using robotic green staple loads. The specimen is placed in a large laparoscopic extraction bag and is retrieved through the Airseal incision, which will need to be enlarged. A 24 Fr chest tube is placed and the lung is reinflated under direct vision.

Multiple pitfalls exist throughout this portion of the operation. One must be very careful to protect the left mainstem bronchus, while dissecting the esophagus at the level of the carina. Moreover, our service does not routinely ligate the thoracic duct. If necessary, this is performed with a braided, non-absorbable suture ligature.

4.2.2.1 Postoperative Care

The first night of recovery is spent in the ICU setting with close monitoring of cardiac rhythm, urine output, and pulmonary status. Postoperative day one, the patient is ambulatory with a strict incentive spirometry routine. A multimodal pain regimen is employed in an attempt to minimize opioid use. If the patient is progressing well, they are transferred to an intermediate care setting. Postoperative day four or five, a swallow study is performed and the chest tube is closely monitored. If no leak is appreciated, the patient starts on a clear liquid diet. Subsequently, the chest tube is removed. Normally, the patient is discharged about postoperative day seven on a tailored soft-mechanical diet.

4.3 Robot-Assisted Esophagomyotomy

4.3.1 Preoperative Assessment

A comprehensive preoperative workup is tantamount to a successful esophagomyotomy. A complete history and physical exam guide intervention. Diagnosis begins with a barium swallow. The classic esophagram with a "bird's beak" is not always the case. In the real world, patients are referred with unclear clinical presentations and complex findings. Esophageal manometry is necessary to confirm clinical suspicions and accurately diagnose disorders of the esophagus. The esophageal musculature and contractility are seen segment by segment. Achalasia can thus be classified and appropriately treated.

Moreover, endoscopic ultrasound (EUS) is a helpful tool to guide surgical intervention. An effective and durable myotomy is the goal. EUS helps guide length and location of the incision. It is an accurate and time-tested evaluation to assure maximal effect.

Complex cases of esophageal motility are discussed at length at a multidisciplinary meeting. This is similar to the concept of a tumor board. Patients are discussed in the presence of minimally invasive surgeons, thoracic surgeons, and gastroenterologists (specializing in motility). Imaging and diagnostic tests are collectively reviewed. Patient plans are made via consortium leading to superior and individualized care.

4.3.2 Heller Myotomy

The Heller myotomy is a procedure well suited for the robot. Our service employs a standard foregut port placement with a Nathanson liver retractor. Electrocautery is used to dissect out the greater curvature in preparation for a partial wrap (i.e., Dor fundoplication). Moreover, a hiatal dissection is employed to fully assess the distal esophagus. Anatomy is crucial with specific identification and protection of the anterior vagus nerve fibers. The vertical line of incision is then plotted out starting at the distal esophagus and ending at the proximal stomach with strict preservation of the vagus nerve. Often the fat pad at the angle of His needs to be excised. Moreover, it is common that the myotomy traverses under the preserved vagal fibers (Fig. 4.3).

To begin the dissection, a 44 Fr bougie is passed, with utmost care, by the anesthesia provider (or surgical team member). Gentle traction and hook electrocautery allow for exposure of the muscular fibers. Binocular vision allows for the layers of the esophagus to become overtly clear. The superficial longitudinal fibers and inner circular fibers are identified.

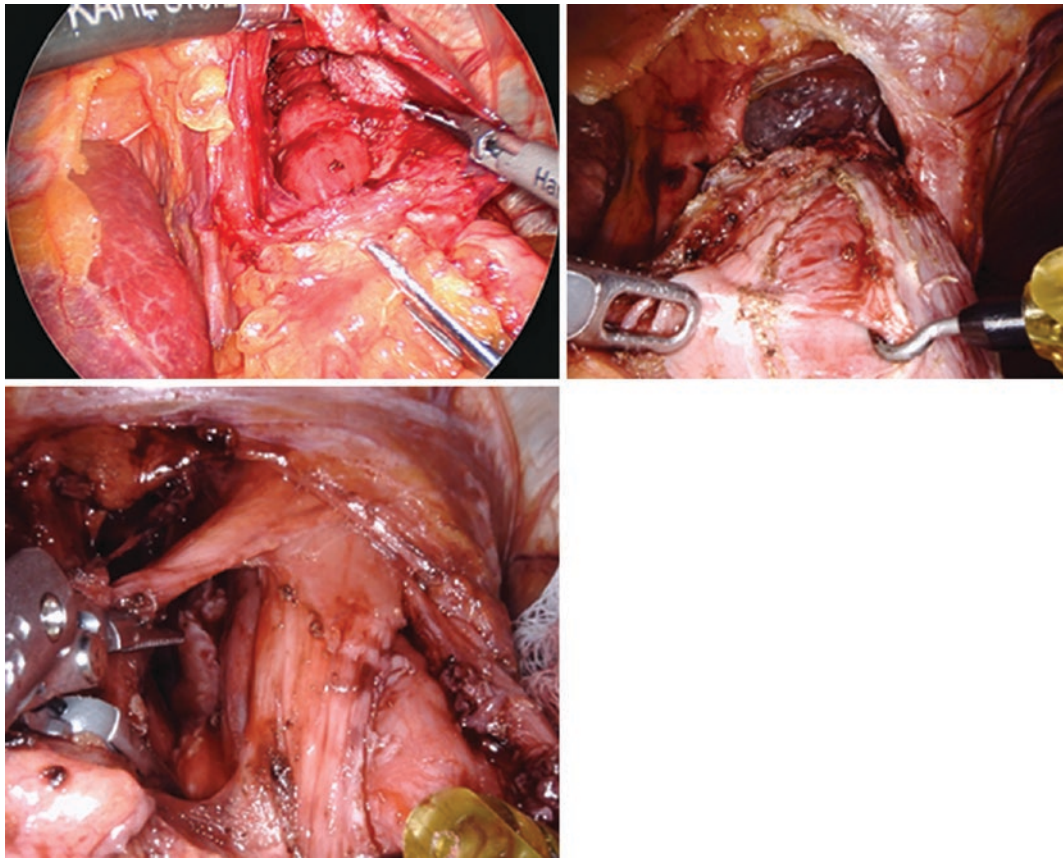

Fig. 4.3 Long myotomy from multiple angles. In this patient, the myotomies were made in parallel with incisions spanning the thorax and abdomen. The anterior vagal fibers are protected and preserved

Dissection is carried out starting at the Gastroesophageal (GE) junction heading superiorly toward the esophagus. The extent of the dissection should be pre-planned based on EUS findings. Fibers are carefully teased and dissected away from the esophagus to avoid injury to the mucosa.

If bleeding is encountered during this dissection, it is a pitfall to employ cautery in close proximity to the mucosa. Pressure from a surgical sponge (e.g., Ray-Tec) will tamponade the bleeding in a safe manner. This ensures the integrity of the mucosa and protects against a delayed thermal injury. If an enterotomy is encountered, the defect is repaired with a 4–0, permanent, monofilament suture. The classical teaching of closing the entire myotomy and relocating the site is not practiced.

An intra-operative esophageal perforation rate ranging from 1 to 15% is still being reported for laparoscopic Heller myotomy [7]. The most common area of enterotomy is at the GE junction. One clinically proven strength of using the robot for myotomy is the significant decrease in inadvertent esophageal perforation versus laparoscopy [8]. Meta-analysis has proven this encompassing the results of many surgeons at multiple institutions [7]. A perforation rate less than 1% with the robot is achievable.

A classic Heller myotomy is performed with at least a 4 cm esophageal myotomy extending to 1 to 2 cm onto the proximal stomach [9]. However, the preoperative EUS should be incorporated into the decision-making. In an effort to avoid an "incomplete myotomy," muscular fibers of at least 1.8 mm should be incised.

As the dissection passes distally onto the stomach, the muscular fibers are noted to travel in a diagonal fashion. Traversing the sling fibers of the proximal stomach is an important landmark. This leads to an effective and durable surgery. Large case studies still report up to a 10% recurrence rate and it has been observed that laparoscopic and robotic methods have equivalent rates [7].

In an attempt to combat postoperative reflux, a partial (Dor) fundoplication is performed. Interrupted silk sutures secure the fundus on the left and right of the myotomy. The most superior sutures also incorporate the left and right crura. Not only does this re-approximate the valve mechanism of the GE junction, but it also buttresses the hiatal defect and myotomy. To ensure a wide-open GE junction and an intact mucosa, a post-operative EGD is performed.

4.3.3 Long Thoracic Myotomy

In theory, a long myotomy should begin with the abdominal portion first. This focuses on the main area of concern, the GE junction. Moreover, this avoids having a gap in the myotomy and the increased chance of recurrence. Ideally, the myotomy should be continuous, leading up into the chest. If this is not feasible, a parallel myotomy is indicated.

Patient setup and positioning is the same as the thoracic portion of a transthoracic esophagectomy. Intubation with a double-lumen endotracheal tube is performed allowing for single lung isolation. The patient is prepped and draped in a left lateral decubitus position. Ventilation to the right lung is stopped. Access to the right chest is gained via blunt insertion of the 8-mm robotic port at the eighth intercostal space (ICS). This incision is made posterior to the posterior axillary line and anterior to the inferior angle of the scapula. Insufflation is started at 10 mmHg. Subsequent 8-mm and 12-mm robot ports are placed in the fifth and 11th ICS respectively.

A 12-mm Airseal port is placed between the camera and the 11th ICS incision. This serves as an accessory port. The robot is then brought to the field and docked. The left instrument is a fenestrated, bipolar forceps and the right, a monopolar hook.

Again, the procedure is guided by the preoperative endoscopic ultrasound. Certain landmarks can be ascertained such as the level of the azygous vein or the carina. As one extends the myotomy, it is crucial to avoid injury to the vagus nerves. The surgeon is essentially performing a right lateral esophageal myotomy. Superficial cautery scores the length of the esophagus at the area of concern. The longitudinal and circular fibers are dissected without cautery to avoid thermal injury to the esophageal mucosa.

4.3.4 Perioperative Care

Post-myotomy patients are cared for with a liberal ERAS protocol. A multimodal pain regimen is employed with minimal narcotics being standard. Patients are mobilized on post-operative day zero without a urinary catheter. Patients are cared for on the "med-surg" hospital floor with appropriate DVT prophylaxis. Patients are on our post-esophageal diet (soft-mechanical) for the short term, until clinical evaluation at two weeks. A 24-Fr chest tube is placed at the time of surgery and routinely removed on postoperative day one. An uncomplicated hospital stay consists of about 24 hours, rarely necessitating a patient to stay for two nights.

4.4 Robot-Assisted Anti-Reflux Procedures

4.4.1 Preoperative Assessment

A busy foregut practice will see a spectrum of referrals for hiatal hernias: asymptomatic, small hernias seen on routine imaging to large paraesophageal hernias with intrathoracic bowel. A standardized approach will help guide surgical intervention. A small hiatal hernia without symptoms obviously does not need robotic (or surgical) intervention. Larger, more complex hernias benefit from robot-assisted procedures, especially in the setting of hernia recurrence.

An extensive history and physical are obtained. An upper GI study or CT scan with oral contrast is used to identify the anatomy. An upper endoscopy is performed with a pH probe if indicated. Preoperative esophageal manometry will guide the decision for a partial or full wrap (fundoplication).

For a true informed consent, a frank discussion of hernia recurrence must occur. Current literature shows recurrence rates as high as 50% (paraesophageal hernias at four years postop) [10]. Moreover, it is important to discuss the relationship between obesity and recurrence [11]. To achieve an ideal body habitus for safe operating conditions, our service will enlist the help of a nutritionist and a preoperative diet.

4.4.2 Hiatal Hernia Repair

Using our standard positioning for foregut procedures, the robot is docked. After a brief inspection of the hiatal defect, a full hiatal dissection will begin. One begins by taking down the superior greater curvature attachments of the stomach including the short gastric vessels. This begins approximately at the level on the inferior pole of the spleen and ends at the phrenoesophageal membrane. In large paraesophageal hernias, tension-free reduction of the hernia can only occur with a circumferential esophageal dissection. Gentle caudal retraction and a keen understanding of the hernia sac anatomy are key. Finding the anterior and posterior vagus nerves**,** aorta, and IVC are all crucial steps to a safe hiatal dissection. The GE junction should be within the abdominal cavity without tension. If this is not the case, one would consider an esophageal lengthening procedure (i.e., Collis gastroplasty).

A self-locking, barbed, non-absorbable monofilament is used to re-approximate the crura (size 0). Special care is taken to not kink or obstruct the natural alimentary pathway of the esophagus. Re-approximation of the crura can occur in an anterior manner, posterior manner, or both.

For large defects and recurrent repairs, a biosynthetic mesh is placed to buttress repair. Our service uses an absorbable mesh made of polyglycolic acid (PGA) and trimethylene carbonate (i.e., Gore Bio-A). The mesh is then secured with fibrin sealant (i.e., Ethicon Evicel). This circumvents the use of tacks or sutures into the diaphragm decreasing the likelihood of postoperative pain, nerve injury, or cardiovascular injury.

Diaphragmatic relaxing incisions have been well described [12]. These are rarely necessary, but an effective way of decreasing crural tension for a lasting closure. Diaphragmatic defects are traditionally patched with synthetic, non-absorbable mesh.

4.4.3 Fundoplication

Restoration of the myoarchitecture of the GE junction not only involves re-approximation of the crura but also an appropriate fundoplication. In the setting of anti-reflux surgery, this involves a full or partial wrap. This decision is made by analyzing patient symptomatology and data gathered from high-resolution esophageal manometry. Patients with high frequencies of failed swallows and weak contraction would benefit from a partial fundoplication. This avoids postoperative issues with dysphagia.

The standard, full, 360 degree, Nissen wrap is routinely employed. After a full hiatal dissection, a Penrose drain surrounding the GE junction is used for gentle anterior retraction of the esophagus. With a patent posterior space between the esophagus and the posterior confluence of the crura, the greater curvature is grasped and transferred from patient left to right. The traditional "shoeshine" procedure is performed ensuring that the greater curvature of the fundus will be used. A 52 Fr bougie is passed, with utmost care, by the anesthesia provider (or team member). This appropriately sizes the wrap. It should not be overly taut; the first suture placed should leave room for an instrument to pass beneath it. Routinely, a total of three interrupted sutures are placed creating a wrap that is approximately 2 cm in length. Bilateral coronal sutures are placed anchoring the posterior portion of the wrap to the esophagus and right and left crura. These sutures are performed with a 2–0 silk.

The partial, posterior 270 degree, Toupet wrap is the procedure of choice for patients with high potential for postoperative dysphagia. Requiring additional knot tying, the surgeon is able to showcase their dexterity with the robot. For a Toupet, after the shoeshine maneuver, the fundus of the stomach is secured via two rows of three interrupted sutures. The anterior 90 degrees of the esophagus remains exposed. Again, coronal stitches are used to anchor the posterior portion of the wrap.

4.4.4 Sphincter-Augmenting Magnet (LINX)

Another important tool for a modern practice in foregut surgery is the sphincter-augmenting magnet or LINX (Torax® Medical, Ethicon). First approved by the FDA in 2012, it is steadily gaining popularity in the United States. Surgeons are becoming more comfortable with the device as a versatile anti-reflux solution, which has led to its success.

There are many indications for LINX implantation. Patients who present with a positive pH study and good correlation of reflux symptoms are candidates. Moreover, patients must have good esophageal motility per high-resolution esophageal manometry (with at least 7 out of 10 intact swallows). Devices can be implanted in patients with up to a moderate-sized hiatal hernia. As per FDA trials, Torax recommends patients with a body mass index of less than 35. Recent studies have tested this BMI threshold. Case series have shown good results for patients with BMI over 35 even in postoperative gastric bypass patients [13].

Patients seek out the LINX device due to the decreased incidence of bloating versus fundoplication. As per recent studies, severe gas and bloating within one year have been quoted at 0% for LINX and 10.6% for laparoscopic Nissen fundoplication [14]. This advantage, among retaining the ability to vomit and belch, aids in patient popularity. Moreover, studies show that there is no significant difference in postoperative dysphagia with LINX versus fundoplication. Thus, many surgeons will recommend this as first-line therapy in patients with mild to moderate reflux disease.

The LINX device is amenable to robot-assisted surgery and our service has found its greatest utility in redo surgeries. As compared to a fundoplication, a less invasive dissection is required. As other anti-reflux procedures, the surgery starts with a full hiatal dissection with complete mobilization of the esophagus [15]. The GE junction should be resting within the abdominal cavity. If there is a hiatal hernia, it should be reduced and repaired.

The most important step of the procedure is identification of the posterior vagus nerve. A tunnel is carefully dissected between the posterior vagus and the esophagus at the level of the lower esophageal sphincter. The nerve then serves as a physical bracket holding the LINX device in place, pegged posteriorly at the GE junction. The esophagus circumference is then sized using the provided laparoscopic sizing tool. The LINX is then passed through the aforementioned tunnel and secured via clasp, anteriorly.

Research showing similar effectiveness as fundoplication with less dietary restriction is an obvious plus for the patient. The surgeon benefits due to the need for less mobilization and suturing. Moreover, both parties benefit from a majority of patients being discharged the same day of the procedure. Another positive for both parties is the ability to perform a future fundoplication. Thus, device removal is relatively easy and unencumbering if in need of a follow-up fundoplication.

4.4.5 Redo-Foregut Procedures

As previously stated, recurrence rates for paraesophageal hernias are as high as 50%. Logically, a busy surgical referral center will see its share of hernia recurrence. After a full diagnostic reassessment, the patient will be considered for re-operation. As previously mentioned, particularly complicated patients are discussed at a multidisciplinary conference with a panel of surgery and medicine specialists.

Redo-foregut surgery is another area of advantage of the robotic modality. Early on, it is crucial to delineate planes of dissection. A bloody, non-delineated plane leads to inaccurate and potentially harmful dissection. For a careful lysis of adhesions, one should employ forceps and scissors. These instruments are hooked up to bipolar and monopolar energy sources, respectively. A 12-mm lateral accessory port and a keen assistant are crucial for a smooth procedure. The 12-mm port allows for easy transfer of surgical gauze, sutures, Penrose drains, staplers, and laparoscopic instruments. Well-placed counter-traction is invaluable throughout a dense lysis of adhesions.

Often in a "hostile" surgical field, the anatomy of the foregut becomes blurred. The modern minimally invasive surgeon has multiple tools to combat this. ICG can help delineate vascular structures. An EGD can confirm the level of the GE junction and help guide the surgeon away from an incidental enterotomy or unrecognized mucosal injury.

Starting the dissection from the patient left, the surgeon can take down the short gastric vessels with an energy device (e.g., Vessel Sealer or SynchroSeal). Special care is taken to avoid damaging the splenic vessels. Once the fundus is freed, the left crus can be identified.

Attacking the hiatus from the patient right, one can run into many pitfalls. When starting the dissection, it is wise to stay close to the liver, readjusting the liver retractor as needed. This provides much needed counter-tension. Effort should be taken to identify and preserve the left gastric vascular bundle. Moreover, identifying the IVC is a milestone of the operation. It is not unheard of to confuse the right crus for the inferior vena cava. This would have disastrous consequences.

If there is an inadvertent enterotomy of the stomach, it can be closed using a stapler or running permanent suture. The enterotomy and repair can be easily examined using an EGD. Mesh erosion, obstruction, and migration have all been described. Excision of permanent mesh can greatly benefit the patient, easily taken down with monopolar scissors.

A surgeon's goal, in a redo field, should be a safe and complete dissection. Proximal dissection of the esophagus should be carried to the spongy tissue of the mediastinum. The anesthesia team should be cognizant of the high risk for an inadvertent incision of the pleura resulting in capnothorax. This can be treated by speedy repair of the pleural defect and therapeutic Valsalva maneuvers. Rarely, the patient necessitates a chest tube.

A modern foregut practice will be consulted for conversion from Nissen to Toupet, the recurrence of a paraesophageal hernia, or the conversion of a gastric sleeve to bypass. The robotic is invaluable to the approach of a recurrent field.

4.4.6 Perioperative Care

A postoperative EGD allows for assessment of the wrap (or device). The distal esophagus is inspected for mucosal injury. A retroflexed view is obtained and the wrap is examined from within the stomach.

Hiatal hernia repair and fundoplication patients are cared for with a liberal ERAS protocol. A multimodal pain regimen is employed with minimal narcotics being standard. Patients are mobilized on postoperative day zero without a urinary catheter. Patients are cared for on the "med-surg" hospital floor with appropriate DVT prophylaxis. Patients are on our post-esophageal diet (soft-mechanical) for the short term, until clinical evaluation at two weeks. An uncomplicated hospital stay consists of about 24 hours, rarely necessitating a patient to stay for two nights.

4.5 Conclusion

Throughout this chapter, robotic esophageal procedures were discussed in detail, but the robot is obviously not bounded to this rigid list. Our service attempts to push the envelope, using the robot for esophageal diverticular resection, substernal gastric conduits (in the setting of esopha-

gectomy), and tumors of the foregut. In fully committing to a robotic approach, our service has benefitted greatly from the platform.

One area where the robot is rare to be employed is a true acute care setting. One could understand the utility in acute esophageal perforation or repair of diaphragmatic trauma. Time will tell if it will be employed in this manner.

Multiple trends have emerged showing case studies and meta-analyses of the benefits of robotics. Just as a significant decrease in perforation rate has been seen in robotic versus laparoscopic Heller myotomy, other areas of benefit will be teased out.

One may ask, "What is next for the robot?" There will be a definite increase in machine learning. One can extrapolate ICG fluorescent imaging with paired imaging guidance. Haptics will be added to the control console to give the surgeon a sense of touch. Single incision and natural orifice surgeries will become more common as technology scales down. Moreover, there is a current telemedicine trend, which could lead to further adoption of remote surgery.

Currently, the robot offers superior intracorporeal dexterity with impressive binocular visuals. This is done adhering to minimally invasive principles. There is less reliance on a surgical assistant, appealing to those seeking more operative control. Moreover, physician comfort is improved with the ergonomics of sitting down at the console. The end result is a new generation of surgeons seeking operative time with robotic consoles.

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Challenges in Robotic Colorectal Surgery

5

Am Otero-Piñeiro, R. Bravo, and Am Lacy

5.1 Background

Technology has become a very important and almost essential tool in daily life, with impact in multiple fields including medicine.

As we speak, multiple new techniques are evolving or being developed in the fields of nanotechnology, medical tele-assistance, and image-guided and robotic surgeries.

Medicine is going through a technologic revolution that produces a paradigm shift and makes us think in new ways of treating and diagnosing our patients and also how to teach medicine, especially surgery [1].

Minimally invasive surgery development and routine application in multiple procedures have been the main evolution in the last 50 years, bringing great benefits to patients, surgeons, hospitals, and even insurance companies. This well-known advantages include, to name a few, less postoperative pain, shorter hospital stays (if necessary at all), a quicker return to daily life and work activities, less risk of infection, and better cosmesis [2].

In laparoscopic surgery, the surgeon keeps control by handling patient tissue inside an insufflated cavity with an external fulcrum point for instrumentation. It changes drastically in robotic surgery, with the surgeon taking place in a virtual environment outside the operative field, with distant and indirect control.

Surgical robotics is rooted in the strengths and weaknesses of laparoscopic surgery, being able to avoid the fulcrum effect, overcome the limited range of movements and depth perception, and dismiss the surgeon physiological tremor, while keeping its minimally invasive nature [3].

SAGES defines robotic surgery as a surgical procedure that adds a computer technology-enhanced device to interact between a surgeon and a patient during surgical operation and assumes some degree of control heretofore completely reserved for the surgeon.

Surgical robots have been envisioned to overcome the limitations and extend the capabilities of human surgeons, allowing them to perform precise and reproducible tasks [4].

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5.2 Advantages and Limitations

Da Vinci System® by Intuitive Surgical, Inc., the most commonly used device, consists of a surgeon's console, a slave robot with four interactive arms, instruments, a graphic interphase, and an image-capturing system. The design allows the surgeon to operate from a seated position with ergonomic comfort with enhanced vision of the patient up to 20 times its real size and in a 3D fashion. Surgeon's assistant makes the incisions and assembles the arms according to the surgical procedure and the anatomic location of the organ to intervene. Both the optic and instrument movements are originated by the surgeon using no more than two fingers of each hand and are transmitted to the patient with great precision and dexterity after been interpreted.

As attractive as it sounds, there are several limitations to robotic surgery. The more prominent is the size of the equipment, which limits the space in the operating room and may require extra staff to operate, rising the costs of the procedures and making it unaffordable to every health systems. Lack of haptic (force feedback) and problems with multi-quadrant surgery suppose additional constraints. Another consideration is that it requires a number of delicate connections and interactions that can be out of control and cause damage to the patient. Besides, the assembling of the device and arms takes considerable amount of time and a rise in operative and anesthetic timings [5].

5.3 Indications and Contraindications

5.3.1 Indications

The indications for this surgery are similar to those of conventional laparoscopic surgery [6].

- Adult patient candidates for elective surgical resection.
- Patients able to provide written informed consent.
- Colorectal disease diagnosis.
- Any ASA.

5.3.2 Contraindications

- Intolerance to general anesthesia.
- Severe bleeding disorder.
- Pregnancy.
- Extensive abdominal or pelvic metastases.
- Occlusive tumor with retrograde distension.
- Perforation of the tumor with acute peritonitis.
- Extensive adhesion syndrome.
- Massive ascites, intra-abdominal bleeding or shock.

5.4 Setup Fundamentals

Following the **five setup fundamentals** [7] creates important setup **advantages:**

- It helps enable instrument tips to reach where needed to complete the procedure.
- It adjusts the da Vinci robot to an appropriate starting position.
- It allows for a reproducible setup.
- It minimizes external arm-to-arm interferences.
- It minimizes intraoperative range-of-motion limits.

Proper setup is crucial for a successful da Vinci procedure.

5.4.1 Port Placement

5.4.1.1 Identify the Surgical Workspace

Identify where the instrument tips must reach in order to complete the procedure. If the surgical workspace of any procedure requires access to more than two quadrants, consider dual docking.

5.4.1.2 Determine the Target Anatomy

The target anatomy is not the pathology. It is the area where the midline of the surgical workspace intersects with the far edge of the surgical workspace boundary.

5.4.1.3 Place the Initial Endoscope Port

Place the initial endoscope port 10–20 cm from the target anatomy on the opposite edge of the surgical workspace boundary.

5.4.1.4 Decide on the Hand Controls

Decide whether to control two instruments with the left hand or with the right hand. This determines port placement. Two da Vinci instrument ports will go to one side of the initial endoscope port and one da Vinci instrument port will go to the other.

5.4.1.5 Place the Da Vinci Ports

Place the remaining da Vinci ports 8 cm apart, along a line perpendicular to the target anatomy (Fig. 5.1).

- Port distance should range between 6 and 10 cm and be adapted according to the patient's body habitus.
- Place the ports at least 2 cm away from any bony structures.
- Do not place ports between other ports and the target anatomy.

5.4.1.6 Place the Assistant Ports

Place the assistant ports as needed, as far away as possible from the da Vinci ports (at least 7 cm).

- Ensure that port location enables you to reach the desired anatomy.
- Ensure that port location gives you physical access to the port.

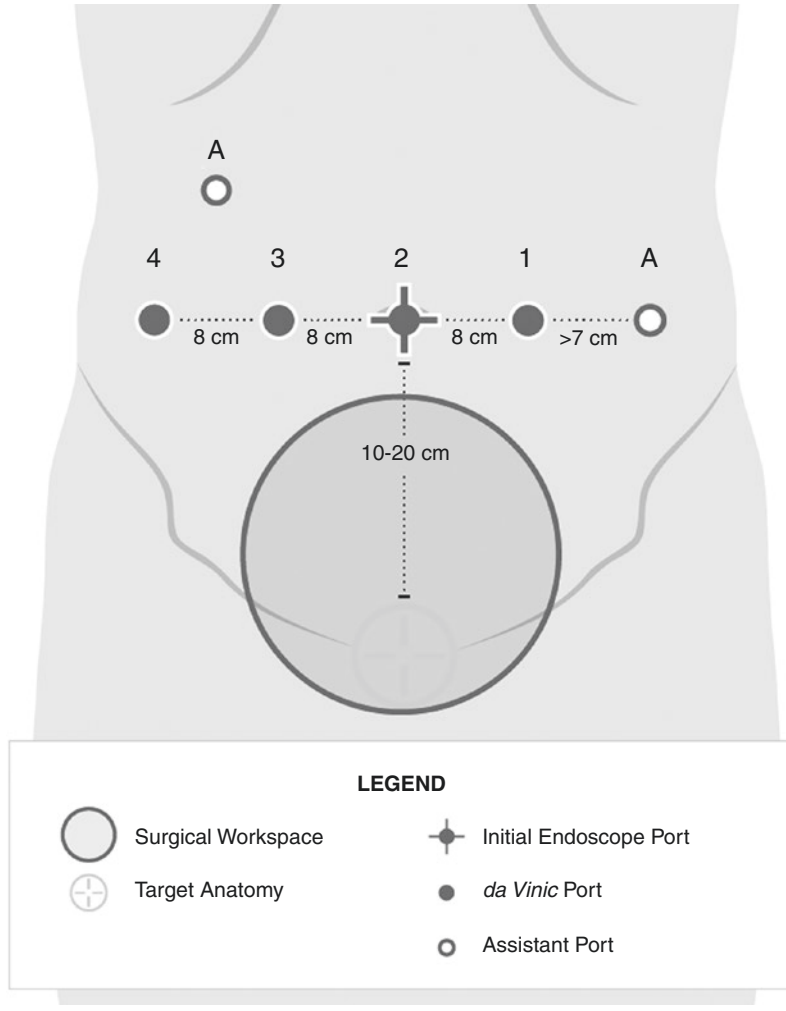

Fig. 5.1 Port placement

- Consider placing the ports lateral to the da Vinci ports or triangulated between the da Vinci ports.
- Use bariatric-length laparoscopic instruments with assistant ports.
- Do not place any assistant ports between the da Vinci ports and the target anatomy.

5.4.2 Deploy for Docking

5.4.2.1 Select the Anatomy

Select the anatomic region of the desired surgical workspace on the Patient Cart helm.

5.4.2.2 Select Cart Location

Select how the Patient Cart will approach the patient: from the patient's right, the patient's left, or the patient's legs.

5.4.2.3 Press and Hold Deploy for Docking

Deploy for Docking adjusts the da Vinci to an appropriate starting position automatically.

- It automatically rotates and pivots the boom to optimize access to the patient.
- It readies the da Vinci to be driven to the patient.

5.4.3 Drive the Laser Lines to the Endoscope Port

5.4.3.1 Drive the Cart

Grasp the handlebars and the cart drive enable switches and slowly drive the Patient Cart to the operating table, monitoring patient clearance (Fig. 5.2).

5.4.3.2 Drive the Laser Lines to the Scope Port

Drive the laser lines within 5 cm of the initial endoscope port. This positions the center of the da Vinci boom over the initial endoscope port.

5.4.4 Target

5.4.4.1 Dock the Initial Endoscope Arm

Dock the initial endoscope arm to the initial endoscope port. Insert the endoscope and ensure it is rotated to a neutral horizon position before targeting.

5.4.4.2 Point the Endoscope at the Target Anatomy.

The target anatomy is not the pathology. It is the area where the midline of the surgical workspace intersects with the far edge of the surgical workspace (Fig. 5.3).

5.4.4.3 Target

Hold the cannula with one hand to support it while it moves. Press and hold the targeting button on the endoscope.

The boom will automatically rotate and orient itself toward the target anatomy. Hold the targeting button until the audible countdown completes and motion stops.

Performing targeting simultaneously adjusts column height, boom extension, and boom rotation, and achieves the following:

- It centers the boom over the initial endoscope port.
- It rotates the boom to point toward the target anatomy.
- It adjusts column height to maximize sterility and ensure that arms reach to all ports for docking.

5.4.5 Perform Manual Arm Adjustments

5.4.5.1 Align the Endoscope Arm

Adjust the flex on the initial endoscope arm, using the laser lines as a positioning guide. Make the back of the arm parallel to the laser line. This aligns the arm with the target anatomy.

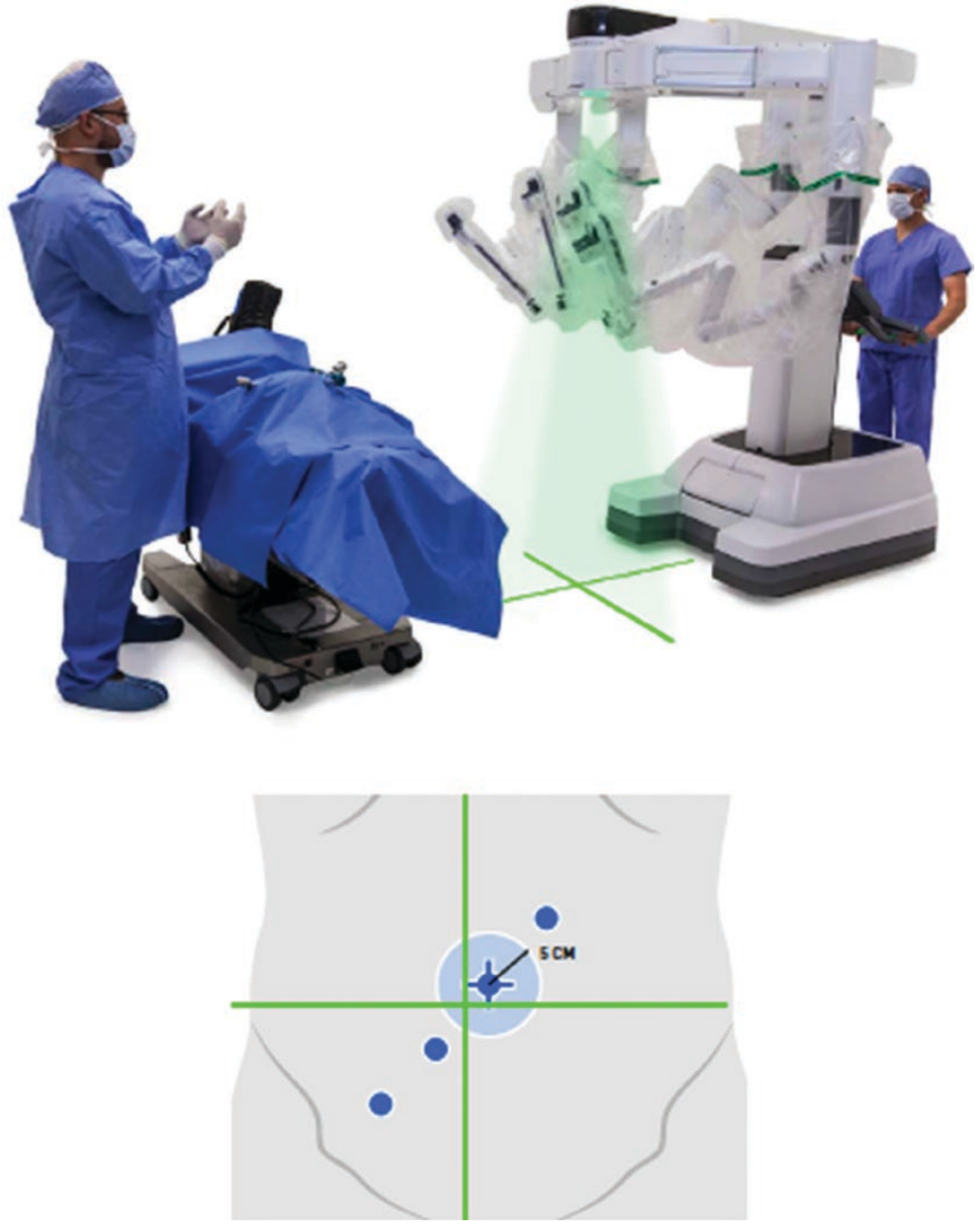

Fig. 5.2 Drive the cart and laser

Fig. 5.3 Target anatomy

5.4.5.2 Dock the Remaining Arms

Dock the remaining arms to the corresponding ports.

5.4.5.3 Adjust the Side with One Arm

Adjust the flex on the arm to maintain a minimum distance of one fist to the initial endoscope arm.

5.4.5.4 Adjust the Side with Two Arms

Flex the outer arm away from the inner arm (the arm nearest to the endoscope) to get it out of the way for initial adjustment.

Adjust the flex on the inner arm to maintain a minimum distance of one fist to the initial endoscope arm.

Go back to the outer arm and adjust the flex back toward the inner arm to maintain a minimum distance of one fist (Fig. 5.4).

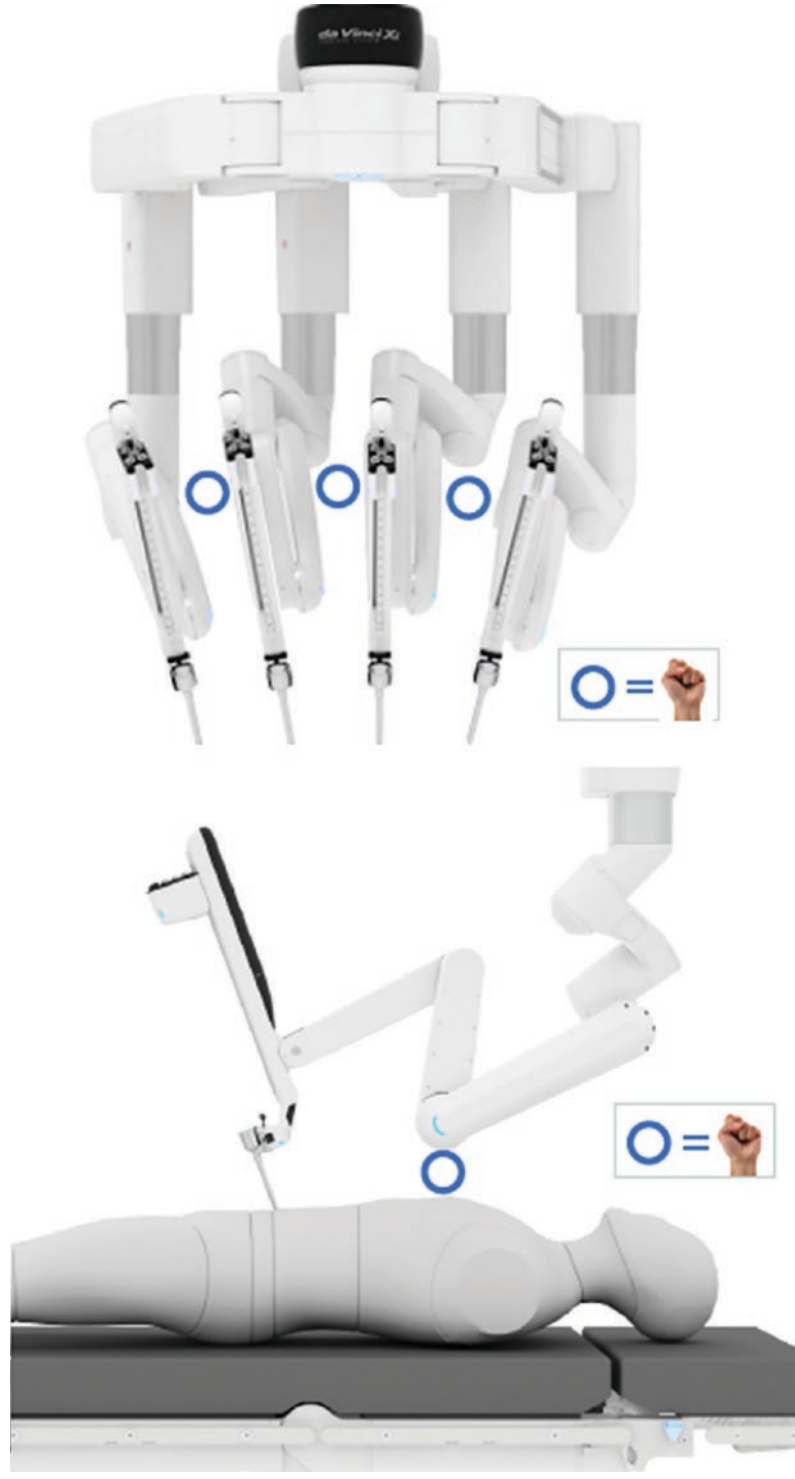

Fig. 5.4 Arm adjustments

5.5 Specific Configurations Based on the Surgical Procedure

5.5.1 Left Colectomy, Sigmoidectomy, and High Anterior Resection

Left colectomy, sigmoidectomy, and robotic high anterior resection are used for colon disease located in the left colon, sigmoid, and rectum.

Position: The robot cart is placed to the left of the patient (Fig. 5.5) who is in the supine position with open legs, in the Trendelenburg position (>10°), lateralized to the right (>10°). Before connecting the robotic system, the patient's position must be adjusted to ensure sufficient exposure of the surgical field. Subsequently, the operating table cannot be mobilized.

Trocar placement: For trocar placement, a line can be drawn from the right femoral head (lateral edge of the inguinal triangle) to the left midclavicular line, crossing the left subcostal border. Port 2 should be placed at the junction of this line with the middle line, this port being the initial one. Then we place 1, 3, and 4 at a distance of 8 cm between them. Finally, the assistant's port must be positioned as far as possible from the da Vinci ports and lateral to the right of the midclavicular line.

Mobilization of the splenic flexure: In order to mobilize the splenic flexure, it is necessary to mobilize the orientation of the robotic arms toward the upper left quadrant of the patient, beginning by adjusting arm 1 to the maximum possible flexion. The goal is to open up space between the arms to increase reach and avoid interference.

5.5.2 Low Anterior Resection, Tumors Located in the Pelvis

Low resection is used for colon disease located in the mid- and lower rectum.

Position: The robot car is placed to the left of the patient (Fig. 5.6) who is in the supine position with open legs, in the Trendelenburg position (>15°), with no lateralization and with the surgical table at the lowest possible height to avoid conflicts with the robot. Before connecting the robotic system, the patient's position must be adjusted to ensure sufficient exposure of the surgical field. Subsequently, the operating table cannot be mobilized.

Trocar placement: In this case, the initial port where the camera will go should be placed at the umbilical level. Port 1 on the left side, 8 cm from ports 2 and 3, port 4 on the right side to port 2, 8 cm from each other. The auxiliary port must be placed triangulating, as far as possible from the da Vinci ports between 3 and 4.

5.5.3 Right Colectomy and Extended Right Colectomy (Intracorporeal Anastomosis)

Right colectomy and extended right colectomy are used for colon disease located in the right colon and proximal transverse.

Position: The robot car is placed to the right of the patient, who is in the supine position, in the Trendelenburg position (>10°), lateralized to the left (>10°), and with the surgical table at the lowest possible height to avoid conflicts with the robot. Before connecting the robotic system, the patient's position must be adjusted to ensure sufficient exposure of the surgical field. Subsequently, the operating table cannot be mobilized.

Trocar placement: The first trocar should be placed 4–5 cm above the pubic symphysis. A line can then be drawn from port 1 to where the left clavicular midline crosses the left subcostal margin, placing ports 2, 3, and 4 at a distance of 8 cm from each other on the line. The auxiliary port should be placed triangulating, as far as possible from the da Vinci ports and lateral to the midline clavicular left (Fig. 5.7).

Another option would be chosen for localized tumors either in the hepatic flexure or in the transverse colon. In this case, we can draw a transversal line 3 cm higher than the pubic symphysis. Place ports 2 and 3 on the transverse line,

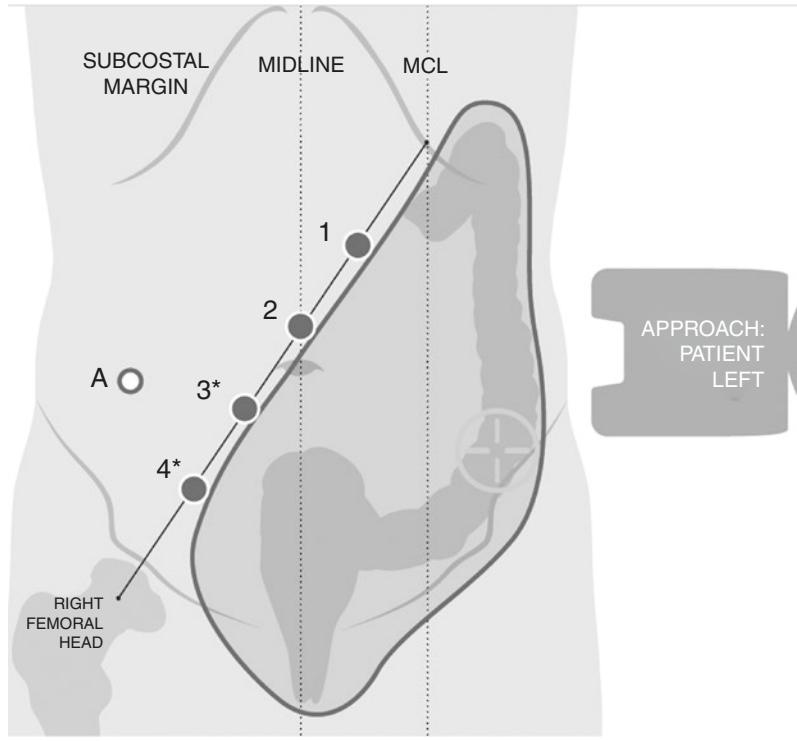

Fig. 5.5 Position: Left colectomy, sigmoidectomy, high anterior resection

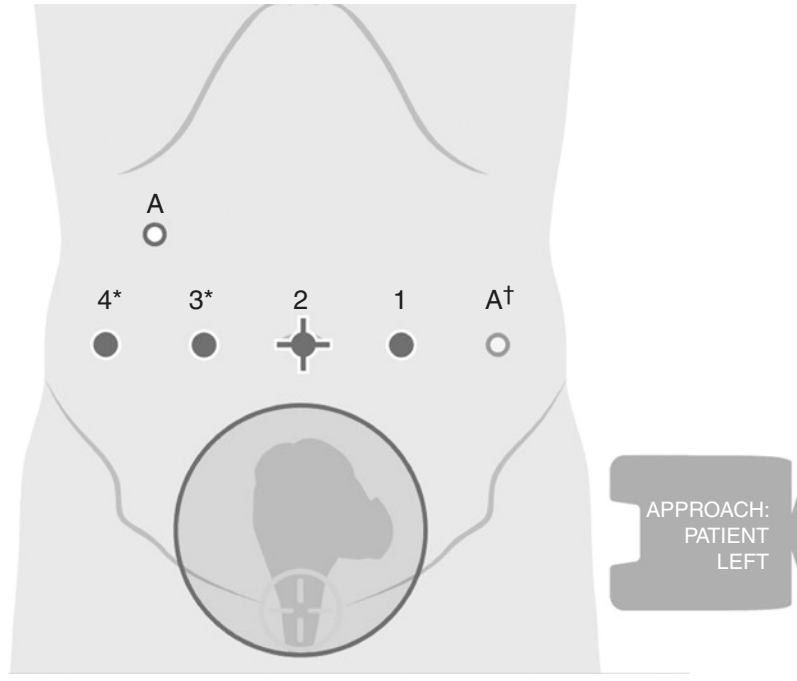

Fig. 5.6 Position pelvis

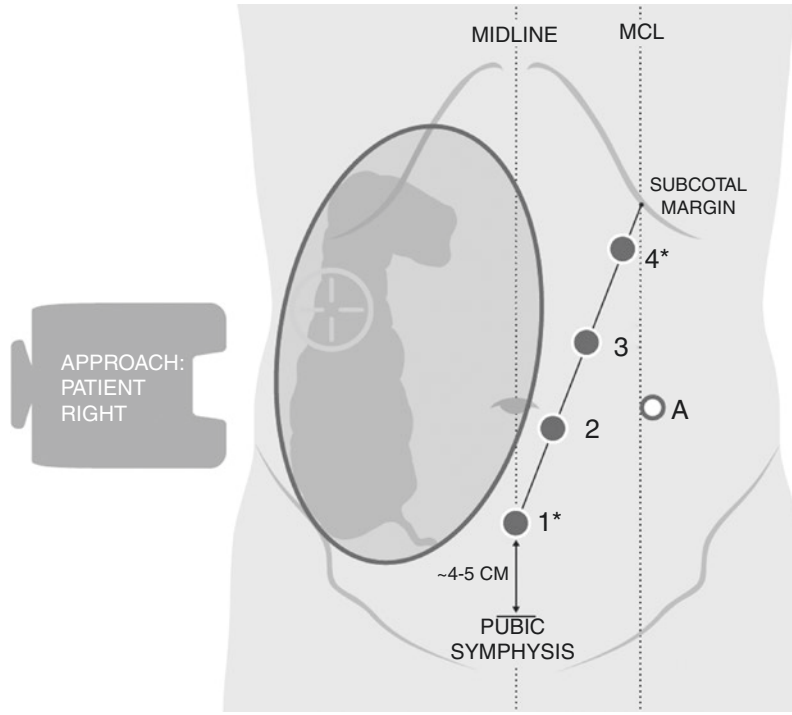

Fig. 5.7 Right colectomy option 1

equidistant to 6 cm around the middle line. Port 1 is positioned 6 cm right side to port 2; port 4, 6 cm left side to port 3; and auxiliary port 5 cm directly top and side to 4 (Fig. 5.8).

In this section, it is necessary to highlight the importance of the robot in extended lymphanectomy. Complete mesocolic excision was first described in May 2009 by Werner Hohenberger and his colleagues [8]. It arose from the concept of total mesorectal excision illustrated by Heald [9] and consists of sharp dissection of the visceral fascial layer from the parietal one, complete mobilization of the mesocolon with an intact fascia, and true central vascular ligation of the supplying arteries and draining veins at their origin. Current evidence suggests that this technique is associated with better specimen quality, lower recurrence rates, higher disease-free survival, and also higher incidence of intraoperative injuries and surgical morbidity. It has become the standard of care in some groups and is also performed in subjective, selected cases [10]. Several studies suggest that extended right hemicolectomy with complete mesocolic excision and D3 lymph node dissection is a feasible option and facilitated by robotic approach, which improves visualization and instrument dexterity [11, 12].

5.5.4 Segmental Colon Resections

Segmental colon resections can be used for diseases located in the transverse colon or at the splenic flexure.

Both robot position and trocar placement depend on the location of the tumor, being able to use a pelvic location or right, following the principles previously described depending on where the target anatomy is located.

5.5.5 Double Docking

Double docking is used when the surgical field is too large to be reached with single docking. After working toward the first target anatomy, the user undocks the da Vinci Xi, rotates its boom 180°, and docks again to the same ports. This enables reach toward the second target anatomy.

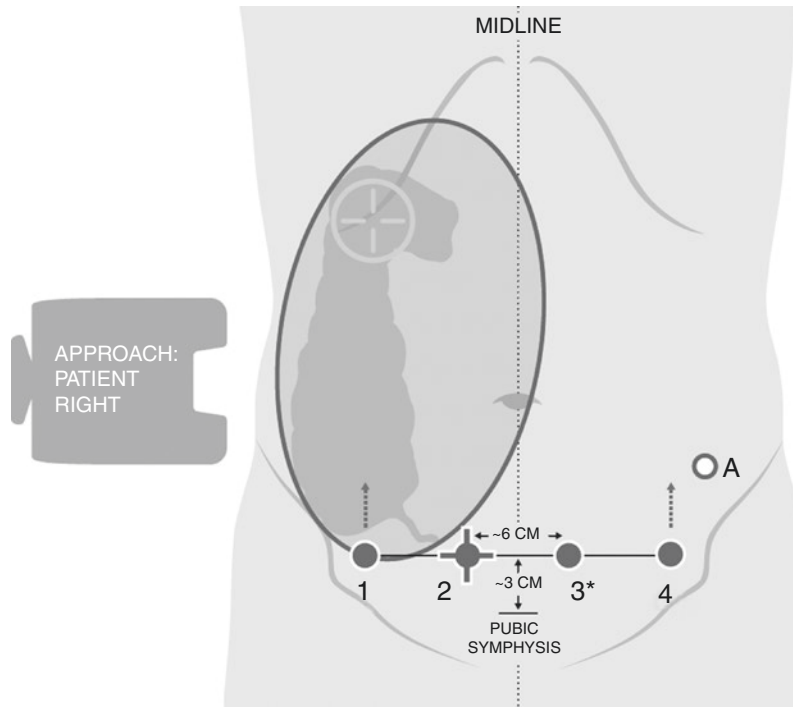

Fig. 5.8 Right colectomy option 2

It is used mainly:

- When the surgical field extends beyond two quadrants
- When the initial port of the endoscope is within the planned surgical field and is surrounded by most of it

5.5.6 Multi-Organ Resection

Local invasion and distant metastasis are common in patients with colorectal cancer and, therefore, multiple organ resection is an important measure for radical resection of colorectal cancer. Robotic surgery is also applicable in combined resection, although it should only be performed by experienced surgeons after consultation with a multidisciplinary team [6]. For locally advanced colorectal cancer with invasion of adjacent organs (mainly tumors that invade the urinary bladder, ovary, and uterus), robotic surgery can be performed safely. This type of surgery can also be applied in the synchronous resection of colorectal cancer with distant metastases, such as liver metastases.

In addition, during resections of different lesions, the same ports can be used to minimize trauma. Currently, hepatic robotic resection has been shown to be safe and effective, but the long-term effects of synchronous resection of colorectal cancer and hepatic metastasis lesions are yet to be assessed.

5.5.7 Combined Transanal Total Mesorectal Excision (taTME) and Abdominal Robotic Surgery in Rectal Cancer

Robotic-assisted colorectal surgery has been developed to help overcome technical difficulties and improve functional outcomes. Most of the published articles show that the real benefit of a robotic-assisted approach is in the mid- to low rectal dissection, with most studies using the laparoscopic approach for the abdominal part and a robotic approach to the pelvic dissection. Lately, transanal total mesorectal excision (taTME) was

developed in order to improve resection quality and facilitate dissection in the lower pelvis [13–16]. We think we can perform the rectal dissection combining taTME and robotic surgery [17]. The surgery is performed with two teams working concurrently (Fig. 5.9). The transanal team introduces a Gel POINT Path Transanal Access Platform (Applied Medical, Rancho Santa Margarita, CA, USA) in the anal canal. Three 12-mm trocars are inserted in the platform in a triangular position. A 3D camera with flexible tip (Olympus, Tokyo, Japan) is inserted through the inferior trocar. Pneumorectum is created at 15 mmHg with AirSeal insufflators (SurgiQuest Inc., Orange, CT, USA). During rectal insufflations and until the lumen has been occluded, the abdominal team clamps the sigmoid colon, preventing its proximal distension. An airtight purse-string suture is made 4–5 cm distal to the tumor to occlude the lumen and prevent tumor spillage. Then, rectal mucosa is tattooed with monopolar electrocautery to delineate the distal margin of resection. Full-thickness dissection is performed until the avascular perirectal plane is reached. In the abdomen, the inferior mesenteric vein is identified near the ligament of Treitz and transected. Following a medial-to-lateral approach, the sigmoid colon and intraabdominal rectum is mobilized robotically. Once the left ureter, gonadic vessels, and hypogastric nerves have been identified, proximal inferior mesenteric artery is divided and the splenic flexure is mobilized. The rectum and mesorectum are dissected from the surrounding pelvic structures, preserving the mesorectal fascia. Posteriorly, the presacral plane is identified and dissection is performed following the "holy plane," and these planes were followed laterally and anteriorly. Simultaneous dissection is performed by both abdominal and transanal teams until cephalad dissection achieved a "rendez-vous" near the midportion of the rectum. We demonstrate that concurrent abdominal robotic and taTME may be a quick and feasible option for safe and oncologically sound resection of low rectal cancer. taTME makes it possible to choose a distal resection margin under direct vision and avoid multiple stapler firings, associated with a higher risk of anastomotic dehiscence [14]. In our hands, taTME had a shorter operative time, similar achievement of oncologic resection principles, and lower early readmission rate than laparoscopic rectal resection [18]. We have found that transanal access has additional advantages during the pelvic dissection in men, patients with narrow pelvis or fibrotic mesorectum, and obese patients.

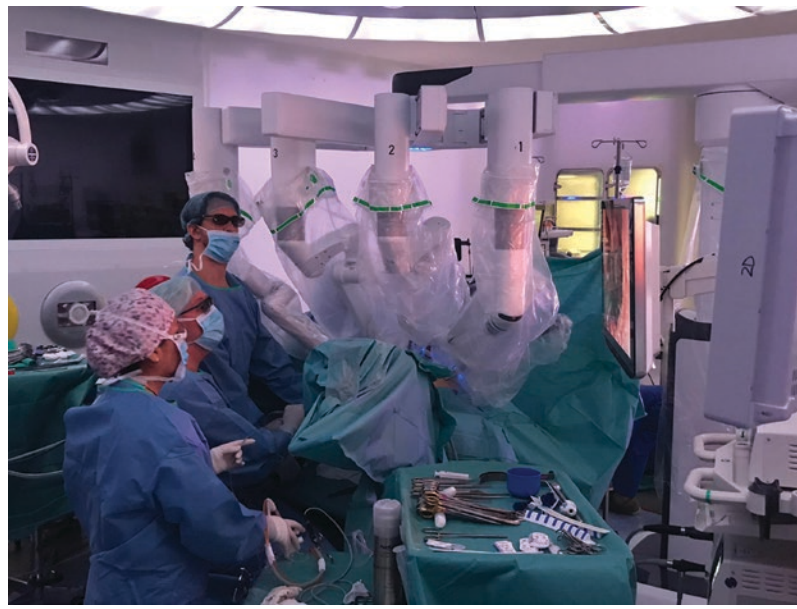

Fig. 5.9 TaTME + robotic abdominal approach. Hospital Clinic (Barcelona)

There are only few reports of combined abdominal and taTME approach in the literature. Gomez et al. presented results for five patients who underwent both robot-assisted abdominal and transanal dissections [19]. While being safe and feasible, operative time was long (range 270–450 min), not least because robotic abdominal and transanal surgeries were performed sequentially. Robotic technology with endo-wristed instruments and 3-dimensional high-definition imaging are of great help in overcoming the limitations of traditional laparoscopic transanal surgery.

Robotic transanal surgery is a newer approach to rectal dissection whose purpose is to overcome the limits of the traditional transabdominal approach, improving accuracy of distal dissection and preservation of hypogastric innervation [20]. An increasing interest on this new technique has raised, thanks to the excellent pathological and acceptable short-term clinical outcomes reported.

5.6 Training

Despite numerous advances in technology, surgical training has not yet experienced significant change in over a century. Residents have to acquire experience through intervention of real patients in a supervised system, making it rely completely on the number of patients available, which prolongs learning curves and compromises patient safety [21]. Robotic surgery is the perfect tool to acquire surgical skills and learn every surgical technique available through simulation.

Three-dimensional simulators and soft tissue models with force feedback technology are available for teaching purposes [22]. It is expected that these systems allow the acquisition of surgical skills in a reduced period of time and avoid human mistakes. With time, this applications will become a very important tool in the formation and accreditation of surgeons and will give objective parameters to evaluate surgical aptitudes [23].

Today, there are 2100 robots in the USA and 520 in Europe, including about 20 in Spain. Despite that, there are no formal training programs in robotic surgery. A program of the American Society of Colorectal Surgeons and Intuitive Surgical, Inc., allows residents to take a course of three days with animal and cadaveric experimentation. Urologists of North America and the UK have developed a curriculum based on virtual reality to acquire abilities in robotic surgery including orientation and motor and surgical skills. Also a 3-months program design by the European Society of Robotic Urology includes theoretical sessions and hands-on training.

The European Academy of Colorectal Robotic Surgery was funded in June 2014, coordinating 10 participating centers. Training includes system familiarization, intervention in animals and cadavers, and observation and participation in real cases. Apart from deciding whether robotic surgery is indicated or not, we can say minimally invasive surgery revolutions traditional surgical learning by highlighting communication and team work.

5.7 Robotic Surgical Systems and Future of Robotics

Robotic surgery or computer-assisted surgery is an interactive system so fast and intuitive that allows the computer to disappear from the surgeon's mind, sensing as real the environment generated by the system. Through virtual reality, the surgeon defines the maneuvers that the robot performs in the patient. The console-manipulator device can be placed in the same operating room, in a different place, or eventually in another city or country.

Robotic or remote tele-presence surgery is based on two fundamental concepts: virtual reality and cybernetics. Virtual reality achieves 3D immersion effects, navigation, interaction, and simulation in real time, thereby making real what the surgeon sees and touches. Cybernetics makes possible the movement digitalization, promoting the development of mechanically articulated parts programmed with motion degrees, cameras, sensors, information saving, and data-processing

devices capable of performing specific tasks called robots.

So far, tele-presence surgery uses slave robots that are not programmed to do any movement without the surgeons' command and, therefore, are completely dependent on their judgment, knowledge, and skills. It has a structure that resembles the anatomy of human arms and articulations, capable of imitating movements such as that of the shoulder, elbow, wrist, and fingers, but exceeding its natural range of motion increasing the degree of freedom.

Linda van der Bedem, researcher at Technische Universiteit Eindhoven, wrote an article in Science Daily about the development of a more compact surgical robot called Sofie that uses force feedback control [24]. Another ongoing research since 2010 is the development of an artificially intelligent surgical robot by a group of bioengineers at Duke University – a robot that is able to find a lesion in simulated tissue and guide a device toward the lesion to take samples or biopsies (Duke robot Biopsy guided by 3-D ultrasound).

Nevertheless, this race is not over as the development of nano-robots takes the lead. Nano-robots are robots that are of a cell's size and can be introduced into blood flow to eliminate cancer cells, repair tissues, or capture toxic radicals, among other uses.

Despite limitations, the obtained results are promising and it seems to be just a matter of time until robotic surgery becomes the gold standard for an important amount of surgical procedures.

We consider that objections robotic surgery has experienced in the past years are part of a natural path that every new technique has to overcome until it is able to prove that its benefits are justified. Not long ago, papers like this were written to compare and evaluate laparoscopic versus open surgery, with very similar considerations.

Although future is uncertain in many aspects of life, it seems to be full of exciting possibilities for robotic surgery. Every day, we witness new developments that bring surgery closer to the digital age showing us that future of robotics is limited only by imagination.

5.8 Take-Home Messages

- Robotic surgery is growing rapidly in the world and will possibly become a standard tool in the future.
- A good learning curve with a sufficient number of cases is very important.
- The robot is a particularly useful tool in the dissection of the rectum, especially in male patients, obese patients, and patients with large tumors.
- It should be reserved for experienced centers and surgeons with a high volume of cases.
- The use of robotic surgery is promising but still limited and still requires randomized studies.
- Large-volume tumors and the involvement of neighboring or distant organs do not represent a contraindication to perform robotic surgery.

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Robotic Flexible Endoscopes

6

María Rita Rodríguez-Luna,
Margherita Pizzicannella, and Silvana Perretta

6.1 Introduction

Technology has dramatically revolutionized our society and our way of living, continuously transforming the world around us. In medicine, robotic and digital innovations are substantially changing patient management and in particular therapeutic interventions. In surgery, robotic technologies contributed to increase dexterity, facilitate standardization, control potential risks associated with the procedures, and ultimately bring minimally invasive and precise operations to many more patients. Additionally, flexible endoscopy is replacing surgery in the management of an increasing number of diseases [1]. However, standard flexible endoscopes have several limitations such as poor stability and lack of triangulation and precision, precluding the execution of more advanced tasks such as tissue manipulation, dissection, and apposition. In addition, the architecture of the current scopes is archaic; the long distance between the handle and the tip, the lack of stability, the small size, and parallelism of the working channels do not allow triangulation and limit the use of sealing and suturing devices. The success and popularity of robot-assisted surgery and the appeal of no-scar, organ-sparing, and function-preserving endoluminal surgery have encouraged the design of systems which could overcome the limitations of current flexible endoscopes.

Robotic technology has in fact been applied to enhance both diagnostic and therapeutic endoscopic capabilities (Table 6.1). For diagnosis, efforts have been mostly focused on implementing scope navigation [2], tissue inspection, assessment, and patient comfort [3, 4]. The development of therapeutic robotic endoscopes has mainly targeted endoluminal and full-thickness resection of early gastric [5] and colorectal cancers [6], with the hope of performing translumi-

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Table 6.1 Endoscopic robotic platforms

Device	Phase	Certification status	Company	Visual	Additional information
Diagnostic robotic endoscopes					
Endotics endoscopic system	Commercially available Preclinical and clinical trials	CE trademark	ERA endoscopy SRL, Peccioli, Italy	2D	~ 200cm flexible length Self-propelling disposable
Aer-O-scope	Preclinical and clinical trials	FDA-approved CE trademark	GI view Ltd. Ramat Gan, Israel	2D	>150cm flexible length Frontal view and 360-degree omniview Electromechanical sensors of <60 mbar
Neoguide	Preclinical and clinical trials	FDA-approved	NeoGuide systems, Inc. Los Gatos, CA, USA acquired in 2009 by Intuitive Surgical, Inc. Sunnyvale, CA, USA	3D colon mapping	173cm flexible length
Invendoscopy E210 system	Preclinical and clinical trials	FDA-approved CE trademark	Developed by Invendo medical GmbH Weinheim, Germany, acquired in 2017 by AMBU A/S Copenhagen, Denmark	HD	~ 170cm flexible length Self-propulsion by electromechanical actuation Single use
Therapeutic robotic endoscopes					
Endoluminal assistant for surgical endoscopy (EASE)	Preclinical trials	CE trademark	IRCAD (Strasbourg, France) / Karl-Storz (Tuttlingen, Germany)/ ICube laboratory (Strasbourg, France)	2D	Master-slave, upgraded version of STRAS with a 53.5cm flexible length
Master and slave transluminal endoscopic MASTER	Preclinical and clinical trials	Awaiting CE trademark	Endomaster Pte Ltd., Singapore	2D	Mounted on a therapeutic double-channel endoscope
Flex robotic system	Commercially available in Europe Preclinical and clinical trials	FDA-approved CE trademark	Medrobotics Corp., Raynham, MA, USA	HD-2D or HD-2D/3D	50cm flexible length

FDA Food and Drug administration, *CE* Conformité Européenne marking certifies that a product has met EU consumer safety, health or environmental requirements. Some of the technical information is proprietary and was not available at the time of this publication. Companies have been contacted in order to clarify information

nal surgery keeping the patient whole, intact, and functional. Over the last few years, many digital robot-driven platforms have been developed and tested in preclinical and clinical studies [3, 7]. This chapter reviews the main robotic platforms developed so far and provides perspectives into the future of robotic-assisted flexible endoscopic therapy.

6.1.1 Diagnostic Robotic Endoscopes

The use of robotics in diagnostic endoscopy has the potential of improving diagnosis and overall outcomes for patients who may have gastrointestinal diseases. Artificial intelligence and computer-assisted diagnostic technologies could change the daily practice, supporting the physician in gaining access and identifying mucosal lesions, especially those which can be difficult to reach and detect and may be missed out. Robot-assisted devices also have the potential to change the experience of the patient undergoing a diagnostic procedure, such as minimal discomfort and short procedure time. This is particularly true for colorectal cancer screening. Although many imaging techniques have recently been implemented for colorectal cancer screening, such as virtual colonoscopy based on CT or MR imaging [8], conventional colonoscopy remains the reference standard because it allows both the visualization of the entire colonic mucosa and tissue sampling or resection whenever necessary. However, the pressure and forces needed to insert, advance, and orientate the endoscope are often correlated with patient discomfort. In addition, colonoscopy is technically demanding with a high learning curve, a high rate of missed neoplastic lesions, and some variability in the adenoma detection rate (ADR) among operators [9].

Robotic technology may also improve scope locomotion with a self-propelling [10] scope or electro-pneumatic propulsion [11, 12].

The *Endotics Endoscopy System (ERA Endoscopy SRL, Peccioli, Italy)* is a disposable self-propelling platform which incorporates a workstation, a disposable probe (Fig. 6.1), and a console. The proximal and distal clamping devices allow sequential anchoring with inchworm movement generated using an iterative process of mucosal suction, extension, and retraction. The system is CE-marked but not FDA-certified. The 3mm working channel allows to carryout biopsies and polypectomies [13]. Clinical studies report a 93.1% rate of complete colonoscopy in patients with prior incomplete

Fig. 6.1 Endotics endoscope (ERA Endoscopy SRL Peccioli, Italy). (With permission of Endotics (http://www.endotics.com))

standard colonoscopy [14] and a statistically significant decreased time to cecal intubation in the robot-assisted colonoscopy group (p=0.0007) [15].

6.1.1.1 Aer-O-Scope (GI View Ltd., Ramat Gan, Israel)

The *Aer-O-Scope* is a CE-marked, FDA-approved disposable 360-degree viewing self-propelling colonoscope which navigates through the colon with sequential inflation/deflation of two balloons [7, 10]. It consists of a disposable unit, a 19mm rectal introducer which is a hollow silicone tube with an external balloon, also called "stationary balloon," an hourglass-shaped balloon with an embedded endoscopic capsule, and a supply cable which provides light, suction, air, and water, and connects to the PC-based workstation (Fig. 6.2). The 360-degree "omniview" was designed to enhance polyps detection [16, 17]. The first human trial including 12 healthy volun-

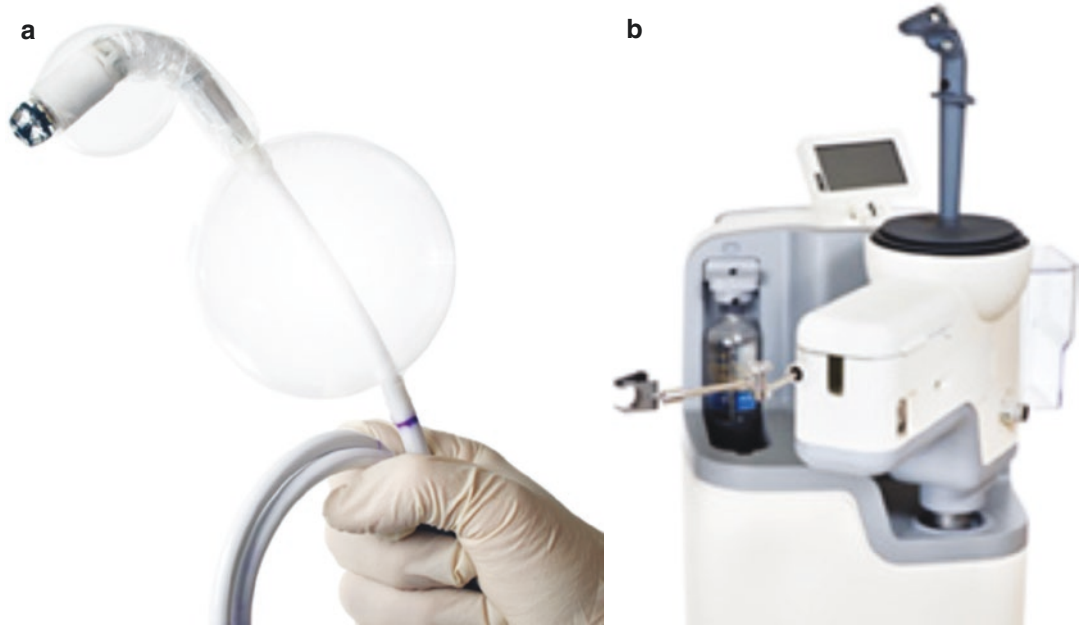

Fig. 6.2 Aer-O-Scope (GI View Ltd. Ramat Gan, Israel) (**a**). Disposable colonoscope: the pneumatic self-propulsion mechanism uses balloons and low-pressure carbon dioxide gas for self-propelled intubation. (**b**) The workstation provides all necessary elements to operate the disposable scanner. (With permission of GI View (www.giview.com))

teers failed to demonstrate superiority with 83% of cecal cannulations [7]. A more recent trial including 56 participants showed a higher cecal intubation rate (98.2% of patients) and a detection rate of polyps (87.5% of cases) [18].

6.1.1.2 NeoGuide™ Endoscopy System (NES) (NeoGuide Systems, Inc., Los Gatos, CA, USA)

This computer-assisted colonoscope was designed to avoid loop formation. It uses a fully articulated insertion tube built out of 16 articulated segments with two DOFs (degrees of freedom), each of which can be actively controlled. Upon insertion, the position and angle of the tip are encoded into a computer algorithm which automatically creates a three-dimensional map of the colon and then directs these segments to follow the path taken by the tip.

The first prospective non-randomized human clinical trial "PACE study" enrolled 11 consecutive patients. Cecal intubation was achieved in 10 patients, with a median time of insertion of 20.5 minutes [19]. NeoGuide™ was FDA-approved and acquired by Intuitive Surgical.

6.1.1.3 Invendoscopy™ E210 System, Invendo Medical, GmbH Weinheim, Germany, Acquired by Ambu Ballerup, Denmark

The Invendoscopy system was initially designed by Invendo Medical and acquired by Ambu (Ballerup, Denmark) in 2017. It was CE-marked in 2011 and FDA-approved in 2016. Invendo™ is a single-use computer-assisted 170cm colonoscope with a robotically assisted deflecting tip allowing for a 180-degree bending in all directions and a 3.1mm working channel [20]. The propulsion is powered by means of an "inverted sleeve technology." The tip is controlled with a handheld joystick [21, 22]. A clinical trial with the Invendoscope SC20 in 61 patients showed a cecal intubation rate of 98.4% with a median time to reach the cecum of 15 min (range: 7–53.5) [23]. The company expects to launch a sterile single-use colonoscope in 2021.

6.1.1.4 Robotic Endoscopic Capsules

Wireless endoscopic capsules (WEC) have been used since 2001 [24]. They allow to visualize the entire GI tract to diagnose conditions such as polyps, malignant lesions, and bleeding. WEC is a very attractive diagnostic tool since the capsule only has to be swallowed by the patient.

Self-propelling capsules and active endoscopic capsules are under investigation since they can add therapeutic capacity and intelligent data collection to the conventional purely diagnostic capsules. Technology integration remains challenging due to size constraints. Although most of these improved WEC are still in an experimental phase, Olympus Medical Systems Corporation and Siemens Healthcare designed a robotically driven steerable capsule with a magnetic guidance system. A dedicated control interface allows the navigation of the capsule system with five degrees of freedom. It has allowed to clinically test 53 gastroscopy patients with a technical success rate of 98% [3]. Magnetic field gradients have also been used to steer a tethered capsule platform with an embedded permanent magnet by Taddese et al. [25]. The capsule preserves all the functionalities of a traditional endoscope via the soft tether which allows the use of traditional endoscopic tools.

6.1.1.5 Artificial Intelligence (AI) and Deep Learning (DL) to Enhance Detection

Diagnostic endoscopy is a particularly fertile ground to apply artificial intelligence (AI) and computer-aided diagnosis (CADx) to enhance real-time lesion characterization and decision-making. Over the last decade, with the expansion of AI and in particular with deep learning (DL) computer vision, CADx has been increasingly used to detect polyps during colonoscopy. CADx has benefited from raised interests due to its ability to increase adenoma detection [26, 27]. AI algorithms include a convolutional neural network (CNN) trained to use as ground truth images annotated by experts and verified histologically. Once trained, these AI systems can detect colorectal polyps in real time. Wang et al. [28] published the first randomized controlled trial in 2019. The authors showed that the use of real-time automatic polyp detection systems (computed-aided detection (CADe)) based on deep learning could well increase the adenoma detection rate (ADR) with respect to the conventional colonoscopy group (0.29 vs. 0.20, $p<0.001$). The mean number of polyps and adenomas detected in the CADe group also increased from 0.50 to 0.95 ($p< 0.001$) and from 0.31 to 0.53 ($p< 0.001$) respectively, when compared to conventional colonoscopy. A multicentric randomized controlled trial by Repici et al. [29] also found that the CADe system was associated with a higher ADR with an odds ratio (OR) of 1.30 (95% CI: 1.14–1.45). Subgroup analysis showed that size, shape, and location of the polyps did not affect the performance of the CADe system. A brand-new AI system (GI-Genius, Medtronic) was trained and validated using a series of videos of 2,684 histologically confirmed polyps from 840 patients who underwent high-definition white-light colonoscopy. The AI system could detect all lesions with anticipation of the diagnosis as compared to the human reader in the vast majority of cases. The rate of false-positive results was negligible with nearly 100% sensitivity per lesions. This promising system will be tested in clinical studies [30]. Computer science has also been implemented to enhance diagnosis in WEC, since one of the main drawbacks in endoscopic capsules is the acquisition of a large volume of images, which requires intense clinician attention and time to avoid missing lesions during analyses. In this framework, CADx has been used to enhance bleeding [31], gastric ulcers [32], and polyps detection [33, 34]. The previously described GI-Genius technology will soon be incorporated into the endoscopic PillCam™ (Medtronic) to assist with polyp detection.

6.1.2 Therapeutic robotic endoscopes

Before examining specific technologies, it is essential to provide the framework for a change in such a magnitude. Since 2004, several endoscopic platforms have been developed for

advanced endoluminal and transluminal therapeutic procedures at the intersection of surgery and interventional endoscopy [35]. With the aim of replicating the founding principles of laparoscopic, namely magnified view, triangulation, stability, traction-countertraction, and tissue apposition, multiple research and commercial entities across the world worked on flexible systems. However, it became apparent that operating through the scope with purely a mechanical flexible platform [36–39], although possible, presented multiple challenges and that robotics would probably be needed to achieve surgical proficiency, consistency, and finesse. The first robotic platforms were mostly designed with manually driven instruments using a system called tendon sheath mechanism (TSM). These systems experienced difficulties with hysteresis, lost motion, and precision due to internal friction and backlash, and for this reason, they never reached the stage of clinical trials. Although most of these TSM-based platforms have been abandoned, they were undoubtedly the launchpad for new robotic systems improved by means of computer-aided design and motorized technology for robotic actuation.

We will focus on systems which have yielded CE or FDA clearance and which have reached clinical or preclinical testing.

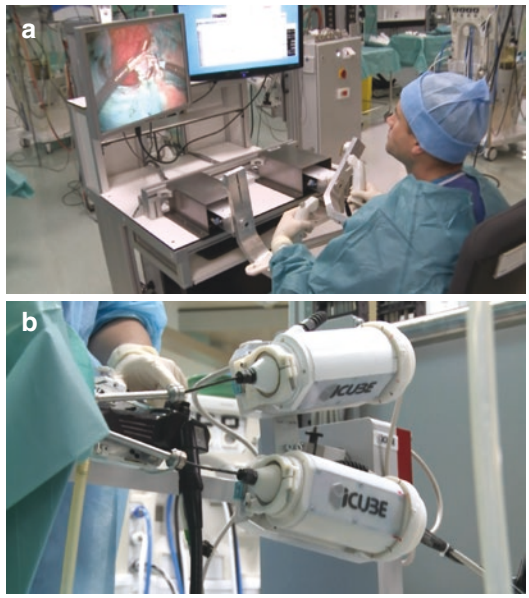

Fig. 6.3 (**a**). Tele-operation regarding the use of Single Access and Transluminal Robotic Assistant for Surgeons (STRAS) during ESD. (**b**) Translation rotation modules with the instruments inside

6.1.2.1 Endoluminal Assistant for Surgical Endoscopy (EASE): IRCAD Strasbourg, France, Karl Storz Tuttlingen, Germany; ICube Laboratory, Strasbourg, France

The Single Access and Transluminal Robotic Assistant for Surgeons (STRAS) (Fig. 6.3) was the first digital version of the Anubiscope™ (Fig. 6.4), [40] which was an upgraded endoscopic platform allowing to perform endoluminal

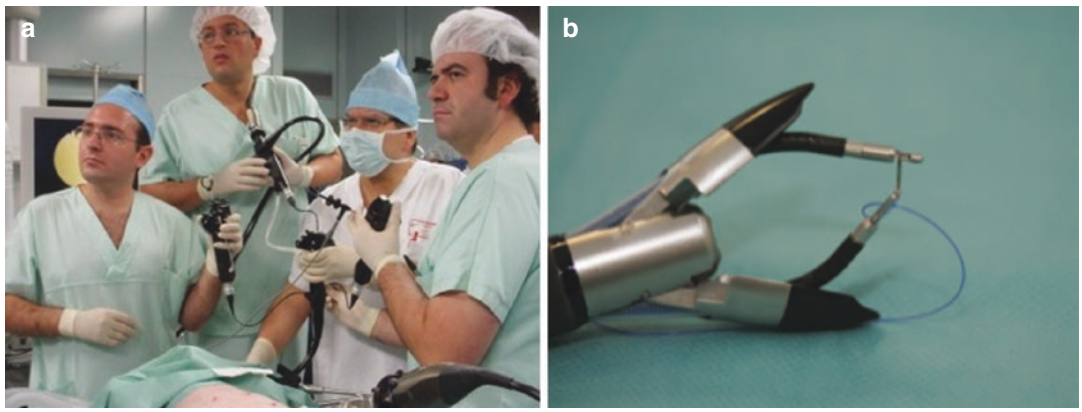

Fig. 6.4 (**a**) Anubiscope™ platform set-up: notice the need for multiple operators per procedure. (**b**) Endoscope's tip with the two arms fitted

and transluminal surgery. The Endoluminal Assistant for Surgical Endoscopy (EASE) (Fig. 6.5) is the latest robotic version with a total of ten DOFs. The system contains a mobile cart and a 53.5cm long detachable flexible endoscope. The endoscope has a shaft diameter of 16mm, two 4.3mm lateral working channels for flexible instruments, and one central 3.2mm working channel for conventional ones. The cart contains instrument modules and endoscope rotation/translation modules connected to the endoscope by a U-shaped arm. The "master-slave" configuration allows the operator to sit at the console controlling the endoscope and the robotic instruments by means of a joystick. The assistant can control the insertion of the endoscope and the third working channel for injection/suction purposes [41]. In 2017, Zorn et al. described the use of EASE in twelve ESDs during a preclinical trial [42], and two years later, the comparative preclinical trial was performed versus the conventional colonic ESD [41] (Fig. 6.6). The comparison was performed in the robotic group including surgeons with no previous experience in ESD or conventional ESD (experimental group) and endoscopic experts (>1000 ESDs) who performed ESD under conventional flexible endoscopy (control group). The results favored the robotic platform in terms of safety with a statistically significant lower perforation rate and a dissection speed of 57.05±29.42mm^2/min vs. 35.21±16.20mm^2/min (p = 0.049) for the control group and the robotic group respectively. EASE has recently obtained CE trademark and is ready for clinical trials.

Fig. 6.5 Master unit of the Endoluminal Assistant for Surgical Endoscopy tele-operation by Dr. Bernard Dallemagne during a colonic ESD in a preclinical trial; notice the open joysticks which allow for arms control

6.1.2.2 EndoMaster's Robotic System (Endomaster Pte Ltd., Singapore)

EndoMaster is a robotically driven instrumentation platform with "master-slave" configuration and nine DOFs. The system consists of two arms

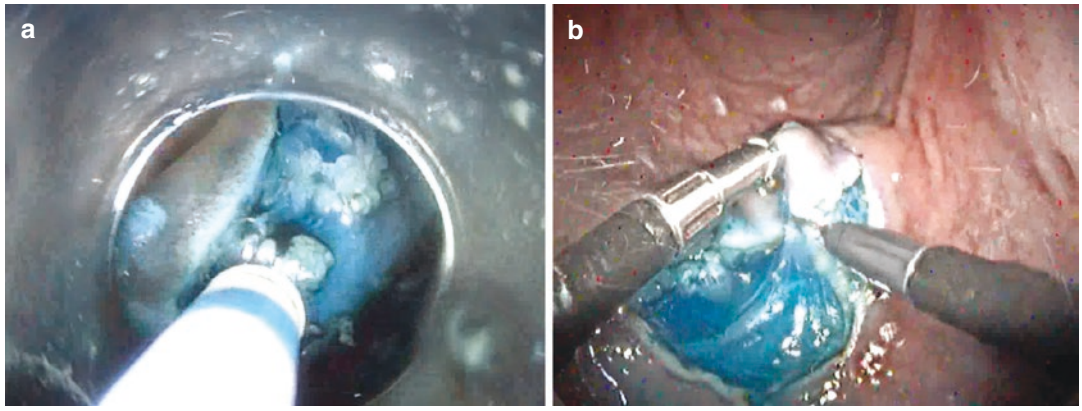

Fig. 6.6 (**a**). Intraoperative image of conventional colonic ESD in the preclinical study. (**b**). Robot-assisted ESD using the Endoluminal Assistant for Surgical Endoscopy (EASE) platform; notice the triangulation and effective mucosal traction

Fig. 6.7 (**a**) Setting of EndoMaster EASE system (Endomaster Pte Ltd., Singapore). (**b**) Endoscope and effectors for distal arms. With permission from Endomaster Pte Ltd. (http://www.endomastermedical.com)

attached to a conventional double-channel endoscope. The slave manipulator controls the end effectors, which includes an L-shaped monopolar diathermy and a grasper with seven DOFs, making it possible to apply a greater force than during conventional endoscopic procedures (Fig. 6.7). The latest version of the system provides haptic feedback [43] and interchangeable instruments.

EndoMaster has been used in preclinical studies in porcine models since 2010 [43, 44]. The clinical validation is underway for gastric, esophageal [45], and colonic ESD [46]. The EndoMaster versatility and dexterity have also been successfully tested during a preclinical trial for hepatic wedge resection through NOTES [47]. Robotic endoscopic suturing has also been described with the addition of the OverStitch™ system [44, 48]. CE marking and commercial availability are promptly anticipated for clinical use.

6.1.2.3 Flex Robot (Medrobotics Corp., Raynham, MA, USA)

The Medrobotics Flex® Robotic System is a snake-like robot consisting of a flexible endoscope with a stable semi-robotic platform. It has three parts: the Flex® Cart which carries the Flex® Base and Flex® scope, the Flex® console, and the mechanical 3.5 to 4.0mm single-use flexible instruments. The surgeon's console controls the instruments with haptic feedback [49]. Recently, the company created the upgraded system, the Flex® Robotic colorectal system, which provides a prolonged insufflation that is fundamental to GI tract interventions.

The initial clinical experience in head and neck surgery, including 70 patients, was published in 2018 [50]. Turiani et al. then conducted a preclinical trial comparing robotic ESD with the conventional approach. Their results reflected the higher effectiveness for 'en bloc' resection and lower operative times in the robotic group [51]. The system has been applied to transanal total mesorectal excision (TaTME). Carmichael et al. [49] reported their results in a trial including six human cadavers simulating mid-rectal lesions, achieving complete dissection and adequate peritoneal entry. The system allowed the proximal dissection up to 17cm from the anal verge, which is a major advantage over the robotic surgical system. However, the low rectal lesion could not be resected in two cadavers.

More recently, Paull et al. [52] compared the Flex® Colorectal Drive with the da Vinci Si™ system in 21 patients. Transanal full-thickness resections of rectal premalignant and early malignant lesions were successfully completed with both systems, without cancer recurrence. The endoscopic robotic system achieved a shorter operative time and a lower conversion rate, as it was more ergonomic for pelvic anatomy. A modified version of the Flex Robotic System, which could reach the upper gastrointestinal tract and proximal colon, is under development, and preclinical feasibility studies on full-thickness resection and suture of the transmural defect, as well as myotomy for Zenker's diverticulum have been described so far [53]. The first version of the Flex robot obtained FDA approval in 2015 and the Flex® Colorectal Drive obtained FDA approval in 2017.

6.1.2.4 ColubrisMX Endoluminal Surgical (ELS) System (ColubrisMX, Houston, TX)

The new endoluminal robotic surgical system manufactured by ColubrisMX is the first completely robotic endoluminal surgical system for upper and lower GI procedures. The key feature of the system is the Colubriscope, which is a flexible robotic overtube which allows navigation in the curved and complex endoluminal anatomy. The Colubriscope allows to access the interface for two fully articulated robot-controlled surgical instruments with 7 DOFs. A clinical prospective single-arm, open-label, multicenter feasibility study to evaluate the safety and efficacy of ColubrisMX ELS System in patients undergoing colorectal ESD is currently underway [54].

6.2 Discussion and conclusions

Robots have dramatically expanded diagnostic and therapeutic capabilities of endoscopes, and they extend the frontiers of science and technology in modern medicine. Although many advances have been made to improve robotic performance, this biotechnology applied to flexible endoscopy is still mostly under development or pending for clinical validation. The development of a flexible system capable of delivering a fully robotized procedure represents an outstanding technical and economic challenge. As a resul, despite the efforts made and the increasing number of companies targeting this field, the implementation of robotics in clinical practice is still not a reality, with the exception of some diagnostic platforms and CADx. Still, the potential benefits of flexible endoscopic robots are clear. It is apparent that flexible endoscopic robots can well disrupt the current endoscopic practice and that their clinical impact will be even more marked than their laparoscopic counterpart. While surgical robots may "*enhance"* the surgeon's innate capabilities but do not change the surgical procedure, the intended benefits of robot-assisted endoscopy are to *"enable"* new procedures, generating a freedom to operate for physicians who can "reach it all and see it all". It is a freedom which can transcend the limitations related to size, dexterity, and sensory perceptions, which restrain the use of current flexible scopes. Flexible robotic platforms have the potential to change patient experience promoting a rapid healing and a scarless surgery which will leave patients whole, intact, and functional.

Undoubtedly, the increased proficiency achievable with robot-assisted endoscopy will also have a positive impact on the learning curve and decrease inter-variability among operators, allowing more physicians to deliver endoluminal and transluminal organ-sparing therapies and allowing more patients to benefit from such therapies. Most likely in the near future, endoscopic diagnosis will be computer-assisted and capsule-based, and scope-based procedures will be reserved for interventional purposes only. Robotics and computer-assisted diagnosis will also directly impact the endoscopic workflow, allowing "solo" endoscopy, thereby reducing the number of operators, or home-based self-administered capsule exams, optimizing time and improving diagnosis and patient acceptance. Finally, the cost-effectiveness of these systems

will be evaluated once their use has been widely adopted, and as it happens for surgical robots, they will probably become more affordable over time.

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7 Robotized MIS Instruments: Filling the Gap Between Rigid Tools and Large Robotic Systems

Amir Szold and Nienke Warnaar

Current MIS instruments have limited degrees of freedom (DOF) and are not ergonomic. This results in severe limitations in performing simple, let alone complex tasks in surgery, holding many surgeons back from engaging in a variety of minimally invasive procedures, in different fields, like colon surgery, hernia repair, gynecology, and when MIS surgery is still not widely adopted in many parts of the world. Until recently there were only two categories of MIS instruments: conventional straight manual instruments and a large, console-based, robotic system. Surgical robotic systems (that are not truly robotic, but electromechanical systems, having no autonomous features) offer excellent enhanced articulation and very good 3D vision, but at substantial costs and logistic complexity [1].

Intuitive Surgical (Sunnyvale, CA, USA) initially developed "Mona," a robotic system which evolved from the telepresence machines developed for NASA and the US Army [2]. The first trial with this system was performed in 1993, on a mannequin containing pig intestines, and was followed by the first actual operation using "Mona" on a human in 1997 after substantial animal testing. In 1998 Intuitive was able to start the first human trials with their next and improved development, the da Vinci. That same year, the first commercial sale of a da Vinci was a fact. However, FDA clearance including full instrumentation for general surgery indications was not obtained until 2000.

Most initial trials showing a clear benefit of this da Vinci system were bench tests, done in controlled laboratory settings. Those trials demonstrated superior dexterity, precision, ergonomics, and learning curve for complex MIS tasks over the regular MIS instruments [3, 4], but the evidence that these metrics translate to an advantage in patient outcome or other measurements of performance in the clinical arena was far less convincing [5] and was demonstrated only in defined niches of clinical practice [6].

Today, a simple PubMed search of the term robotic surgery reveals some 21,050 citations including almost every single surgical speciality. Nevertheless, unlike urologists who massively adopted the technique of "robotic prostatectomy" after almost immediate published reports of significantly improved outcomes [7], most gastrointestinal surgeons are still reluctant to use the da Vinci system in everyday practice because no clear evidence of added benefit of using robot technology has yet been shown. The bulk of the system, practical concerns around the "docking" procedure, and, of course, financial issues remain as deterring factors.

Given the very high costs of these systems, the *cost* part of the cost-benefit equation becomes prohibitive, and unless either the *benefit* proves to

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be overwhelming, or the cost and logistic complexity are driven down dramatically, these devices cannot become standard in most operating rooms around the world.

Attempts to improve the surgeon's dexterity come in several categories:

1. Console-based systems, such as the da Vinci system, have become the benchmark for robotic systems. The motivation to separate the surgeon from the patient and create a remote surgery capability was driven by the original design by NASA and DARPA, which was aimed to enable treatment of patients in remote or hazardous environments required by space missions and operations carried out in contaminated areas. This dictated a large, heavy, and complex system that requires a bedside surgeon in addition to the console surgeon, and except for the ergonomic sitting position of the surgeon, the disconnection between the user interface and the surgical manipulator and vision system seems to have a limited added value. Recently introduced competing systems (Versius, CMR Surgical Ltd., Cambridge, UK/Dexter, Elemental Healthcare, Hungerford, UK/Senhance, TransEnterix Surgical, Inc., Morrisville, USA) that are commercially available or are close to the market have a similar design, with some variations. The common variations are separate arm units and a slimmer user console, but the fundamental configuration is substantially the same. When analyzing what features of the da Vinci robot are responsible for the improved performance in bench tests, it seems that the combination of additional degrees of freedom, stereoscopic vision, and a very good user interface are the core features. One study has even demonstrated that simply turning off the stereoscopic vision on the da Vinci system has dampened the performance dramatically both in novices and experienced surgeons [8].
2. Bed-mounted systems, with a design of robotic arms attached to the operating room table, are a potential configuration with no currently available systems on the market, although several companies had a good working prototype, like the DLR lightweight robot III (LWR III) (Institute of Robotics and Mechatronics, Munich, Germany). There are several potential advantages of this configuration: flexibility, when the number and positioning of the arms is not dictated and can be modified according to the procedure, and patient repositioning during surgery, which does not require undocking the system and can be done without interrupting the operating room workflow.
3. Handheld robotized MIS instruments are novel, small robotized instruments that enable articulation and the degrees of freedom similar to large robotic systems, while not attached to the bed or a platform but are freely operated by the surgeon's hand.

Since many high-quality 3D/stereoscopic visualization systems are currently available on the market, there is an opportunity to develop handy instruments that enhance the surgeon's performance at a much lower cost and combined with the visualizations system will create a "plug-and-play" robotic system, enabling the surgeon to customize the components to the procedure, the surgeon's skill, and the economic and societal environment in which the surgeon works and the procedure takes place.

Several reviews of this technology were published recently [9, 10]. Current mechanical articulating surgical instruments exhibit a wide range of user interfaces, wrist mechanisms, and uses; however, there currently is no clear consensus on what makes an articulated mechanical instrument easy to use. Some articulated mechanical instruments have reached the commercial market and others are under development. As articulated mechanical surgical instruments mature, they have the potential to impact the minimally invasive surgery market by providing some of the capabilities currently only found in robotic systems at a lower cost.

Table 7.1 summarizes all available mechanical and robotic laparoscopic instruments that can be found. We will focus however on the more market-ready instruments, the JAIMY®, the

Table 7.1 Summary of mechanical and robotized handheld laparoscopic devices

Device	Type	Instrument	DOF[a]	Market availability
FlexDex® (FlexDex Inc., Brighton, MI, USA	Mechanical	Needle holder	6	Worldwide
SILS® Hand (Medtronic, Minneapolis, MN, USA	Mechanical	Interchangeable	7	Worldwide
r2 CURVE (Tuebingen Scientific Medical GmbH, Tübingen, Germany)	Mechanical	Interchangeable	7	Available, mostly Europe
r2 DRIVE (Tuebingen Scientific Medical GmbH, Tübingen, Germany)	Mechanical	Interchangeable	7	Available, mostly Europe
JAIMY® (Endocontrol, Grenoble, France)	Robotized	Multifunctional	6	Available, mostly Europe
DEX™ Robot (Dexterite Surgical, Annecy, France)	Robotized	Interchangeable	7	Available, mostly Europe
HandX™ (Human Xtensions, Netanya, Israel)	Robotized	Interchangeable	7	Available, mostly Europe
Autonomy Laparo-Angle® (Cambridge Endoscopic Devices, Framingham, MA, USA)	Mechanical	Needle holder	7	Not available
RealHand® (Novare Surgical System, Cupertino, CA, USA)	Mechanical	Interchangeable	7	Not available
Kymerax® (Terumo Europe NV, Leuven, Belgium)	Robotized	Interchangeable	5	Not available

[a]*DOF* degrees of freedom

DEX™ Robot and the HandX™, and the most widely available mechanical instrument, the FlexDex®.

The FlexDex® (FlexDex Surgical, Brighton MI, USA) is based on a mechanical design, translating the movements of the forearm, wrist, and fingers to the tip of the instrument without electrical components [9, 11]. It provides articulated control and successfully enables suturing in limited spaces with 6 DOF. The tool frame is attached as a forearm brace, and with regard to limitations of this product, changing instruments may be challenging and time-consuming [8, 12, 13]. In addition, it is compatible with an 8-mm trocar only and the current instrument does not allow changing the end effector. Only a needle holder is available.

The JAIMY® device (Endocontrol, La Tronche, France) has a one-finger control of motorized movements and an ergonomic handle for improved surgical posture, evaluated and demonstrated to be significantly better in bench tests measuring skill and dexterity [14]. It is a 5-mm articulated reusable instrument, with an unlimited jaw rotation and speed control, providing an advantage under ergonomically difficult conditions [15]. The device has limited (6) degrees of freedom, with articulation on one plain only, which makes it easier to control but limits its functionality. In addition, it is currently available as a needle holder only and is connected with a cable.

The DEX™ Robot (Dex Surgical, Verrières-le-Buisson, France) is a robotized instrument with a grip-type handle, working independently from the shaft, resulting in better ergonomics for the surgeon's hand posture [16]. The end effectors are 8 mm, multiple use, and currently a needle holder, dissector, scissors, and a hook are available. The device has 7 DOF and is connected via a cable to a control box.

HandX™ (Human Xtensions, Netanya, Israel) is a lightweight, handheld device that translates natural hand motions into complex movements inside the patient during laparoscopy. The instrument is composed of a sophisticated user interface that enables unrestricted hand movement and a novel, motor-driven articulating tool that is controlled by the computerized interface. The system is connected to a power cord only, doesn't require any setup time, and can be easily moved between regular 5-mm laparoscopic trocars and perform complex motions in the surgical field with 7 DOF. In has been used on hundreds of patients so far, in multiple countries in Europe as well as in the USA and Israel. The operations included upper GI procedures (sleeve gastrectomies, paraesophageal hernia repairs, gastric bypasses), inguinal and ventral hernia repairs, cholecystectomies, hysterectomies, colectomies, prostatectomies, and nephrectomies. Like all other systems described, it is FDA and CE approved.

Articulating instruments increase the degrees of freedom of a device, and articulation is a critical feature to enable complex motion; however in handheld laparoscopic instruments, it may be harder to control for several reasons: first, in contrast to a rigid instrument, the articulating part of the device is disconnected from the proprioceptive system of the user, and there is a greater dependency on the visual information to close the feedback loop and enable precise control of the tip. For some surgeons, a 3D/stereoscopic visualization system can enhance the user experience and shorten the learning curve [17]. Second, the combination of an articulating tip with a handheld device (that moves inside the patient in an opposite direction due to the fixed entry point to the abdomen) requires getting used to, and adds additional motion complexity and mental load on the user. In some devices (HandX™), it is addressed by allowing the surgeons to customize the device to the procedure and the surgeon's skill level, by reducing the degrees of freedom. In another (JAIMY®), the device originally has less degrees of freedom and thus is easier to control initially. The learning curve with robotized instruments seems longer than with conventional laparoscopic; however, the quality of dexterity, i.e., force and impulse, was better in a recent though small study [18].

It is important to discuss the differences between mechanical devices and robotized ones. Mechanical devices require manual force to operate and in prolonged procedures may add to the

strain placed on the surgeon's hand, especially the wrist. More importantly, mechanical devices can only translate the surgeon's hand movements directly to the end effector, without potential modifications that may be necessary because of the type of procedure, patient characteristics, or surgeon's skill level.

A robotized instrument, especially one with significant "brain power," can serve as a platform that enhances the surgeon's capabilities exponentially. The device can have features that stabilize the surgeon's hand and scale the articulation or roll movement of the tip up or down, allowing for scaled dexterity that could be tailored to the specific task. Potentially, some of the tasks can become assisted or even partially automated once the device is co-driven by the surgeon and the onboard computer. In addition, robotized devices can measure forces involved in any type of motion and block or warn the operator from exerting excessive force in specific tasks or even provide valuable information about tissue characteristics, thus enhancing the safety profile of the device and procedures performed with it.

Furthermore, performance metrics can be stored and manipulated and, given that data on the surgeon and procedure are cross-referenced, may serve as a valuable database to improve results, assist quality control, and enhance training.

From a logistic point of view, a computerized device that connects to the hospital data grid can assist the hospital's inventory management and purchasing, instrument maintenance, and utility analysis.

Robotized handheld devices essentially have three major components: a user interface, a drive unit that includes motors and a computer, and end effectors. Different companies configure these components and the connectivity between them in various ways. In order to fully utilize the advantages of a handheld configuration, it makes sense to build the three components as independent components and use them as building blocks to build different configurations of the same basic technology. This way, one can use a robotized handheld device to drive a heavy-duty end effector, like a stapler, a 3-mm articulating instrument for pediatric surgery, or even a flexible endoscope. Deconstructing and reconstructing the three components can lead to a remote-controlled configuration, bed-mounted configuration, and a plug-and-play combination of several configurations all driven by the same user interface.

When looking into the functionalities of medical devices, one can find reference to other known industries; the same way most motorized vehicles, from a small car to a large truck, a tractor, and even a boat, use the same physical object, the wheel, and the same body movement to control them, it would make sense that different articulating, flexible, and catheter-based therapeutic devices will be driven by a similar user interface, using the same body gestures to achieve similar functionalities at the end effector.

Handheld devices have the advantage of an unmediated, bedside interaction between the surgeon and the patient. This can save an additional, experienced, bedside surgeon and allows the surgeon to better interact as a team leader or member and switch roles easily. This configuration also allows the use of as many devices as necessary, in regular operating rooms without a special infrastructure, moving them freely between entry points.

Computer-assisted interventions require a therapeutic active component, and the feedback loop is fed by a data feed component that can be a video feed, an imaging feed, or data from other sensors. In this regard, a console-based system has a big advantage, integrating all components into one system and allowing for a relatively seamless data flow to close the feedback loop. Handheld devices need a much more complex data acquisition system and the integration of data, lacking precise position data, and a plug-and-play configuration requires a lot more computing power and software-based data processing, but it is feasible and will require a longer development time and market acceptance.

Robotized handheld instruments have a great potential to fill the large gap between large, expensive systems and the simple, mechanical instruments used around the world to perform MIS, providing robotic-like functionality to every operating room every day. In the near

future, a growing number of procedures will be enabled not by big robotic systems but by small, smart instruments, with growing sophistication that will allow for wide acceptance to the surgeon's toolbox.

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8 The Role of Endoscopic Technology in Gastrointestinal Surgery

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8.1 Introduction and Historic Development

The history of endoscopy in the gastrointestinal (GI) tract demonstrates the early desire of physicians to explore the esophagus and stomach as well as the intestine to document findings, which may lead to a better information and a confirmed diagnosis. The latter is the "condition sine qua non" for an optimal therapeutic decision-making.

Surgeons have participated in the development of flexible endoscopy, since they are usually deeply involved in the decisions for patients with GI disease prior to surgery. Frequently important questions do emerge: Where exactly is the tumor located with respect to certain anatomical landmarks? Which GI surgeons use endoscopy as orientation during a procedure? How far is the distance between very important structures (nerve; vessel) and the resection line and tissue layer to be dissected? What options are available regarding the individual anatomy of a given patient, if the procedure cannot be performed as initially planned?

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Since diseases in the upper gastrointestinal tract, especially gastric problems, were a frequent issue among patients in the twentieth century, both internists and general surgeons were very keen to have a tool to more accurately explore the esophagus, stomach, and duodenum as well as the colon to solve diagnostic questions. Early on, only radiography could be of assistance. In the 1950s and 1960s of the last century, flexible endoscopic technology emerged and was integrated in clinical routine in the 1970s and 1980s [1–8]. Once established and used frequently by endoscopists, both gastroenterologists and surgeons, therapeutic ideas and components were added, leading to a new thinking and a whole new branch in GI medicine, i.e., interventional and therapeutic endoscopy [9–13]. This leads to important endoscopic techniques such as endoscopic hemostasis, ERCP and papillotomy, and endoscopic resections [9–13].

As a consequence, both gastroenterologists and surgeons have pushed the development of flexible endoscopy to an excellent diagnostic and therapeutic tool in the past decades. One of the best examples of transforming endoscopy-generated information into clinical advantage for the patients is the improvement in the management of bleeding gastroduodenal lesions based on endoscopic findings [14]. During emergency endoscopy an exact inspection of the ulcer crater helped to determine the probability of recurrent bleeding of the ulcer [14, 15]. This probability of recurrent hemorrhage was classified based on endoscopic visible characteristics of the bleeding

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lesion. Endoscopic hemostasis was performed in all cases of active bleeding. Ulcers with a big visible vessel stumps were operated early elective after an interval of intensive care, because definitive endoscopic hemostasis seemed not to be sufficient. This concept decreased the operation frequency of bleeding gastroduodenal ulcers in the 1980s and decreased mortality of bleeding ulcers [14–18]. Emergency endoscopy not only enabled an accurate diagnosis but also provided a prediction and prognostic judgment of recurrent bleeding. This gave the surgeons valuable information on deciding for further operative or conservative treatment. Therefore, emergency endoscopy fulfilled three previously unmet needs: (1) localization of the bleeding lesion, (2) possible hemostasis, and (3) prognostic interpretation of the stigmata of the lesion, transformed in surgical decision-making.

Since the introduction of endoscopy in diagnosis and treatment of gastrointestinal bleeding in the early 1970s, emergency endoscopy has changed the therapeutic concept of this disease. At first the task of emergency endoscopy was limited to location of the bleeding site. Later endoscopic hemostasis was established in many hospitals. In addition, preselection of patients who will benefit from surgery has become possible by endoscopic means. These factors have reduced significantly mortality due to GI bleeding.

The important issue here is the ability of the surgeon to use actual endoscopic information for modifying surgical therapeutic decision-making at the moment, when this is needed for the patient's advantage. Therefore, GI surgeons should be integrated in the interpretation of endoscopic findings, which is important for further decisions [14–18].

Today, many flexible endoscopic therapeutic procedures have been developed by gastroenterologists and surgeons, which have even totally or partially replaced traditional surgery for these indications such as endoscopic resection of early cancers in the esophagus and peroral endoscopic myotomy (POEM) in esophageal motility disorders [19]. Foregut surgery is involved in the therapeutic spectrum of gastroesophageal reflux disease (GERD), esophageal motility disorders such as spasm and achalasia, esophageal cancer, Barrett's esophagus, gastric cancer, obesity and several gastric and gastroduodenal functional disorders such as delayed gastric emptying, and gastric outlet obstruction [13, 20]. For all these entities laparoscopic surgical procedures are established since years and have been further developed toward endoscopic techniques [13, 18–21].

In the past years a substantial part of these laparoscopic procedures have been partially replaced for certain indications by flexible endoscopic procedures [11–13, 17–22]. Some endoscopic techniques have almost replaced their laparoscopic counterparts such as myotomy in esophageal motility disorders by POEM; esophagectomy for early esophageal cancers by endoscopic resections, gastric, duodenal, and colon resection for mucosal tumors, and cancers throughout the GI tract by endoscopic submucosal dissection (ESD); as well as various endoscopic procedures for obesity [11–13, 17–22]. These procedures are performed by specialized endoscopists with gastroenterologic and surgical background [11–13, 17–22].

8.2 The Role of Flexible Endoscopy in General and GI Surgery

8.2.1 Diagnostic Endoscopy

Endoscopy has a role in surgical management of GI disease in several dimensions. Some diseases can be diagnosed primarily best by endoscopy such as malignomas of the GI tract. Furthermore, in functional GI disease such as GERD and achalasia, endoscopy can reveal a typical diagnose-specific picture within the esophagus and stomach, helping substantially in establishing the final diagnosis [23–26]. But even in functional GI disease with no specific alterations inside the GI tract or even without any endoscopic visible alterations whatsoever such as functional dyspepsia, the information harvested from upper GI endoscopy is essential and very helpful in excluding certain disorders and diseases, which will

allow for enclosing the correct diagnosis more easily. Therefore, endoscopy is a mainstay in the diagnostic management of GI disease for gastroenterologists and GI surgeons.

A special issue is the diagnostic assessment of patients with previous surgery and the subsequent changes in anatomy and function, which may be important or even the reason for another revisional surgery [24]. Endoscopy in these patients may be essential (1) in finding possible reasons for the problems after the initial surgery and (2) in detecting previously unknown alterations in anatomy and/or function in the GI tract, possibly changing the operative tactics or even strategy as planned. These findings may be very subtle that will only be evident for very experienced surgeons and endoscopists, underlining the importance of a surgical participation in the investigation. It is important that the GI surgeon has a chance to explore the GI tract herself or himself in order to have a chance to appreciate subtle alterations such as a deviation of the esophagus and/or cardia after previous antireflux surgery, which may not be recognized by a gastroenterologist not focused on anatomical perspectives, or vice versa, a subtle change in mucosal appearance, which may escape the GI surgeon, while a focused gastroenterologist is trained especially on these things [24, 26–28].

Clinical experience has shown that these endoscopic investigations should be performed by the involved surgeon and/or her/his team to generate this endoscopic knowledge and insight directly without any loss of information or risk of altered interpretation.

Table 8.1 Role of endoscopy in GI surgery

Diagnostics:
Routine within diagnostic work-up
Special diagnostics after previous surgery:
Finding hints for malfunction
Finding subtle alterations in anatomy
Intraoperative endoscopy:
Verifying anatomy (e.g., locating the cardia during multiple redo-surgery and helping during adhesiolysis
Identifying anatomical important structures such the LES or an esophageal diverticulum
Localizing a small tumor in the colon or small intestine
Assisting in leak control after performing an anastomosis
Performing endoscopic therapy as part of a rendezvous maneuver
Identifying a leak intraoperatively
Therapeutic role:
Identifying a postoperative leak and treating it initially by cleaning the site with debridement and rinsing (drainage)
Identifying and closing a leak after a surgical procedure by tissue sealant or by suture
Treating a leak by endo-sponge therapy
Endoscopic hemostasis in a postoperative hemorrhage from a surgical suture site
Covering a leak with an endoscopic placed stent
Endoscopic placement of drainage
Any other advanced method of interventional endoscopy to perform the adequate therapy

8.2.2 Endoscopy and Specialized GI Surgery

As demonstrated in Table 8.1, there are multiple tasks for endoscopy in specialized GI surgery. These indications can be performed by gastroenterologists; however it is important for the clinical experience of specialized GI surgeons to gain this experience in flexible endoscopic procedures themselves [29, 30]. Only then the ability to establish a critical judgment about the potential of endoscopic findings, the critical judgment of establishing the indication for an endoscopic intervention in the process of surgical decisions and therapy, and also the critical judgment of leaving the necessary endoscopic procedure better to a high-end endoscopist and gastroenterologist can grow in a surgeon's mind and experience [31]. As a consequence, it is of utmost importance to have GI surgeons involved in these procedures and go through adequate training themselves to gain sufficient proficiency [31].

Unfortunately, there is few evidence generated in the past decades emphasizing these points, but rather the experience and impression of those surgeons that have gone through both pathways of endoscopy and surgery, especially minimally

invasive surgery [31–38]. Those GI surgeons with both educations are sure that they are having improved their skills and judgments by performing both disciplines, endoscopy and surgery. There is some evidence that the ability to gain proficiency with image-related procedures is connected and that correlations in gaining experience exist [39].

The armamentarium of a GI surgeon is larger with the knowledge about the potential diagnostic and therapeutic alternatives, which can be provided by flexible endoscopic technology. The latter is important, if she or he is faced with a clinical or intraoperative situation, in which these alternatives may be worth or even necessary to consider.

The evident connection between endoscopy and GI surgery is intraoperative endoscopy, which is very often indicated in minimally invasive surgery, since the haptic experience when exploring the intra-abdominal cavity is limited, and therefore an endoscopic assistance can be of advantage.

Table 8.2 provides an overview on some studies regarding intraoperative endoscopy and the clinical experience in different institutions [32–38]. An important indication is identification or confirming of anatomical structures during revisional minimally invasive surgery. A frequent indication of intraoperative endoscopy is the identification of the cardia during laparoscopic redo-antireflux surgery. Figure 8.1 demonstrates this situation after dissection of the hiatal region and the distal esophagus. The identification of the precise location of the lower esophageal sphincter is important to identify a possible short esophagus. Flexible endoscopy will help identify the esophagogastric junction from intraluminally, which can be correlated with the laparoscopic view and the location with respect to the hiatal level.

8.2.3 Endoscopy Integrated in General and GI Surgery

In the United States, endoscopy has become one of the mainstays in the practice of a general surgeon as published recently [40, 41]. In an overview on the workload on a general surgeon and

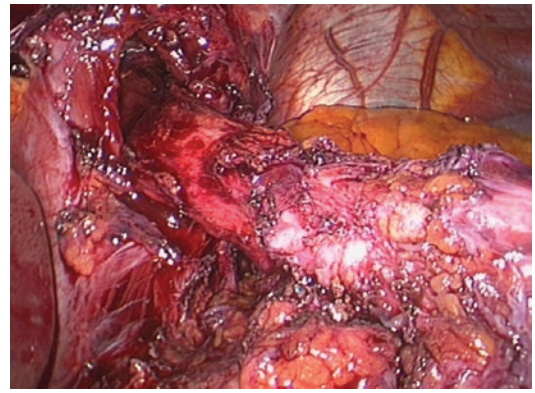

Fig. 8.1 Intraoperative view of the hiatal region and the cardia, as scoped simultaneously showing the intraluminal characteristics of the lower esophageal sphincter (narrowing and change toward gastric folds) as a reference to the intra-abdominal, laparoscopic view of the cardia in a field of dissected adhesions, which does not allow for a precise identification of the esophagogastric junction

Table 8.2 Overview on clinical experience with intraoperative endoscopy

Author (year)	n	Identification of anatomy, localizing lesions	Mechanical assistance	Leak test
Strodel (1984)	92	81	11	0
Zmora (2002)	57	57 lesion localizing 66% change of concept	0	0
Mihara (2004)	10	10 Bleeding localizing	0	0
Park (2005)	33	33 cancer localizing	0	0
Sekhar (2006)	340	0	0	340
Wilhelm (2008)	98	98 tumor localizing	0	0
Fuchs (2017)	132	78% identifications and localizing	3%	18%

practice patterns, it was shown that the number of endoscopic procedures has doubled from 1999 to 2011 [42]. In rural areas endoscopy has become the most commonly performed procedure by general surgeons. These facts require an adapted step in endoscopic education for surgeons [41, 43].

The Board of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) has promoted several activities in the past decade to stimulate both clinical activities and education in flexible endoscopy for surgeons such as the FES program (FES™ = Fundamentals of Endoscopic Surgery), an education program and test of knowledge and skill in flexible gastrointestinal endoscopy [40, 41]. In addition, the American Board of Surgery (ABS) has initiated the Flexible Endoscopy Curriculum (FEC) [41]. Studies have been performed to evaluate the current situation to compare the test results for general surgeons as well as for GI surgery fellows [41]. The data shows that training in flexible endoscopy could be improved for general surgeons to pass the FES examinations.

A recent study on surgical trainee performance on laparoscopic and flexible endoscopic simulation showed an interesting correlation [39]. Laparoscopic procedures and flexible endoscopic procedures are both image-based and usually require more training to gain sufficient proficiency compared to an open-surgical technique. In this study senior surgical residents were tested by laparoscopic suturing tasks based on Fundamentals of Laparoscopic Surgery (FLS™) and an endoscopic skills training program. There was a significant correlation between participant's skill in simulated laparoscopic suturing and simulated endoscopic skills [39]. This may imply some shared competency between the two techniques.

Flexible endoscopy should be an integral part of surgical education, especially in specialized GI surgery, since the competency of this technology is required for the diagnostic and therapeutic management in GI surgery [40–45].

8.3 The Controversies Between Gastroenterologists and GI Surgeons

Flexible endoscopy has become a political issue especially in Europe between gastroenterologists and gastrointestinal (GI) surgeons, which limits the full exploitation of this great technology for the benefit of patients with GI disease. History of the development of flexible endoscopy and the distribution of flexible endoscopy within the different disciplines shows substantial variations among different countries and even also among different areas and hospitals. The initial drive to use endoscopy was distributed among internists and general surgeons, which is nicely demonstrated by the early publications about the initial experience with flexible endoscopy [5–11]. With advancement of specialization in medicine, it was a natural development that emerging specialists in gastroenterology would focus on gastroscopy and colonoscopy. For the same reason, the specialization of GI surgeons and furthermore upper-GI surgeons and colorectal surgeons was also focusing on their respective endoscopic tool to cover their special organs also endoscopically.

In the United States this trend has continued over the decades, and the current situation shows a distribution of endoscopic activities in all subspecialties, even among general surgeons [41–46]. In Europe the development is characterized by severe differences in the different countries. Figure 8.2 shows the distribution of flexible endoscopic activities among the two disciplines, gastroenterology and GI surgery, in different countries [38].

In Western European countries obviously gastroenterologists have had the power to occupy these positions and keep surgery out. There is a controversial discussion, whether this is of advantage for the patients or just for the gastroenterologists. In some countries (e.g., in Sweden), the activities are more or less shared between the two disciplines and depend more on the local historic development. In these centers and countries, GI surgeons would get involved, and they have

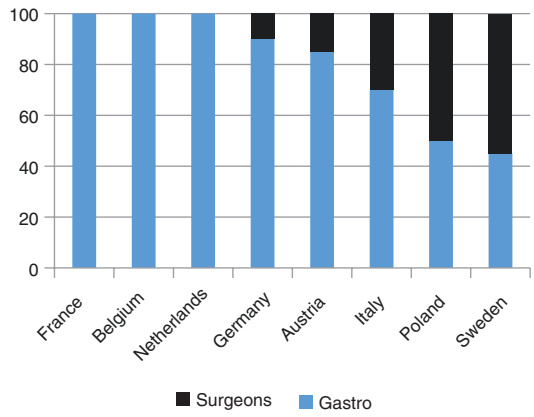

Fig. 8.2 Distribution of endoscopic activity in different European countries

the freedom to develop a large experience and a certain excellence to keep up the referral patterns for endoscopic cases [47]. In other countries flexible endoscopy is not allowed for surgeons and any attempt to start is inhibited.

In some institutions the cooperation between GI surgery and gastroenterology departments has been a success, which usually results in shared endoscopic activities, education, and research resulting for all parties including patients in a win-win-win situation [48, 49].

During the era of natural orifice transluminal endoscopic surgery (NOTES), a number of projects around the world were initiated, combining the forces of gastroenterology and GI surgery to work on these projects and cooperate on different experimental and clinical models [50, 51]. In very few institutions the involved department leaders and managers have even succeeded in creating an interdisciplinary department of endoscopy with residents and fellows from both participating departments, which seems to be a favorable solution.

For GI surgeons it is important to be able to develop endoscopic understanding and skills, the possibility to request at any moment during an operation flexible endoscopic assistance, for example, to locate a tumor, to better interpret an anatomical alteration during revisional surgery, and/or to assess an anastomosis with a leak test. The latter may be of direct advantage for the patient, as shown recently, and must not be time-consuming [52]. Therefore GI surgeons must have the organizational power to integrate this in their schedule at their preference and not have to wait, until somebody from a different department has the time to assist in the operating quarters. Furthermore, it would be very time-consuming and financially unfavorable, if a gastroenterologist-endoscopist would have to interrupt her/his usually tight schedule in a daily endoscopy program to spend sometimes an hour in the operating room helping a GI surgeon to clarify anatomical alterations. The latter task could be better taken over by a learning surgical resident or fellow that is in need for more endoscopic exposure and experience to learn how flexible endoscopy can be used for the advantage of patients in GI surgery.

8.4 The Requirements of Endoscopic Training for Specialized GI Surgeons

The necessary requirements and endoscopic procedures in GI disease are clearly demonstrated in *The SAGES Manual of Flexible Endoscopy* [31]. The content shows an overview in details about all aspects of learning and performing flexible endoscopy in general and GI surgery. Basics of diagnostic esophagogastroduodenoscopy and colonoscopy are demonstrated as well as all steps for emergency endoscopy and endoscopic hemostasis. Furthermore all interventions of therapeutic endoscopy can be viewed such as endoscopic tissue sampling, percutaneous endoscopic gastrostomy (PEG), endoscopic stenting, balloon dilation, foreign body retrieval, Botox injection, endoscopic retrograde cholangiopancreaticography (ERCP), endoscopic ultrasound (EUS), pancreato-biliary disease management, endoscopic radiofrequency ablation (RFA), endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), endoscopic resection (ER), endoscopic full-thickness resection (EFTR), peroral endoscopic myotomy (POEM), peroral pyloromyotomy, endoscopic GERD therapy, and endoscopic bariatric procedures.

Many of these techniques have replaced in the past 20 years several surgical procedures or have at least widened the therapeutic spectrum in GI disease.

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9 Indication, Technique, and Results of Endoscopic Cricomyotomy

Guido Costamagna, Pietro Familiari, and Rosario Landi

9.1 Introduction, Etiology, Epidemiology, and Pathophysiology

Zenker diverticulum is a hypopharyngeal, acquired, pulsion, false diverticulum that develops in an area of weakness of the posterior hypopharynx known as the Killian triangle. Killian triangle is located in the hypopharynx and delimited by two very strong pharyngoesophageal muscles, the horizontal fibers of the cricopharyngeal muscle and the oblique fibers of the inferior pharyngeal constrictor.

Zenker diverticulum was first recognized and described in the second half of the eighteenth century by the British pathologist Abraham Ludlow. After an autopsy performed on a 50-year-old male patient who regurgitated undigested food and died after an episode of "obstructed deglutition," Ludlow observed the abnormality of "pharyngeal preternatural bag, wide sac reaching down into thorax." Ludlow eventually published the observation in 1767 after presenting it to the Royal Society of Physicians where he described it as an esophageal hypopharyngeal diverticulum [1].

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However, only in 1874 the German physicians and pathologists Friedrich Albert von Zenker and Hugo Wilhelm von Ziemssen made a more detailed and precise description and hypothesized a possible etiopathogenesis. Since then, the name of Zenker is chiefly associated with the pulsion diverticula of the hypopharynx [1].

Zenker diverticulum is different from other diverticula of the upper part of the esophagus and especially from the Killian-Jamieson diverticulum, an outpouching of the lateral pharyngoesophageal wall. This pulsion-type diverticulum protrudes through a muscular gap in the anterolateral wall of the cervical esophagus distal to the cricopharyngeal muscle, named the Killian-Jamieson space [2].

The pathophysiology of the Zenker diverticulum has not yet been completely understood. However, it is generally accepted that the significant increase of the intrapharyngeal pressure and the consequent protrusion of the mucosa through a *locus minoris resistentiae* (the Killian dehiscence) is caused by an inadequate relaxation of the cricopharyngeal muscle (and subsequent incomplete opening of the upper esophageal sphincter) during the swallow-induced contraction of the lower pharyngeal constrictor muscle. The cause of this swallowing disorder and miscoordination is largely unknown.

Achalasia or cricopharyngeal spasms, cricopharyngeal incoordination, and congenital weakness have been implicated [3, 4].

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Gastroesophageal reflux may lead to esophageal and cricopharyngeal spasm and may have a role in Zenker diverticulum creation. Gastroesophageal reflux would induce a dyskinetic-hyperkinetic reaction that can involve the upper esophageal sphincter and the cricopharyngeal muscle. Furthermore, gastroesophageal reflux has been observed in up to two thirds of the patients with Zenker diverticulum [5].

Zenker diverticula most commonly present in middle-aged and elderly individuals: diverticula are extremely rare under the age of 40 [6], but more frequent during the seventh and eighth decades of life, with a 1.5-fold male predominance [7].

There is a certain geographical variation in the prevalence of Zenker diverticulum, being higher in Northern than in Southern Europe and higher in the United States, Canada, and Australia than in Indonesia and Japan [6, 8].

Even if the real prevalence of the disease is unknown, because many patients with diverticula remain asymptomatic, it is estimated that the prevalence among the general population is between 0.01% and 0.11% [8].

As development of cricopharyngeal motility disorders and Zenker diverticulum is directly related to aging, the prevalence of Zenker diverticulum is expected to increase due to the increased aging of population [7].

9.2 Symptoms, Clinical History, and Diagnosis

Progressively worsening oropharyngeal dysphagia, both for solids and liquids, is the predominant symptom associated with Zenker diverticulum. Even if small diverticula can be occasionally responsible for very severe symptoms, because the incomplete relaxation of the cricopharyngeal muscle may lead to severe outflow obstruction, usually the worst clinical presentations are in patients with large diverticula. In patients with large diverticula, both the nonrelaxing cricopharyngeal muscle and the extrinsic compression from the enlarged and fulfilled pouch itself are likely to explain the dysphagia experienced by patients [7, 9].

In these cases, patients may experience a kind of "delayed" dysphagia. Swallowing of solids is relatively normal at the very beginning of meal, and dysphagia almost abruptly occurs with the third or fourth bite. At this time drinking can worsen the situation. This phenomenon has a logical explanation. During the first bites, part of the ingested food easily enters into the pharyngeal pouch and the patient has no critical symptoms. However, when the diverticulum, that is comprised and wedged between the spine and the upper esophagus, is filled with food, it compresses and restricts the upper esophagus, until dysphagia becomes critical and complete. This presentation is usually pathognomonic of the Zenker diverticulum.

Regurgitation of undigested food is a very frequent symptom and it is due to bolus entrapment in the pharyngeal pouch. In many cases, especially in the case of large diverticula, regurgitation occurs hours after ingestion (rumination) (Table 9.1).

Pharyngeal stasis of secretions, chronic cough, sensation of a lump in the throat, chronic aspiration, halitosis, and hoarseness are also very common symptoms caused by a pharyngeal pouch and outlet obstruction.

Table 9.1 Symptoms associated with Zenker diverticulum and complications

Most common symptoms
Oropharyngeal dysphagia
Regurgitation
Chronic cough
Sensation of a lump in the throat
Chronical aspiration
Halitosis
Hoarseness
Cervical borborygmi
Rare symptoms and complications
Weight loss
Aspiration pneumonia
Diverticulitis
Ulcerations
Bleeding
Tracheal fistulas
Fistula to the prevertebral ligament
Cervical osteomyelitis
Vocal cord paralysis
Squamous cell carcinoma

Whistling, crepitus, and cervical borborygmi are usually associated with very large pouches and are almost pathognomonic of Zenker diverticula [6]. With time, weight loss may occur, because of inability of patients to have a regular and adequate diet.

Sometimes, particularly in elderly patients, aspiration pneumonia can be the presenting symptom and clearly represents a fearing complication of the disease [6, 7, 10].

More rarely, diverticulitis, peptic ulceration, bleeding, tracheal fistulas, fistula to the prevertebral ligament with cervical osteomyelitis, and vocal cord paralysis may occur [11, 12].

Squamous cell carcinoma may occur in the setting of a Zenker diverticulum. It is a rare situation, with an incidence of 0.4–1.5%, and should be taken into account in the case of abrupt worsening of dysphagia or alarm symptoms including local pain hemoptysis or hematemesis [13–15].

In patients with oropharyngeal dysphagia and suspected Zenker diverticulum, esophagography is often the most useful and reliable diagnostic tool [16, 17]. It is minimally invasive and inexpensive and quickly permits to exclude other possible causes of dysphagia. Pharyngeal pouches are perfectly visible, especially in the lateral view, and a definitive measurement of the size of the diverticulum is possible. Dynamic continuous fluoroscopy is usually preferred to evaluate possible swallowing disorders, especially in the case of small pouches. Additionally, evidence overflows, and aspiration can be seen (Fig. 9.1).

Zenker diverticula should be differentiated from the less common and smaller Killian-Jamieson diverticula [2, 18]. In these cases, diverticula originate from the anterolateral cervical esophagus, distally to the cricopharyngeal muscle. Discrimination between the two diverticula is crucial, because endoscopic treatment is very effective, safe, and reliable for the Zenker diverticula, but much less for the Killian-Jamieson.

Not rarely, upper GI endoscopy is used for the primary evaluation of patients with dysphagia. However, when a pharyngeal diverticulum is suspected, endoscopy should be carried out cautiously, on well-sedated patients, because of a high risk of iatrogenic perforation. From a diagnostic point of view, endoscopy does not add very much to the barium esophagram. Size of the diverticulum and location are more accurately seen on X-ray than by endoscopy. However, the role of endoscopy is particularly important to evaluate patients with recurrent symptoms after transoral cricopharyngeal myotomy, because it permits to reliably evaluate the depth of the residual septum, any possible scarring, and, as a consequence, the possibility of an endoscopic retreatment.

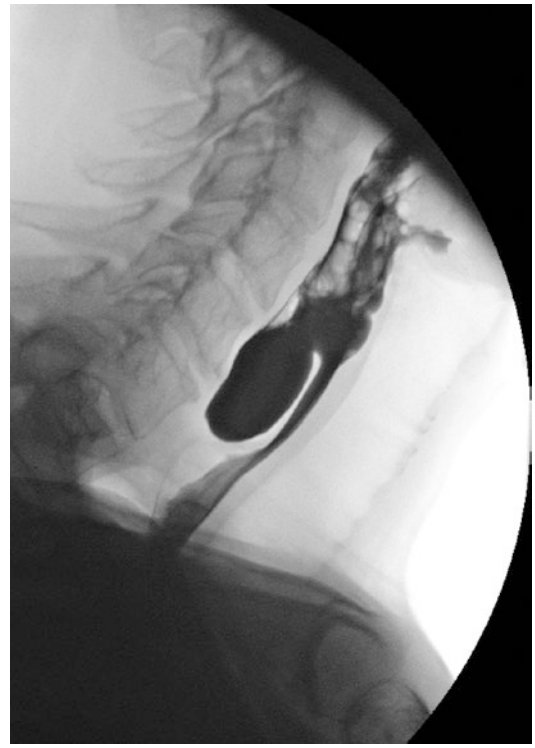

Fig. 9.1 Barium swallow showing contrast within a Zenker diverticulum. Lateral view

Zenker diverticulum may also be diagnosed by transcutaneous ultrasonography [19]. Ultrasonography could be useful to differentiate the diverticulum from a thyroid nodule or a big mass [20]. However, the role of ultrasonography in the evaluation of Zenker diverticulum is limited to some specific clinical situations.

CT scan and MRI are only anecdotally used for the evaluation of a Zenker diverticulum. Usually they are performed to exclude other possible causes of esophageal dysphagia, including

esophageal or pharyngeal neoplasms of mediastinal masses. In contrast, their role becomes predominant when a carcinoma is suspected.

9.3 Indication for Treatment and Aims

Treatment is usually reserved for symptomatic diverticula. Diverticula can remain asymptomatic for years, the natural history of this disease is uncertain, and the risk of operative complications is definitely higher than the risk of aspiration or cancer. This is especially true if we consider that often patients with pharyngeal pouches are particularly old and fragile, with a variety of age-related comorbidities that can additionally compromise the perioperative course.

The primary aims of treatment are to reduce the obstacle to normal pharyngeal emptying, which is essentially represented by the non-relaxing upper esophageal sphincter, and to eliminate the pharyngeal reservoir represented by the pouch.

The upper esophageal sphincter is composed of the posterior surface of the thyroid and cricoid cartilage and three muscles: inferior pharyngeal constrictor, cricopharyngeal muscle, and muscularis propria of the cervical esophagus [21]. Functionally, the cricopharyngeal muscle is the main and dominant portion of the sphincter. It is approximately 1.6–1.9 cm in length [6, 9]. Since the main pathophysiological alteration associated with the Zenker diverticulum is the incomplete swallow-induced relaxation of the cricopharyngeal muscle, a cricopharyngeal myotomy is always necessary, independently of the additional procedures that will be performed to eliminate the pharyngeal reservoir (creation of a plain esophagodiverticulostomy with a transection of the septum, diverticulectomy, or suspension diverticulopexy) [22].

Cricopharyngeal myotomy alone reduces the sphincter resting pressure and normalizes both the upper esophageal sphincter opening (relaxation) and the intrabolus pressure, as demonstrated by pharyngoesophageal manometry [9, 23–27].

Some experts recommend extending the myotomy for 2–3 cm into the *muscularis propria* of the proximal esophagus, beyond the cricopharyngeal muscle, since both these muscles appear to be involved in the pathogenesis of Zenker diverticulum [26]. However, in the case of a transoral approach, it could be associated with an increased risk of mediastinum exposure and perforation or vascular injury, especially in case of huge floating or plunging diverticula [7].

In contrast, the simple elimination of the pharyngeal reservoir and pouch, by means of a diverticulectomy, diverticulostomy, diverticulopexy, or inversion without a cricopharyngeal myotomy, is no longer an acceptable treatment given the high rate of long-term recurrence and complications [28].

Currently there are three main treatment options for Zenker diverticulum: open surgery, with a transcervical approach, transoral rigid endoscopy (including cricopharyngeal myotomy with endoscopic stapling, carbon dioxide laser, or vessel tissue sealer), and transoral flexible endoscopy (including needle knife cricopharyngeal myotomy or submucosal peroral endoscopic myotomy).

9.4 Open Transcervical Approach

The classical open transcervical surgical operations include an external neck incision, usually along the anterior border of the left sternocleidomastoid muscle, the identification, dissection, and exposition of the pharyngeal pouch and of his neck, followed by the myotomy. Myotomy is performed approximately 2 cm proximally into lower pharyngeal constrictor to 5 cm distally through the cricopharyngeal and into the proximal part of the esophagus [10].

Following myotomy, the pharyngeal pouch can be (1) surgically excised, usually with a linear stapling device (diverticulectomy), (2) uplifted and retracted toward the prevertebral fascia and suspended as by suture to the prevertebral fascia or the posterior pharyngeal wall

(diverticulopexy) with the collar of the sac in a non-dependent position, or (3), finally, inverted into the esophageal lumen (diverticulum inversion or invagination) [29–31]. Average-sized diverticula can be treated with a combined cricopharyngeal myotomy and diverticulopexy; smaller diverticula are more frequently treated with suspension or cricopharyngeal myotomy alone [6, 32].

In a large review of more than 2800 patients from 41 studies who underwent open surgery for Zenker diverticulum, overall morbidity occurred in 10.5% of patients, with the most frequent complications being recurrent nerve injury in 3.3%, leaks or perforation in 3.3%, cervical infections in 1.8%, and hematomas in 1% of patients. Mortality after open surgery was reported in 0.6% of patients [33].

In the general trend versus less invasive approaches and therapies, new techniques and new devices have been implemented in the last decades, and transoral endoscopic treatment [34] and flexible endoscopy [27, 35] have gained in popularity over open surgery with a concurrent decrease in mortality and morbidity.

Therefore, open surgery still remains a mainstay in the management of symptomatic diverticula, but it is nowadays recommended almost exclusively for small symptomatic or huge Zenker diverticula and always in patients at low surgical risk [32].

9.5 Transoral Cricopharyngeal Myotomy: Rigid Endoscopy

The transoral approach was especially developed to overcome some limits of the open transoral approach and in particular the relatively high frequency of associated adverse events, complications, and mortality [33]. Many patients with Zenker diverticulum are elderly and with comorbidities.

The rationale behind the transoral approach is that a septum containing the cricopharyngeal muscle and the proximal part of the esophagus divides the pharyngeal pouch from the esophagus. The septum can be easily identified in the hypopharynx and divided until the bottom of the pouch. Therefore, the diverticular sac is joined to the esophagus, eliminating simultaneously the pharyngeal outlet obstruction and the pharyngeal reservoir (Fig. 9.2).

9.5.1 Endoscopic Electrocautery

The first successful endoscopic treatment of a Zenker diverticulum was reported by Moscher in 1917, but this approach was abandoned for years because of a high incidence of complications, especially mediastinal infections [33].

Lately, as early as in 1936, Gosta Dohlman performed the endoscopic cricopharyngeal myotomy

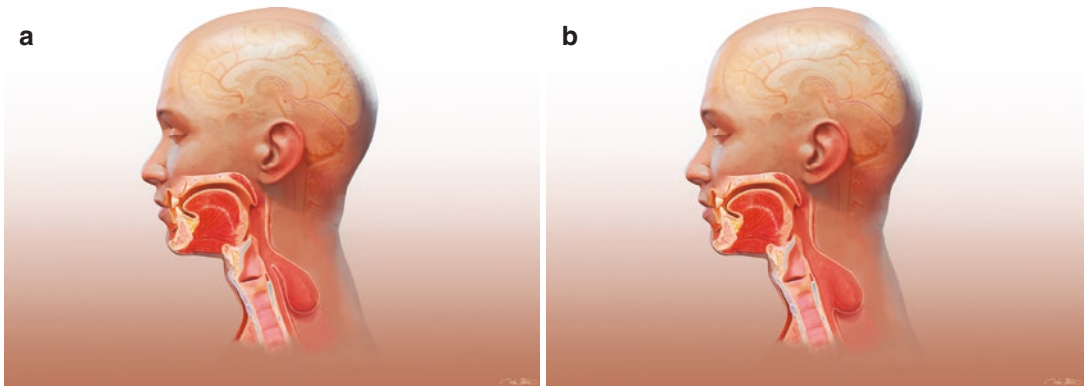

Fig. 9.2 Transoral cricopharyngeal myotomy. (**a**) Zenker diverticulum. The septum between the pouch and esophagus contains the cricopharyngeal muscle and the proximal part of the esophageal wall. (**b**) The septum has been cut until the bottom of the pouch, and the diverticular sac is joined to the esophagus

on a series of patients, but published the results only many years later [36]. Dohlman described substantial key improvements to the Mosher's method, using a bivalved rigid diverticuloscope and employing diathermic excision and hemostasis of the cricopharyngeal muscle and common wall between the esophagus and the diverticulum. In a series of 100 patients, he reported no cases of mediastinitis and a very low recurrent rate (7%). Similar outcomes were reported by other authors by using the Dohlman technique, with a complications rate of 7.8% (the most frequent adverse events being subcutaneous emphysema in 2.9% of patients and mediastinitis in 2.1%) and a mortality rate of 0.2%. Clinical success in some series was reported as high as 91–92% [33].

Since then, the endoscopic approach has evolved quickly over time, and especially in the last 30 years with the introduction of carbon dioxide laser and new surgical devices derived from the laparoscopic armamentarium.

9.5.2 Carbon Dioxide Laser Diverticulotomy

Carbon dioxide laser-aided diverticulotomy was first introduced in 1981 by Van Overbeek [37, 38]. It is a contactless and sutureless technique, where the septum between the diverticulum and esophagus is divided by using the high-energy and high-focus laser beam. The advantages over electrocautery include less tissue trauma, less postoperative pain, and quicker recovery.

The operation is performed under general anesthesia with orotracheal intubation. The patient is positioned supine, and the neck should be completely extended. A bivalved Weerda diverticuloscope in its closed position is introduced into the esophageal inlet under direct vision or better under video monitoring. The diverticuloscope is then retracted slowly and opened to expose the septum between the esophagus and diverticulum: the anterior blade of the diverticuloscope is placed inside the esophagus, the posterior blade inside the diverticular pouch. The diverticuloscope is then advanced again until the bottom of the diverticulum is completely exposed. The septum will become clearly visible between the two valves of the diverticuloscope.

An operating microscope with a 400-mm lens and attached CO_2 laser micromanipulator is introduced into the diverticuloscope and focused on the common wall. The septum is transected at the midline, down to the bottom of the pharyngeal pouch. During transection, the fibers of the cricopharyngeal muscle can be clearly identified, as they retract laterally when they are cut [7].

No sutures or stitches are applied after the transection of the septum on the edges of the septum. The high-power laser energy provides less thermal tissue damage compared to electrocoagulation and favors a rapid healing of the cut surface [39, 40].

On the other hand, the procedure is strictly operator-dependent, and the risk of perforation and mediastinitis in unexperienced hands should not be underestimated.

In 2013, in a review about the surgical treatment of Zenker diverticulum [33], more than 1000 patients who underwent carbon dioxide laser procedure were included. Overall complication rate was 9.4%, and mortality rate was 0.2%. Common complications were subcutaneous emphysema (3%), mediastinitis (1.3%), fistula (1.1%), and bleeding (1%). Another review included 894 patients in 13 studies. Overall, clinical failure occurred in 21.7% of patients, being the vast majority early failures (88.6%) [41].

The benefits of laser-assisted approach include the relative elegance and simplicity of the procedure in expert hands and, more important, the possibility of extending the myotomy almost until the bottom of the diverticulum. On the other hand, laser is not available in every center, and the learning curve can be challenging.

9.5.3 Stapler-Assisted Diverticulotomy

In 1993, Collard in Belgium and Martin Hirsch in England performed the first cases of cricopharyngeal myotomy with the use of a laparoscopic linear cutting stapler. The procedure is performed with the patient supine, with the extended neck

and under general anesthesia. A bivalved Weerda diverticuloscope is introduced in order to expose the party wall between the diverticulum and the esophagus. The small caliber linear cutting stapler is introduced through the diverticuloscope down to the septum. The cartridge blade is put into the esophagus and the anvil blade in the pouch. Then, the stapler is secured with the septum between the two blades, and the two double (or triple) lines of staples are fired, in order to seal the diverticulum and the esophageal wall. The cutting blade is thus advanced and the septum between the two staple lines is divided.

In the last years, stapler-assisted cricopharyngeal myotomy became very popular. The sealing of the diverticulum and the esophagus, before the myotomy, minimizes the risk of complications. In addition, as compared to the carbon dioxide laser-assisted myotomy, this technique is less operator dependent, more reliable, quicker, and more easily available in every surgical center.

Antibiotics are not routinely given before or after the procedure. Absence of skin incision, shorter operative time, minimal or absent postoperative pain, quicker resumption of oral feeding, reduced hospital stay and overall operative costs, and lower rate of complications are some of the advantages of stapler-assisted cricopharyngeal myotomy over standard open surgical procedures.

On its counterpart, a careful selection of patients is necessary, with a special attention to the size of the pouch. Stapler-assisted procedure is not indicated for diverticula that are smaller than 3 cm, essentially because of some intrinsic characteristics of the laparoscopic staplers. The stapler anvil extends for 1–1.5 cm beyond the end of the staples, and the staples extend for few millimeters beyond the distal end of the knife blade: it means the residual pouch after the treatment is usually 1.5 cm deep. Some staplers with shorter not-functioning ends are available now, or the ends of the stapling device can be trimmed, in order to approximate the end of the cut to the bottom of the diverticulum.

Endoscopic stapling is better suited to medium-sized diverticula, 3–5 cm in depth. Smaller pouches will not accommodate the anvil of the stapler; diverticula deeper than 6 cm may represent a relative contraindication, because the cartridge is only 5 cm long and a too large residual pouch will remain after a single stapling [24, 25].

Over time, the technique was modified by applying traction sutures through the lateral edges of the common wall to provide proximal tension on the cricopharyngeal bar to ease engagement of the septum inside the stapler jaws [42, 43].

Clinical outcomes of this approach vary a lot in the different studies. Overall complication rate is 7%, which is comparable to the complication rate of carbon dioxide laser-assisted myotomy. Mortality rate is 0.3%. The most frequent complications are dental injuries (2%), caused by the large and rigid diverticuloscope, esophageal mucosal damages (1.6%), and perforations (1.6%) [33].

In a large cohort study by Bonavina et al. [29], 181 patients underwent stapler-assisted cricopharyngeal myotomy and were followed for a mean of 27 months. Mean operative time was 19 minutes, and postoperative hospitalization was 3 days. No mortality or severe complications occurred, but 1.1% of patients experienced dental injury. Conversions to open surgery were necessary in eight cases: seven were due to poor exposure and one to mucosal tear during the endoscopy. Of the patients undergoing the endoscopic stapling approach, 92% were symptom-free at the date of last follow-up.

In another cohort retrospective study published by a North American group [44], 337 patients underwent attempted staple-assisted myotomy. Technical failures, due to inadequate septum exposure, occurred in 3.9% of cases. Mean operative time was 28.8 minutes. The average hospital stay was 0.36 days, with 300 (92.6%) patients being discharged home on the same day of surgery. Symptom improvement was recorded in 93.5% of patients who were treated with success. There was a 4.0% major complication rate.

In a large review of 1089 patients treated by stapler-assisted myotomy, overall success rate was recorded in 81% of patients. Perioperative failures, due to a variety of reasons, were recorded in 6.2% of patients [41].

9.5.4 Harmonic Scalpel-Assisted Myotomy

Harmonic scalpel is used in laparoscopic surgery to simultaneously coagulate and cut vessels and tissues, with a minimal thermal injury to surrounding organs and structures. The harmonic scalpel uses ultrasounds inducing protein denaturation such that vessels are sealed, providing adequate and effective timely hemostasis.

Recently, harmonic scalpels have been successfully used for the cricopharyngeal myotomy, in combination with a rigid Weerda diverticuloscope [45] or with a soft diverticuloscope in combination with flexible endoscopes [46]. This technique can be particularly effective for the management of small diverticula, which are known to be more difficult to be treated with a linear stapler. The cutting surface of the harmonic scalpels reaches the very distal end of the device, and therefore it is possible to extend the diverticulotomy almost until the bottom of the pharyngeal pouch. Furthermore, the diameter of the harmonic scalpel (5 mm) is significantly smaller than the diameter of the vast majority of laparoscopic linear stapler (10 mm), the rigid articulated end is shorter, and it is easier to be maneuvered inside the rigid diverticuloscope. Few studies have been published so far including few patients [45, 47–49] with technical and clinical outcomes similar to those of stapler-assisted myotomy.

9.6 Transoral Cricopharyngeal Myotomy: Flexible Endoscopy

The management of Zenker diverticulum has undergone a series of revolutionary changes in recent years, one of the most important being the use of flexible endoscopy. In 1995, Ishioka in Brazil and Mulder in the Netherlands reported on the first patients with Zenker diverticulum treated by using a flexible endoscope and a precut needle knife or monopolar forceps [27, 35]. Lately, argon plasma coagulation was used, instead [50]. The principles of treatment are the same as rigid endoscopy: the septum between the diverticulum and the upper esophagus contains the cricopharyngeal muscle, and when it is cut during the procedure, the myotomy is completed, creating at the same time a common opening between the esophagus and the pouch.

If at the very beginning, immediately after the first pioneering experiences, the flexible approach was indicated only in patients at high risk for surgery, elderly and malnourished patients, or those with cardiovascular severe comorbidities, nowadays, in many centers, the treatment of Zenker diverticulum became an almost exclusive prerogative of interventional GI endoscopists. Bremner and De Meester considered the “flexible endoscopy” approach to the pharyngeal pouch to be a milestone in the field of gastrointestinal endoscopy [51].

The use of a flexible endoscope for the management of the Zenker diverticulum has some crucial and key advantages as compared with the use of a rigid endoscope. First cricopharyngeal myotomy can be performed in the endoscopy suite, without the need for general anesthesia and orotracheal intubation, because the flexible endoscope has a small diameter, usually less than 10 mm, and it does not cause any trauma or injury to the hypopharynx. Theoretically the procedure could be performed on outpatients, dramatically reducing the costs of hospitalization. Furthermore, the flexible endoscope approach can be virtually performed on all the patients, including those where the rigid endoscope cannot be correctly placed, because of upper teeth protrusion, inadequate jaw opening, or insufficient neck mobility, the last being very frequent in elderly patients [10].

When comparing flexible endoscope cricopharyngeal myotomy versus stapler-assisted procedure, similar outcomes in terms of hospital stay, dysphagia symptom score improvement, and complication rates are usually reported, at the cost of a significantly longer procedure time for endostapling [52].

There are at least three different techniques for cricopharyngeal myotomy by using a flexible endoscope: (1) the freehand, cap-assisted procedure, (2) the diverticuloscope-assisted, and (3) the peroral endoscopic myotomy or Z-POEM.

9.6.1 Preparation of Patients

Patients are kept fasting for 8–12 hours. However, they are usually recommended to drink a lot the

day before the procedure, to flush the debris away from the pharyngeal pouch, especially in the case of large diverticula. Accidental aspiration during anesthesia can be a cause of severe complications. Furthermore, the visualization of the diverticular pouch during the myotomy can be compromised if debris are not carefully removed before.

The flexible endoscope cricopharyngeal myotomy can be performed either in the operating theater or (preferably) in a well-equipped endoscopy suite. Even if the procedure can be performed under propofol sedation in the vast majority of cases, the anesthesia equipment, including all the necessary for orotracheal intubation and ventilation, should be available in the room.

Any diagnostic endoscope can be used for the procedure, even if a certain preference goes to small caliber endoscopes (about 9 mm) with a water jet channel. Water jet can be extremely useful in case of incidental bleeding during the procedure, although a certain attention should be kept if the patient has not been intubated, because of the risk of aspiration.

Although there are no comparative data, there is a sufficient body of evidence in a relatively comparable treatment modalities that carbon dioxide reduces the risk of subcutaneous emphysema and pneumomediastinum. Therefore, carbon dioxide insufflation should be preferred over room air insufflation [17].

Antibiotic prophylaxis is not routinely administered before the procedure, because it does not reduce the risk of complications [17].

The procedure can be performed either with conscious sedation or under general anesthesia with propofol or endotracheal intubation according to local practice and expertise [7]. The choice between sedation and orotracheal intubation may depend also on the final technique used for the myotomy. The preliminary placement of a soft diverticuloscope protects the airways and minimizes the risk of aspiration. In such cases, the procedure can be safely performed under propofol sedation. In contrast, when the hand-free cap-assisted technique or the Z-POEM is used, intubation may be someway preferred by some operators.

Patients are placed in a left lateral position. The head, the neck, and the dorsal spine should be perfectly in line, in order to improve the visualization of the septum and of the diverticular pouch. If the head of the patients is turned on a side, the diverticulum may appear distorted or compressed and the procedure becomes trickier. A vacuum surgical mattress, if available, can be used to maintain the patient in the correct lateral left position under general anesthesia.

9.6.2 Freehand, Cap-Assisted Myotomy

A large bore nasogastric tube is sometimes inserted in the esophagus to obtain a better exposure of the septum, stabilize the diverticulum, and protect the esophageal wall by accidental thermal injury during sectioning of the septum [53].

Other experts prefer to use transparent caps or oblique-end distal hoods on the tip of the endoscope to help improve visualization and exposure of the septum and stabilize the endoscope in the hypopharynx and the cautery instrument [54]. The choice between one and the other device basically relies on the local availability and the preferences of the endoscopist (Fig. 9.3).

When the septum is well exposed and visualized, it can be divided by using a variety of cutting methods and needle knives. Again, none is definitely superior to the other; however needle

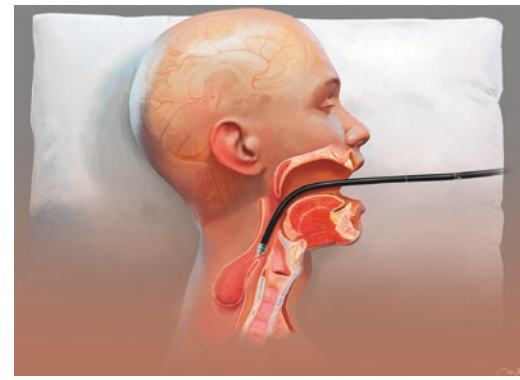

Fig. 9.3 Cap-assisted cricopharyngeal myotomy. An oblique cap is fixed of the tip of a flexible endoscope, to improve the visualization of the septum during the myotomy

knives should be thick enough to favor coagulation of tissue during the cutting of the septum. Thick precut needle knives, hook knives, or other devices from the ESD armamentarium, monopolar or bipolar forceps, and argon plasma coagulation have been successfully used over the years.

A hook knife enables the cricopharyngeal muscle fibers to be isolated, pulled upward, and then cut. Theoretically, the upward pull of the septal fibers minimizes the risk of perforation. Scissor-shaped cutting tools (like SB knife Jr., Sumitomo Bakelite Co., Tokyo, Japan) allow for an incision from the apex to the base of the septum but with a scissor-like movement, which pulls the muscle fibers toward the endoscope while cutting [17].

One of the cheapest needle knives is more than enough to complete the procedure safely and efficiently. However, in a recent multicenter, retrospective study, clinical success was found to be higher with hook knife (96.7%), compared to needle knife (76.6%) or insulated tip knife (47.6%) [55].

Argon plasma coagulation has been used in the early experience instead of needle knives or scissors. Argon plasma can offer the benefits of a deep coagulation of tissues and vessels, therefore reducing the risk of bleeding. On the other hand, the procedure needs more sessions, and the risk of thermal injuries to the surrounding structures is higher than with the needle knife [56]. Nowadays the use of argon plasma coagulation for the treatment of Zenker diverticulum has been almost completely abandoned.

Blended current is usually applied through the knives, to cut the septum by minimizing the risk of bleeding and thermal injuries to the surrounding structures and organs. However, the proper settings for every cutting device should be asked to the manufacturer of the electrosurgical generator.

The septum is usually divided in the middle by moving the tip of the endoscope and the knife from the inside of the esophagus toward the posterior esophageal wall or in the opposite direction. The two edges of the septum will immediately split and separate after the incision, showing the fibers of the cricopharyngeal muscle and of the posterior esophageal wall [7, 10].

Mild bleedings may occur during the myotomy and are usually stopped by using forced coagulation deployed with the same needle knife or, if necessary and available, coagulation forceps. Only anecdotally, spurting severe bleeding should be controlled using different measures, including epinephrine injection or fibrin glue.

The major issue of the procedure remains the correct balancing of the extension of the myotomy. A short myotomy may be insufficient and lead to early recurrences of symptoms. A cause of failure can be an incomplete myotomy of the cricopharyngeal muscle and/or insufficient marsupialization of the diverticular sac that leaves the food still entrapped inside the pouch. On the other hand, if the myotomy is extended beyond the bottom of the diverticulum, there will be an increased risk of perforation and mediastinitis. In the vast majority of cases, the septotomy is stopped between 5 and 10 mm from the bottom of the pouch.

In order to minimize the risk of perforation after the myotomy, clips are widely used at the base of the septotomy by the majority of endoscopists, despite there is no evidence of their impact on adverse events [17, 57].

After the procedure, the patients are usually kept fasting for 24 hours and allowed liquid diet the next day if their course is unremarkable. Contrast studies are not usually performed after the cricopharyngeal myotomy, before feeding [17].

9.6.3 Soft Diverticuloscope-Assisted Myotomy

Another device employed for the endoscopic treatment of Zenker diverticulum is the flexible diverticuloscope (ZD overtube, ZDO-22–30; Cook Medical, Winston-Salem, NC, USA), which mimics the effect of the rigid Weerda diverticuloscope. The flexible diverticuloscope significantly improves the fixation of the septum, its exposure, and visualization and, at the same time, protects the posterior diverticular and anterior esophageal wall by accidental thermal injuries (Fig. 9.4).

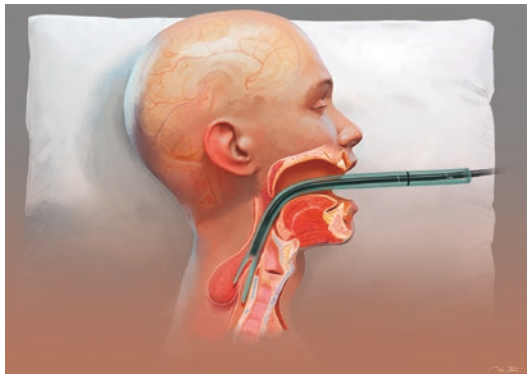

Fig. 9.4 Soft diverticuloscope-assisted myotomy. The soft diverticuloscope is in place, with its shorter distal flap inside the diverticular pouch and the longer one into the esophagus

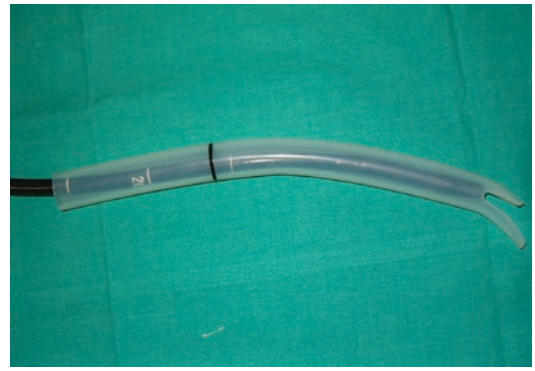

Fig. 9.5 Soft rubber diverticuloscope with an endoscope inside. The *black* marker on the overtube is placed approximately at the level of the upper incisors

The diverticuloscope consists of a soft rubber overtube with two distal duck-bill flaps of 40 and 25 mm that, respectively, protect the esophageal and diverticular wall (Fig. 9.5).

For the placement of the diverticuloscope, a current and precise alignment of the head of the patient, neck, and chest is necessary, as explained before. The overtube is loaded over the endoscope that is pushed through the esophagus into the stomach. The diverticuloscope is then advanced over the endoscope up to a black marker indicating the average distance (16 cm) between the septum and teeth line. When the overtube is pushed forward, the short flap is kept aligned to the posterior side of the neck (where the diverticulum is) and the long flap is aligned anteriorly. In order to ease the passage of the diverticuloscope into the pharynx, the neck of the patient can be slightly hyperextended and two fingers inserted into the patient's mouth to protect the posterior pharyngeal wall and push the distal end of the diverticuloscope inside. Once the diverticuloscope is in place, the endoscope is withdrawn to finally check under direct visual control the correct alignment and make further adjustments. After positioning of the diverticuloscope, the septum should be clearly visible in the center of the overtube, ready to be cut (Fig. 9.6).

Sometimes, the positioning of the diverticuloscope can be a little bit more difficult. The placement of a very stiff guidewire (Savary guidewire, Cook Medical, Winston-Salem, NC, USA) into the stomach can facilitate the introduction of the overtube and the additional adjustments of the diverticuloscope under direct endoscopic control.

Cricopharyngeal myotomy can proceed now normally, by using the same variety of knives or scissors that can be used for the hands-free cap-assisted myotomy.

Some authors reported on the use of harmonic scalpels alongside the flexible endoscope, usually by using a small caliber endoscope (4.5 mm) to control the procedure [58].

The soft diverticuloscope really permits a clear vision of the septum of the diverticulum and a better control of the endoscope and devices. In the case of bleeding or need for flushing, the risk of aspiration pneumonia is significantly reduced, because the larynx and airways are completely bypassed by the overtube.

The major limit of the diverticuloscope-assisted procedure is the size of the diverticulum. The shorter flap, that is inserted into the diverticular pouch, is approximately 2.5 cm long. Consequently, in the case of smaller diverticula, the position of the diverticuloscope is less stable, with a consequent reduced exposition of the septum. Furthermore, the flexible diverticuloscope is currently not commercially available in many countries, including the United States, and this limited its widespread use.

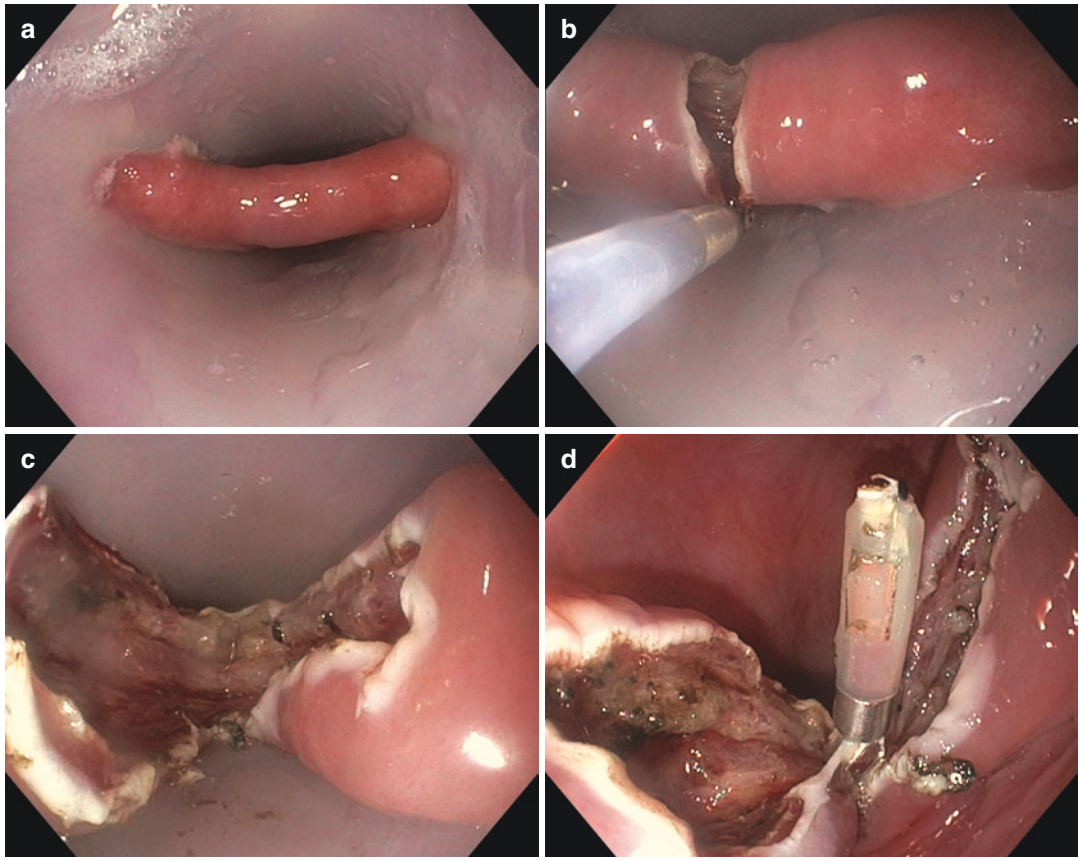

Fig. 9.6 Diverticuloscope-assisted myotomy. (**a**) The diverticuloscope has been correctly positioned, and the septum between the diverticulum and the esophagus well fixed and exposed. (**b**) The septum is cut in the middle by using a needle knife and electrocoagulation. (**c**) The two edges of the septum will immediately split after being divided, showing the fibers of the cricopharyngeal muscle and of the posterior esophageal wall. (**d**) An endoscopic clip is placed on the short residual part of the septum, to minimize the risk of perforation and bleeding

Whether or not a diverticuloscope is mandatory for the safe and effective completion for the cricopharyngeal myotomy has been object of discussion [59, 60]. However, according to the published literature, overall use of a diverticuloscope does not seem to have a significant impact on success or complications, and the choice whether or not to use a diverticuloscope is left to the endoscopist's discretion [17, 57].

9.6.4 Peroral Endoscopic Myotomy (Z-POEM)

On the wake of the treatment of achalasia and gastroparesis, novel procedures have been implemented for the treatment of Zenker diverticulum. Tunneling techniques used to cut the lower esophageal sphincter (peroral endoscopic myotomy, POEM) and the pylorus (G-POEM) have been modified and applied for the treatment of the Zenker diverticula (Z-POEM) [61, 62]. The procedure is still under evaluation, with few data on the long-term follow-up, but is definitely worth full consideration [17]. Z-POEM is performed under general anesthesia or deep sedation. Similarly, to the classic esophageal POEM, a standard high-definition endoscope, with a transparent distal hood attached on the tip, is used. Carbon dioxide insufflation is absolutely necessary, to minimize the risk of gas-related complications and adverse events. The endoscope in inserted into the hypopharynx, until the diverticulum and the septum are identified. A mucosal bleb is created by injection

of 10 ml saline solution and indigo carmine approximately 1–2 cm proximal to the septum. A small longitudinal mucosa incision is performed along the major axis of the septum, with a triangle-tip knife or other ESD knives. The tip of the endoscope is advanced into the submucosal space, with the help of the distal attachment and by gently dissecting the submucosal fibers. Submucosal dissection and tunneling are performed by using the ESD knife and, according to the endoscopist's preferences, spray coagulation, swift coagulation, or blend cut current. Similarly to esophageal POEM, the submucosal dissection is performed in the direction of the septum, along the surface of the muscle layer. Particular attention is devoted not to burn or damage the mucosal layer above the endoscope. Once the septum is reached and identified, a careful dissection on both the esophageal and diverticular side of the septum is completed. Cricopharyngeal myotomy and septotomy are then performed, by using the same needle knife used for the dissection, scissor-type ESD knives or other devices. The septum is cut until the bottom of the diverticular sac, or deeper, without any additional risk of complication, because the area of the septotomy is covered by intact mucosa. At the very end of the procedure, the original small mucosal incision can be secured with the application of 3–5 endoscopic clips. After the procedure patients are kept fasting for 24 hours, and antibiotics are usually administered. The day after a liquid diet is allowed [63].

The procedure is really interesting and promising, even if it is technically more challenging than simple needle knife septotomy. The main advantage is the chance to treat even very small diverticula that may not be amenable to classic transoral myotomy [64] and the possibility to extend very safely the myotomy until the end of the pouch and on the esophageal wall, thus reducing the risk of recurrence [65].

9.6.5 Results of Transoral Cricopharyngeal Myotomy by Using a Flexible Endoscope

Several case series were published since 1995 and demonstrated the efficacy and safety of flexible endoscopy in the management of Zenker diverticula, with very high clinical success rates.

A recent systematic review and meta-analysis included and analyzed a total of 813 patients [57]. Reported pooled success rate was 91% with an adverse event rate of 11.3% and an 11% recurrence rate. Severe complications, including bleeding and perforation, were managed conservatively in all the patients but two, in whom surgical drainage of an abscess was necessary.

In another more recent review study [66], focused on flexible endoscopy and including 589 patients, immediate symptom response after treatment was obtained in 88% of patients, with an overall complication rate of 13%, including 5% of bleeding and 7% of perforations. The vast majority of perforation was treated conservatively. The pooled data demonstrated an overall recurrence rate of 14%. When using the diverticuloscope, pooled success and adverse events rates were 84% and 10%, respectively.

Bleeding is usually intraoperative and is controlled endoscopically by electrocautery devices or clips. Micro perforations may occur during the procedure and are responsible for asymptomatic and uncomplicated subcutaneous emphysema. However, this finding does not mandate surgical operation and have a silent and self-limiting course in the vast majority of cases. The use of carbon dioxide during myotomy significantly reduces this event [10].

Unfortunately, there is a large degree of heterogeneity in the flexible endoscopic approach with no current standardization in the procedure itself or the postoperative care. No formal definition of clinical success exists, and the lower success rate reported in some series is very likely due to the fact that clinical remission was assessed according to the absence of a pool of symptoms and not only dysphagia. When success is defined according to dysphagia alone, clinical success rises to 90–100% [7].

The definition of success should be based solely on improvement and evaluation of symptoms and not on radiological findings. Often, a residual pouch is identified on postoperative radiograms, but if this finding is not associated with dysphagia or other symptoms, it should not

be considered as a recurrence or indicate an unsuccessful treatment.

Furthermore, differently from surgery, flexible endoscopy is easily repeatable, without major problems or difficulties. In some series outcomes were assessed after one treatment session, while in other series it was determined after multiple treatment sessions [7].

Some authors indicate that the size of the diverticulum dictates the safety of the procedure with one-stage approaches for small- to medium-sized diverticula (up to 4 cm) and multiple stages in the approach for large diverticula (>4 cm) [54].

Whether a diverticuloscope is needed for the flexible endoscopic septotomy is still a matter of debate [17]. However, clear indications cannot be retrieved from the literature, because of controversial results. In a retrospective study published in 2007 on a total of 39 patients, 28 were treated with a cap-assisted and 11 with a diverticuloscope-assisted procedure [59]. The procedure time and complication rate was significantly greater with the cap than with diverticuloscope assistance. The clinical remission rate, evaluated using a pool of symptoms, was significantly higher after the diverticuloscope-assisted procedure compared with the cap technique (82% vs. 29%).

Nevertheless, in another recent retrospective study on 77 patients, 60 were treated with diverticuloscope assistance and 17 with cap assistance. Only in three patients treated with the diverticuloscope assistance were reported complications, and treatment success was not dissimilar in the two groups (68% and 60% in the diverticuloscope- and cap-assisted procedures, respectively) [60].

Depth of myotomy and size of the diverticulum may be important prognostic factors that determine clinical success in flexible endoscope approach. A retrospective single-center study on 89 patients recently analyzed the clinical success of flexible endoscopy diverticuloscope-assisted septotomy to identify potential prognostic variables [67]. Success was defined according to the improvement of all Zenker-related symptoms and not only dysphagia. Clinical success at the intention-to-treat analysis was 69%, 64%, and 46% at 6, 24, and 48 months, respectively. Adverse events occurred in three patients: perforation in two (2%) and postprocedural bleeding in one (1%). Independent variables for failure at 6 months were a septotomy length ≤25 mm and pretreatment pouch size ≥50 mm, whereas at 48 months, they were septotomy length ≤25 mm and posttreatment pouch size ≥10 mm. Success rates for ZD ranging in size from 30 mm to 49 mm with a septotomy >25 mm were 100% and 71% at 6 months and 48 months, respectively. Additional studies showed that small diverticula make the transoral procedure more difficult [28, 68].

This limitation may perhaps be overcome by the submucosal tunneling procedure (Z-POEM). Very few case reports and small series have been published so far on this innovative technique [61, 62, 69–71].

One of largest series included 19 patients who underwent Z-POEM and seven patients treated with a conventional needle-knife technique [65]. Clinical success was achieved in 89.5% of Z-POEM patients and 100% of non-tunneled flexible endoscopic patients. Recurrences occurred in 11.7% and 42.9% of patients of the Z-POEM and conventional treatment group, respectively ($p = 0.096$). There were four complications, including one pharyngeal perforation requiring open surgical repair in a patient with a small pouch with an associated cricopharyngeal bar in the Z-POEM group.

Another prospective study specifically focused on the role of a modified Z-POEM, called peroral endoscopic septotomy (POES), in small Zenker diverticula [64]. Differently from the traditional Z-POEM, the mucosal incision is performed directly on the septum, without the need for tunneling, but includes a submucosal dissection on both the sides of the septum and the following myotomy through the submucosal space.

Twenty patients were included in the series and were treated without orotracheal intubation. Mean size of diverticulum was 17.5 mm. Average procedure time was 14 minutes. No complications or adverse events occurred. Dysphagia significantly improved in 19 patients and no recurrences were reported at a mean follow-up time of 12.0 months.

In a multicenter international retrospective study, 75 patients were included [72]. The mean size of pharyngeal pouch was 3 cm. The overall technical success rate was 97.3%. Adverse events occurred in 6.7% (one mild bleed and four perforations, all managed conservatively). The mean procedure time was 52.4 minutes, and mean length of hospital stay was 1.8 days. Clinical success was achieved in 92% of patients. At the 12-month follow-up, only one patient reported symptom recurrence.

Due to the lack of long-term follow-up data, more studies are needed to define the role of Z-POEM in the management of Zenker diverticulum [17].

9.7 Conclusion

The treatment of Zenker diverticulum had a substantial evolution during the last century. Transoral approach, either rigid or flexible, is now considered easier, less invasive, reliable, with decreased morbidity and mortality compared with the open approach and has continued to gain popularity. Once reserved only to few elderly patients with comorbidities, nowadays transoral endoscopic cricopharyngeal myotomy has become the first-line treatment for the vast majority of patients with Zenker diverticula.

The level of evidence for superiority of flexible versus rigid endoscopic techniques for treatment of pharyngeal diverticula is limited based on currently available information.

The flexible endoscope approach is less standardized compared to the Collard operation with stapling devices, being the indications and choice of devices and techniques slightly different among the different centers. Nevertheless, flexible endoscopy is a good choice for the vast majority of patients with a Zenker diverticula. It is really minimally invasive and perceived by the patients more like a gastroscopy than an operation. The limits represented by the age of patients, previous treatments, local anatomy, and comorbidities almost completely disappear when using a flexible endoscope, being the procedure performed under sedation and with a 9-mm endoscope.

Open surgery is still indicated for very large diverticula, because a substantial part of the septum remains after the first endoscopic cricopharyngeal myotomy.

Nonetheless, interventions performed by a flexible endoscope are always repeatable, and the second and third sessions are always much less demanding than the first one.

Therefore, flexible endoscopic approach can be applied even to large diverticula, safely and efficiently, knowing that in these cases the procedure will be completed in two or three sessions.

The recent introduction of the Z-POEM permitted to overcome the limits of flexible endoscopy in the management of small diverticula. Cricopharyngeal myotomy can be now be performed under the mucosal layer, after submucosa tunneling, and be extended to cut completely the cricopharyngeal muscle and some muscular fibers of the upper third of the esophagus, by eliminating completely the pharyngeal outlet obstruction and the pouch.

In conclusion, a variety of different approaches to Zenker diverticulum are currently available, everyone with advantages and shortcomings. An individualized and tailored approach should be utilized. Flexible endoscopy, with its various techniques, plays now a very central role in the management of Zenker diverticulum, being perfectly adaptable, in the vast majority of clinical situations, to the need of patients and physicians.

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10 Transesophageal Tunneling Technique and Peroral Endoscopic Myotomy (POEM)

Karl-Hermann Fuchs, Wolfram Breithaupt, Thomas Schulz, and Gabor Varga

10.1 Introduction

Transmural access to the abdominal cavity and/or the mediastinum by flexible endoscopy has been a challenging aim in the past. In 2007, several publications demonstrated the feasibility to perform a transesophageal and transgastric approach using a tunneling technique to get safely across the gut wall [1, 2]. Gostout and his group reported on experiments on submucosal endoscopy with a mucosal flap valve technique (SEMF) [1]. In the same year, Pasricha et al. demonstrated the tunneling technique in their experimental setting for esophageal myotomy [3]. In 2008, Inoue et al. reported on the first clinical cases of peroral endoscopic myotomy (POEM) in the esophagus [4].

Since then, the success of POEM has expanded its clinical application for several indications for esophageal and gastric myotomy. Today, POEM has reached a clinical acceptance around the world and has been firmly integrated in the therapeutic spectrum of esophageal disease [5–7].

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10.2 The Concept of Peroral Endoscopic Tunneling and Myotomy

If one focuses on the true therapeutic aim of esophageal myotomy, the actual and therapeutically effective step is, for example, in achalasia, the division of a rather small muscle layer of the lower esophageal sphincter (LES). In order to divide this muscle, in earlier times a laparotomy or a thoracotomy was performed to reach the target area [8, 9]. Minimal access surgery helped substantially in reducing the access trauma, which explains the success of laparoscopic myotomy [10, 11].

Pasricha summarized the challenge in using endoscopic technology with a different paradigm in looking for alternative endoscopic technical steps to solve the issue of reduced access [12]. The new ideas followed the principle of minimal access surgery, i.e., a reduction of access size and access trauma aiming for a shorter patient recovery, improved postoperative well-being, better cosmesis, and less inhibiting postoperative restrictions [13, 14].

The submucosal space was found to be an excellent area for endoscopic manipulations [1–5]. This space can be used to travel with a flexible endoscope in one layer quite long distances, for example, 20 cm within the esophageal wall and/or the gastric wall. Carbon dioxide insufflation helps and facilitates the dissection and advance-

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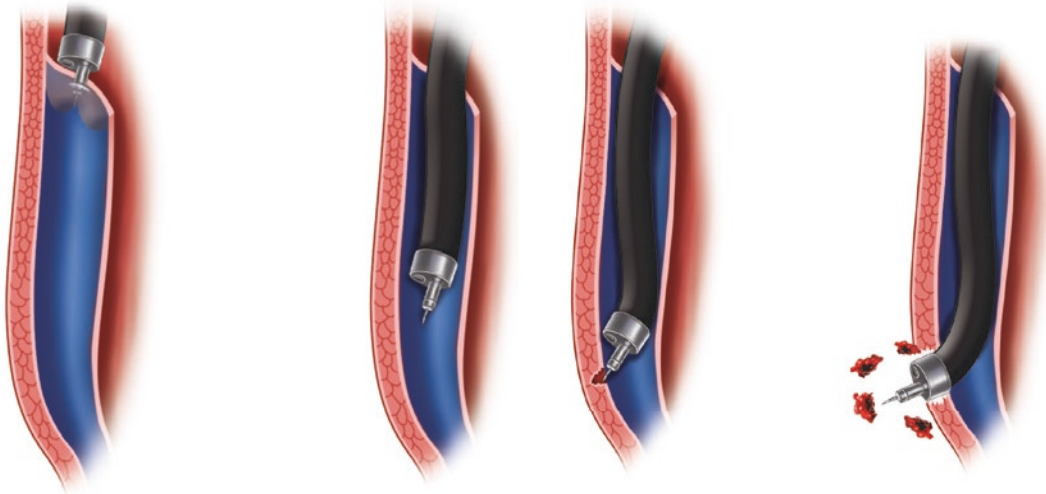

Fig. 10.1 Principle of endoscopic tunneling by injection of fluid in the submucosal space, thus lifting the mucosa from the underlying muscle layer. Via an incision of the mucosa (mucosotomy) and spray coagulation of the submucosal tissue, a tunnel is created between mucosa and muscle layer

Fig. 10.2 Via the submucosal tunnel, the muscle layer and furthermore also the mediastinum can be explored by the endoscope. Thus, esophageal tumors in the wall and mediastinal masses could be reached by endoscopic techniques

ment. Injection of dyed fluid as experienced in the technique of ESD (endoscopic submucosal dissection) allows for a safe dissection staying in the correct plain [4, 5]. Some authors have used a balloon to increase the speed of dissection; however, this may be accompanied with more perforations [15].

The submucosal space can be entered quite easily by incision of the esophageal mucosa after injecting fluid into the submucosal layer, thus separating and elevating the mucosa from the underlying muscularis (Fig. 10.1). This provides access to basically the complete submucosal area and especially the length of the esophagus. Further steps depend on the indications that the endoscopic procedure is based on.

One option is the advancement into the mediastinum and further into the pleural cavity. This could allow for biopsies and exploration of mediastinal or pleural masses or even resections of mediastinal tumors (Fig. 10.2) [16].

Another option is the exploration and/or resection of an intramural esophageal tumor, which can be dissected within the esophageal muscle layer or even a mediastinal tumor [17, 18].

The most frequently used option is an esophageal myotomy for the treatment of esophageal motility disorders [4–7]. Achalasia is most frequent disorder and has been the main indication of POEM [4, 5, 7]. POEM has become also a major therapeutic option for other esophageal spastic motility disorders such as achalasia-like conditions, distal esophageal spasm, and Jackhammer esophagus [6].

10.3 The Technique of Peroral Endoscopic Myotomy

10.3.1 General Perioperative Management

Prior to the operation the patient must be npo for 8 hours. In the 3 days before the procedure, an achalasia patient is asked to eat only semisolid food and drink lots of fluid to prevent food obstruction in the esophagus above the cardia.

The procedure is performed in our institution in general anesthesia, as published earlier [4, 19–21]. The patient is brought into a supine position and the abdomen should be free for

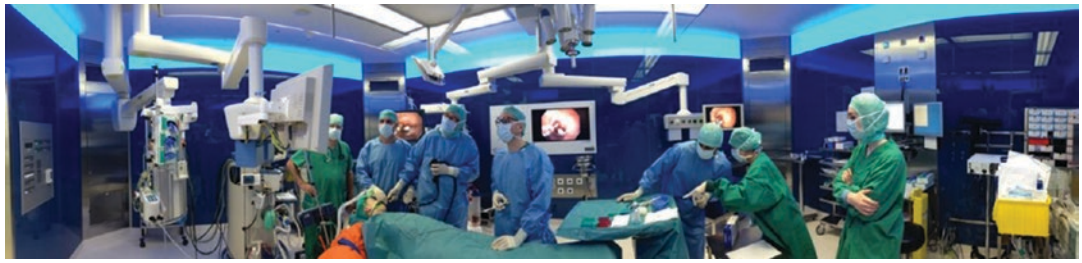

Fig. 10.3 The setting of a POEM procedure in the operating room or the endoscopy suite: The contamination should be kept to a possible minimum. The patient is covered with sterile drape and all directly involved persons wear operative gowns

inspection and palpation during the procedure to check the possible presence of a capnoperitoneum (Fig. 10.3). In this case, a Veress needle would be inserted under sterile conditions to release the CO_2 gas from the abdominal cavity. The infection-contamination issue is addressed by discontinuing all antisecretory drugs of the patient 1 week prior to the operation in order to keep the intragastric environment as acidic as possible to reduce bacterial growth. Also antibiotic prophylaxis (ciprofloxacin and metronidazole) is given intravenously. After the operation daily high-dosage proton pump inhibitors (PPI) are administered for better healing of the esophagotomy.

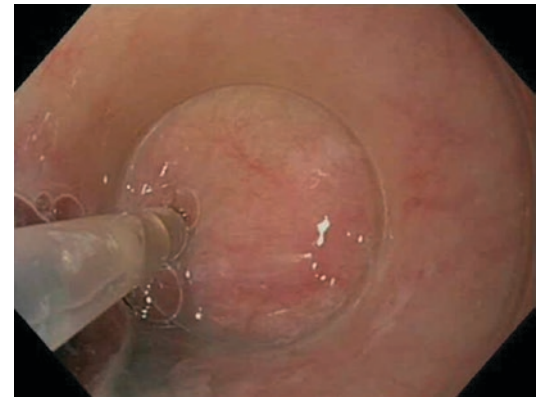

Fig. 10.4 Injection of fluid to separate the mucosa from the underlying esophageal muscle layer in order to create a submucosal tunnel between esophagotomy and the gastric cardia

10.3.2 Description of Technique

Prior to the actual procedure, the upper gastrointestinal tract is checked with an endoscope to remove all fluid and/or food, which can be quite often present in achalasia patients. The esophageal, pharyngeal, and gastric lumen is cleared completely from any food and fluid. In addition, it is rinsed extensively with chlorhexidine.

Then the patient is covered with sterile drapes up to the mouth. A gastroscope is introduced into the esophagus, attached to a CO_2 insufflator. A transparent cap is attached on the tip of the scope for better exposure of the sites. Initially the important esophageal landmarks are measured such as the distal end of the cardia and the narrowing of the cardia in the distal esophagus, representing the upper end of the pathologic non-relaxing high-pressure zone.

The myotomy should start a few cm above the latter area. Thus, the starting point of the myotomy is determined. As a consequence, the point of the esophago-mucosotomy will then be about 5 cm above the starting point of the myotomy, if one aims for a safe tunnel distance of 5 cm. Usually this entrance or esophagotomy will be located between 28 and 32 cm from the teeth.

After the measurement, a 5- to 10-ml depot of blue-stained saline will be injected in the submucosal area (Fig. 10.4). This will lift the mucosa from the muscular layer, and the following incision of the mucosa with a triangle-tip knife will create the entrance into the tunnel (Fig. 10.1). Further careful alternating application of injection of blue-stained saline, spray coagulation, and moderate pushing of the endoscope will complete a tunnel down to the area below the car-

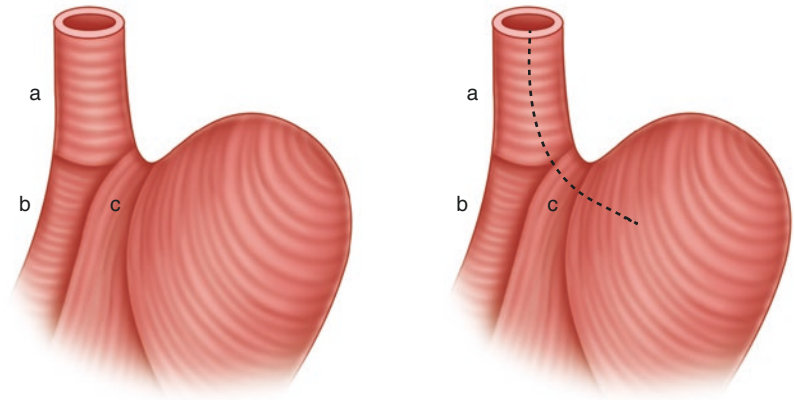

Fig. 10.5 Left: Muscular structure of the gastroesophageal junction according to Liebermann-Meffert [22]; Right: the frequently used anterior myotomy with division of the gastric oblique fibers

dia. These steps should be performed with extreme care and caution in order to prevent damage to the mucosa, which is the only intact layer toward the mediastinum, once the myotomy is completed.

The myotomy can be performed in different locations around the esophageal circumference. The myotomy line of POEM differs somewhat from the classic surgical myotomy line (Fig. 10.5). In open and laparoscopic surgery, most authors favored an anterior esophageal myotomy, which was expanded into the stomach to make sure that the anterior oblique fibers were also cut over about 2 cm to ensure the long-term reduction of dysphagia [7, 8, 10].

During the POEM procedure, it is important to remove the endoscope from the tunnel several times to double-check the correct direction of the tunnel within the esophageal circumference as well as the advancement of the tunnel toward and below the cardia. A final check should include an endoscopic view during intragastric inversion to confirm the blue-stained gastric mucosa at the end of the tunnel below the cardia.

Then the endoscope is repositioned in the tunnel at the starting point of the myotomy and the myotomy is advanced distally with the triangle-tip knife, possibly severing only the circular layer of the muscle and leaving the longitudinal muscle fibers intact.

At the end of the procedure, the extent of the myotomy is checked, all fluids are sucked out of the tunnel, and the esophagotomy is closed by adaptation of the esophageal mucosa and clip closure.

10.3.3 Discussion of Major Elements of the POEM Technique

The technique has four different major elements, which are important for the safety and effectivity of the procedure to perform a successful myotomy in the esophagus [4, 5, 23]:

1. A limited mucosal incision to enter the submucosal space
2. Perform a long submucosal tunneling down to the cardia and below
3. Perform a longitudinal myotomy
4. A robust closure of the mucosal incision

As we have basically remained with the initial techniques as published by Inoue, several authors have modified this procedure creating different variations of the POEM technique [4, 5, 23–25]. Several issues can be discussed.

One major issue is the *orientation of the myotomy* on the circumference of the esophagus. In POEM and tunneling technique, initially Inoue et al. focused on an anterior mytomy on the esophageal circumference [4]. Subsequently, other authors have modified this approach and used also other sectors on the esophageal circumference, mostly the posterior approach (Fig. 10.6) [26].

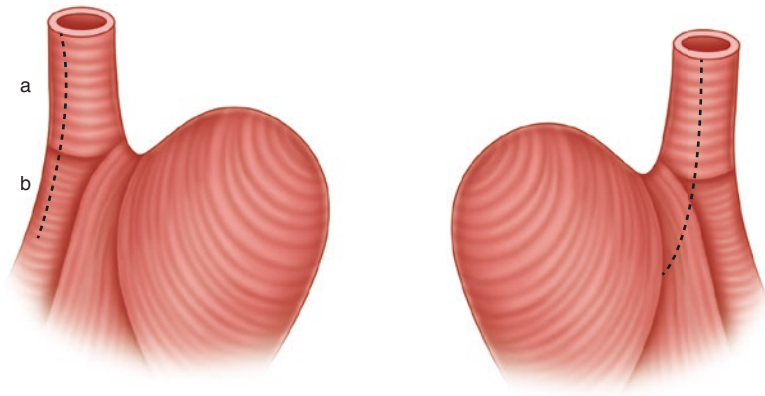

Fig. 10.6 Left: anterior approach of myotomy in the POEM technique by Inoue; Right: posterior approach of myotomy by several other authors

The difference of these techniques regarding their functional changes and patient's outcomes is currently studied in several trials. Early publications gave an overview [26]. Most authors choose either the anterior (1–2 o'clock version) or the posterior approach (5–6 o'clock version). Several studies have focused on this issue, and good overviews and meta-analyses have been published recently [26–32].

The idea and hope behind the anterior approach was the preservation of the posterior attachment of the esophagus with the diaphragm, the phreno-esophageal ligament, and posterior adhesions toward the aorta and surrounding structures, thus preserving part of the antireflux barrier. In addition, the anterior part of the esophagus with the diaphragm may be distended anyway also in achalasia patients. In contrast, the posterior myotomy would destroy the important structures of the antireflux barrier. However, posterior myotomy could have the potential in creating a more substantial reduction in dysphagia.

Table 10.1 demonstrates an overview on some recent randomized trials, as published by N. Parsa and MA Kashab [23]. They stated that both techniques, anterior and posterior myotomy, are effective and safe.

The recent meta-analysis by Rodriguez de Santiago et al. analyzed four randomized controlled trials with 488 patients [33]. The overall clinical success 3–12 months after POEM was 97% (95% confidence interval [CI] 93–100%) and did not differ between anterior and posterior myotomy. The incidence of pathologic reflux after POEM based on pathologic 24-hour pH monitoring (RR 0.98, 95% CI 0.75–1.28), presence of esophagitis (RR 1.04, 95% CI 0.78–1.38), and symptoms (RR 0.89, 95% CI 0.55–1.42) was similar. Posterior myotomy was associated with fewer adverse events (RR 0.63, 95% CI 0.42–0.94), lower risk of mucosal lesions (RR 0.42, 95% CI 0.27–0.66), and shorter incision closure time (mean difference −2.28 minutes, 95% CI −3.46 to −1.10). Anterior myotomy was associated with a shorter length of hospitalization (mean difference 0.31 days, 95% CI 0.05–0.57). No significant differences were found regarding manometric outcomes, total operation, and myotomy time. The authors also stated in their conclusions that the anterior and posterior myotomy are equally effective for the treatment of achalasia, without significant differences in posttherapeutic GERD [33].

The orientation may play a role in re-myotomy after previous laparoscopic myotomy and/or after POEM. It could be speculated that the POEM technique could be applied more often than two procedures on the circumference of the esophagus, while laparoscopic myotomy is probably limited to two procedures. Alternatively, a resection should be discussed.

The *creation of the tunnel* can be quite easy for the experienced endoscopist, since the technique is similar to the ESD technique. Figure 10.7 shows the endoscopic view in the tunnel, which demonstrates clearly the inner circular muscle layer of the esophagus.

Table 10.1 Comparison of anterior versus posterior myotomy, in randomized trials, modified from Parsa and Kashab [23, 30–32]

Study+ design random	*n*	Orientation	Myotomy length (cm)	Proced. time (min)	Clinical success (%)	Abnormal pH test (%)	Esophagitis (%)	Adverse events (%)
Kashab multicenter	150	Ant: 73 Post: 77	Ant: 10.6 Post: 11.2	59 67	Ant: 91 Post: 89	Ant: 49 Post: 42 $p = 067$	–	Ant: 11 Post: 9
Stavropoulos single	215	Ant: 101 Post: 114	–	58 54	92 92.1	69.6 63.3 $P = 0.66$	61.2 61.2	Ant: 8.9 Post: 8.8
Tan single	63	Ant: 31 Post: 32	–	60 57	100 100	26.7 3.33 $P = 57$	16.7 16.7	Ant: 12.9 Post: 3.1 $p = 0.19$

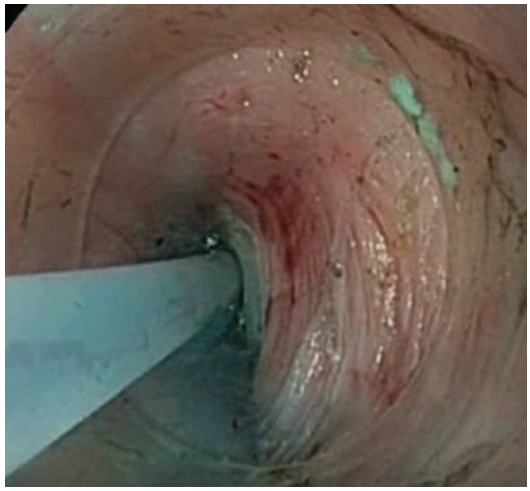

Fig. 10.7 Endoscopic view inside the tunnel with the circular muscle fibers of the inner layer

Another major technical issue is the *depth and extent of the myotomy*, being restricted to the inner, circular muscle layer or being extended to the outer longitudinal muscle layer. The initial experience by Inoue was performed with a restriction to the circular muscle layer [4]. However, clinical experience showed that quite often the longitudinal muscle layer would divide just by mechanical force, applied to the endoscope, when advancing through the tunnel. Therefore, often the intention of staying during myotomy in the inner layer resulted at least in a partial longitudinal separation of some segments of the outer muscle layer.

In addition, our own experience showed a rather substantial, recurrent dysphagia rate in the early series with 18% failure after 1 year, which resulted for our group in the decision to perform a complete myotomy at least at the level of the cardia to prevent early recurrence [21].

The third important technical issue is the *length of the myotomy*. Initially it was suggested to perform a quite long myotomy of 10–12 cm in all cases [4, 5, 18]. With increasing clinical experience and information from other studies, authors started to more individualize the myotomy length depending on the disorder and the functional findings in high-resolution manometry and radiological findings [23–25, 29–38]. Currently most authors tailor the length of the myotomy according to the disease and morphologic and functional preoperative findings of the individual patient [29–38]. Patients with a spastic disorder such as an achalasia type III, a diffuse esophageal spasm, or a Jackhammer esophagus require a longer myotomy toward the more proximal part of the esophagus compared to a muscular spasm just located at the cardia like in achalasia type I [39]. A recent trial showed better results after POEM in tailoring the myotomy length [40].

Regarding length of myotomy and extent of the myotomy toward the stomach, surgical experience has shown that about 2 cm of proximal gastric involvement in the myotomy seems to be important to reach satisfactory relief from dysphagia postoperatively [9–11]. New technology is available to monitor these findings (see special chapter) [41].

10.4 Other Techniques of Peroral Endoscopic Myotomy

A number of different other techniques following the concept POEM have been developed [25]. Along the upper gastrointestinal tract, starting from the pharynx to the duodenum, the principle of myotomy can be applied to provide relief in patients with spastic motility disorders such as cricopharyngeal disorders, esophageal spasm, esophageal diverticula, achalasia, other functional disorders of the lower esophageal sphincter, and pyloric spastic disorders and outlet obstructions leading to delayed gastric emptying. The latter can be treated by *G-POEM* (see special chapter).

In the esophagus, several other options have been published [25]. There is always the choice to perform a classic POEM technique with different lengths of myotomy. One special version is a *short-tunnel POEM* right at the cardia [42]. This can be combined with either a transverse or a classic longitudinal esophageal mucosotomy. The aim of this technique could be limited division of the lower esophageal sphincter.

A *peroral endoscopic dual myotomy* was published by Yuan et al. [43]. The technique includes the creation of a submucosal tunnel covering at least half-esophageal-lumen width. This allows for two separate myotomies within one tunnel at 3 o'clock and at 8 o'clock all the way down to the cardia (Fig. 10.8). This special technique may have less recurrence because of the substantial destruction of the esophageal muscle [25, 43].

Open POEM has been reported as early as 1980 [44]. The authors performed an incision of the esophageal mucosa and subsequently also a myotomy without a tunnel. This technique has been repeated in recent years in a few studies with remarkable success [23, 45].

A very interesting technique is the application of the POEM concept on patients with esophageal diverticula. The *D-POEM technique* has been published recently in a multicenter retrospective study involving three centers [25, 46]. Eleven patients with an esophageal diverticulum (Zenker's diverticulum = seven, epiphrenic = three, and mid-esophagus = one) were included. The important step in this technique is the dissection on both sides of the diverticulum's septum until the very bottom of the diverticulum.

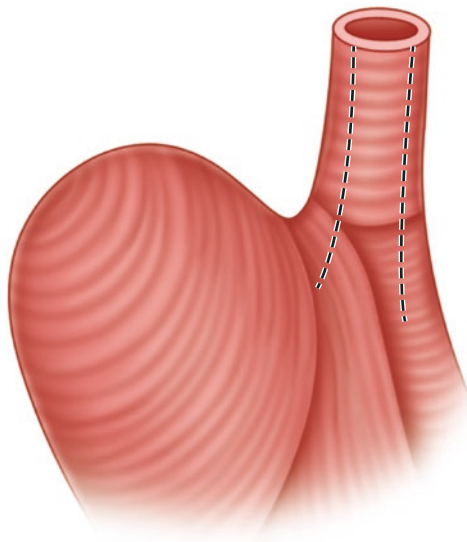

Fig. 10.8 Scheme of a dual myotomy technique; a wide tunnel over more than half of the posterior circumference of the esophagus is created, followed by two myotomy incisions along the esophageal body

This ensures that the mucosa is completely free from all adhesions of the initial bed of the diverticulum. The overall technical success rate of D-POEM was 91%, with a mean procedure time of 63 minutes. There were no adverse events. Clinical success was achieved in 100% in ten cases, with a decrease in mean dysphagia score from 2.7 to 0.1 ($P < 0.001$). The authors concluded that D-POEM offers the distinct advantage of ensuring a complete septotomy [46].

10.5 Clinical Success of POEM

POEM has been increasingly adapted in clinical practice since 10 years. Many studies report satisfying results from these series [5, 6, 21, 27–33, 39]. Randomized trials show similar results between POEM and dilations well as between POEM and laparoscopic Heller myotomy (LHM) [34, 35]. An unsolved question remains regarding the posttherapeutic reflux after POEM, which is in the majority of the patients a minor problem, but may lead in some patients to more severe GERD [47, 48].

The clinical acceptance of POEM among patients depends largely on the information given by the involved medical staff. In the USA, POEM has been promoted tremendously by doctors and institutions leading to large acceptance among patients. In Europe, medical staff has been rather cautious initially to promote POEM as a better alternative to the other therapeutic options such as dilatation or laparoscopic Heller myotomy (LHM). One study shows focusing on the patient's choice for myotomy, a rather balanced response [49]. In this study the patients with proven achalasia, once the indication for myotomy was established, had the choice to select POEM or LHM. Half the patients choose POEM and the other half LHM, and there was no difference between females and males [49].

The European Society of Gastrointestinal Endoscopy (ESGE) has provided guidelines, representing the expanding role of POEM in the therapeutic spectrum gastrointestinal, especially esophageal, and gastric motility disorders [36, 37].

The commission of the ESGE decided and published the following statements based on the available evidence [36, 37]:

1. Graded pneumatic dilatation is an effective and relatively safe treatment for esophageal achalasia.
2. Peroral endoscopic myotomy is an effective and relatively safe treatment for esophageal achalasia.
3. Laparoscopic Heller myotomy (LHM) combined with an antireflux procedure is an effective and relatively safe therapy for achalasia.
4. We suggest age and manometric subtype be taken into account when selecting a therapeutic strategy.
5. Treatment decisions in achalasia should be made based on patient-specific characteristics, the patient's preference, possible side effects and/or complications, and a center's expertise.
6. Overall, graded repetitive pneumatic dilation, LHM, and POEM have comparable efficacy.
7. Botulinum toxin therapy should be reserved for patients who are too unfit for more invasive treatments or in whom a more definite treatment needs to be deferred.
8. We suggest treating recurrent or persistent dysphagia after LHM with pneumatic dilation, POEM, or redo surgery.
9. We suggest treating recurrent or persistent dysphagia after POEM with either re-POEM, LHM, or pneumatic dilation.
10. We recommend follow-up endoscopy to screen for GERD in patients treated with myotomy without antireflux procedure.

The results of prospective studies have been summarized in several meta-analyses, and there are also data from randomized clinical trials [27, 34, 35]. Table 10.2 provides an overview on the POEM results in randomized trials with very accurately assessed details. Overall, it shows very good clinical results. POEM is an adequate therapeutic option next to laparoscopic Heller myotomy and dilatation [34, 35]. The results show a good outcome in 83–92% of patients after 2 years of follow-up. In these randomized trials, POEM is at least a similar successful option for achalasia therapy compared to LHM and dilatation [34, 35].

Table 10.2 Results from POEM patients in randomized trials

	RCT Werner et al. [34] $n = 112$	RCT Ponds et al. [35] $n = 64$
Age-year	48.6 mean	47 (37–56)
Male sex (%)	60.7	52
BMI mean	24.8	23.2
Achalasia subtype (%)		
I II III	13.4 75.9 10.7	16 65 19
Eckardt score	6.8 mean	8 median
Clinical success (%) Eckardt ≤ 3	2-year follow-up 83%	2-year follow-up 92%
Daily reflux symptoms (%)	6.5	
Daily PPI use (%)	38.7	41
Esophagitis (%)	57	42
Esophageal acid exposure mean (%)	7.1	–
Acid exposure 4.5%	44	–

Meta-analyses comparing different treatment options are always problematic in their interpretation, since the parameters among the different studies are not standardized, and therefore, comparison may be incorrect and interpretations may be not justified [50]. One recent meta-analysis comparing POEM with LHM in assessing 893 patients in 12 trials demonstrates for the therapeutic efficacy a slight advantage for POEM (MD = −0.257, 95% CI −0.512 to –0.002; $p = 0.04$) [27]. The reflux issue must be always discussed with POEM, since the post-POEM reflux problem remains an important drawback. In this meta-analysis, there was no statistical difference in postoperative reflux, but an advantage for POEM regarding hospitalization [27].

In conclusion, POEM is based on a genius idea in using flexible endoscopic techniques to reach a target area involved in a functional disease, which can be treated successfully in many

patients with innovative endoscopic means representing a true minimally invasive procedure.

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11 The EndoFLIP™ System Allows a Tailored Peroral Endoscopic Myotomy (POEM) for Achalasia

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Peroral endoscopic myotomy (POEM) is a scarless endoscopic technique developed more than 10 years ago and today widely used for the treatment of achalasia and other esophageal motility disorders. Since its first clinical application by Inoue et al. in 2010 [1], more than 7000 procedures have been performed [2]. As reported by two large European and US multicenter trials, short-term efficacy rates are similar to those of laparoscopic Heller myotomy (LHM) and with response rate of over 90% [3]. Long-term follow-up in a cohort of 500 patients showed excellent symptom control [4, 5].

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Today, POEM has become the standard of care treatment for achalasia, and is preferred over LHM, in many centers worldwide [3, 5, 6].

The most common POEM technique consists of the creation of a submucosal tunnel in the lower part of the esophagus on the anterior or posterior esophageal wall to reach the inner circular muscle bundles of the lower esophageal sphincter (LES) to perform myotomy while preserving the outer longitudinal muscle fibers. The anterior approach may theoretically reduce the risk of injuring the gastric sling-clasp muscle group which provides for the antireflux mechanism [7]. However, many centers also perform a posterior tunnel and myotomy, reporting comparable results in terms of clinical success, gastroesophageal reflux disease (GERD), and adverse events [8]. Additionally, other variations to the original technique consist of the full-thickness myotomy or the so-called progressive myotomy. This latter is a partial-thickness myotomy which then becomes full-thickness and at the level of the esophagogastric junction (EGJ) and cardia. The progressive myotomy has been demonstrated to reduce procedure time with comparable efficacy and risk of complications [9].

Short-term results suggest that POEM may be safer and more effective than LHM in relieving symptoms [10]. However, in contrast to LHM, POEM is performed without a fundoplication and may be associated with a higher incidence of pathologic de novo GERD up to 40% [10–12].

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Due to a lack of objective LES functional assessment at the time of myotomy, it is difficult to predict the precise effect of the surgical muscular disruption on the physiology of the EGJ. Additionally, achalasia is a heterogeneous disease categorized into three different manometric subtypes [13], with subtle differences in clinical presentation, but distinct responses to various treatment modalities. In this broad spectrum of possibilities, it is extremely important to perform an intervention that is patient and disease specific. Ideally the myotomy must be long enough to effectively relieve outflow obstruction, minimizing the risk of residual or recurrent dysphagia, but not too extended, so as to prevent the risk of GERD. Historically it is recommended that the myotomy extends 4–5 cm in the distal esophagus and 2–3 cm into the stomach [14]. Nevertheless for the treatment of esophageal motility disorders and type III achalasia, the myotomy should be tailored to address the obstruction to flow at the EGJ but also the spastic activity of the mid esophagus [15, 16]. It has been suggested that the ability of POEM to create a longer myotomy proximally to the EGJ may especially benefit patients with type III achalasia [16].

Several attempts have been made to monitor in real time, intraoperatively, the physiological changes that occur at the EGJ during myotomy. Barret et al. recently published a case series aimed at investigating the use of high-resolution manometry (HRM) during POEM [17]. The authors concluded that intraoperative esophageal HRM is feasible and might help tailor the length of the myotomy. However, this approach is relatively time-consuming. Other groups have adopted the double-scope technique to properly visualize the extent of the tunneling on order to avoid an unnecessarily long gastric myotomy [18]. This is achieved by placing a slim endoscope in retroflexion in the stomach while the position of the endoscope in the tunnel is verified by transillumination.

The Endoluminal Functional Lumen Imaging Probe (EndoFLIP™, Medtronic, Dublin, Ireland) impedance planimetry system (Fig. 11.1) is a catheter-based tool that uses impedance planimetry to assess EGJ geometry and pressure in response to a volume-controlled balloon distension. EndoFLIP™ measures real-time changes in EGJ distensibility and cross-sectional area (CSA) intraoperatively. Its intraoperative use has previously been described during antireflux surgery and LHM [19–22].

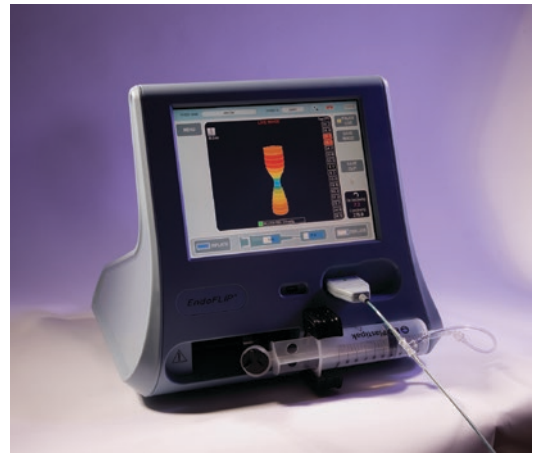

Fig. 11.1 The EndoFLIP™ system

The Functional Lumen Imaging Probe (FLIP) was initially developed in 2009 by Crospon Limited (Dublin, Ireland) and was purchased by Medtronic (Dublin, Ireland) in 2017. The system uses impedance planimetry technology to evaluate the compliance and distensibility of the sphincter. The CSA pooled acquisition and analysis of sphincteric length allow to simulate a three-dimensional profile of estimated diameters for the sphincteric region. The disposable catheter is 240 cm long and 3 mm wide. There are 16 pairs of impedance planimetry electrodes at the distal end of the catheter, which span a distance of 8 cm (EF-325 catheter). These sit between two outer excitation electrodes. These sensors are housed together with a solid-state pressure transducer within a highly compliant balloon (Fig. 11.2). The pressure transducer, located at the catheter's distal tip, allows measurement of intra-balloon pressure. Once centered at the level of the EGJ, the balloon is filled with a specially formulated saline solution of known conductivity and a continuous low current (I) is generated between the two outer excitation electrodes. Because the separation distance (L) between

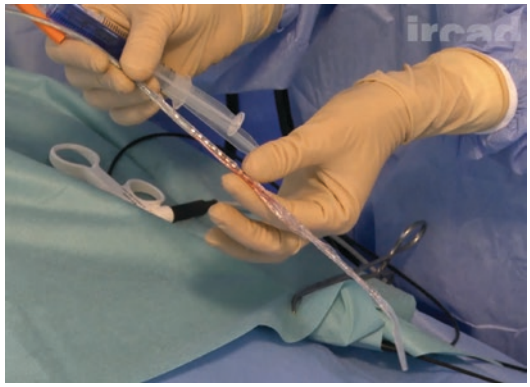

Fig. 11.2 The EndoFLIP™ disposable catheter

electrodes in each electrode pair and fluid conductivity (ρ) are known, the CSA at each electrode position can be determined by measuring the voltage drop (V), between each pair of electrodes, and calculating impedance Z ($=V/I$). Using the principal of impedance planimetry, CSA = $\rho L/Z$. By dividing the smallest CSA by intra-balloon pressure, the distensibility index (DI) is calculated. The DI defines the capacity of the sphincter to stretch in response to increased distending pressure from inside (e.g., a food bolus). Diameter data from each impedance planimetry channel are scaled from 5 to 30 mm and are interpolated and color coded on a hot/cold scale (small diameters are red/large diameters are blue). The system can measure the length of the high-pressure zone and the obstruction to flow, to allow the extension of the myotomy to be precisely tailored to the patient-specific disease.

EndoFLIP™ was quickly identified as an ideal tool for ensuring an adequate myotomy during POEM [23]. Its intraoperative use offers the possibility to evaluate the myotomy in real time, acting as a GPS, to determine the extension of the dissection, thereby preventing incomplete myotomy. As such, intraoperative EndoFLIP™ assessment provides an objective method to "tailor" the EGJ disruption in order to treat dysphagia while limiting chance of reflux afterward.

In addition intraoperative EndoFLIP™ distensibility measurements are also shown to correlate with postoperative outcomes [24].

11.1 FLIP System Configuration

Prior to catheter insertion, an automated purge sequence is used to evacuate air from the FLIP probe, and the pressure transducer is zeroed to atmospheric pressure while holding the catheter in horizontal position.

11.2 EndoFLIP™ Use During POEM

With the patient supine under general anesthesia and endotracheal intubation, after the placement of an Overtube®, an exploratory upper endoscopy is performed using a high-definition flexible gastroscope with carbon dioxide insufflation. In a retroflexed position in the stomach, indigo carmine is injected in the submucosal space on the anterior lesser curvature approximately 2 cm distally to the EGJ in order to mark the end point of the myotomy.

The stomach is deflated and the EndoFLIP™ system is introduced transorally, under endoscopic control, and positioned at the EGJ. The balloon catheter is filled with 30 mL balanced saline solution and pulled back into the EGJ until an hourglass shape appears on the EndoFLIP™ monitor. The "waist" of the hourglass represents the center of the obstruction to flow. Once the correct position is reached, the following parameters are recorded:

- CSA of the narrowest luminal area
- Diameter of the narrowest luminal area (Dmin)
- Intra-balloon pressure at the maximum diameter of the narrowest luminal area
- Distensibility index (DI) at the maximum intra-balloon pressure
- Length and exact location of the high-pressure zone in the EGJ which corresponds to that of the hourglass neck

The balloon is then deflated and removed.

Once the length of the high-pressure zone is known, based on the EndoFLIP™ measurements, the total extension of the myotomy can be calculated.

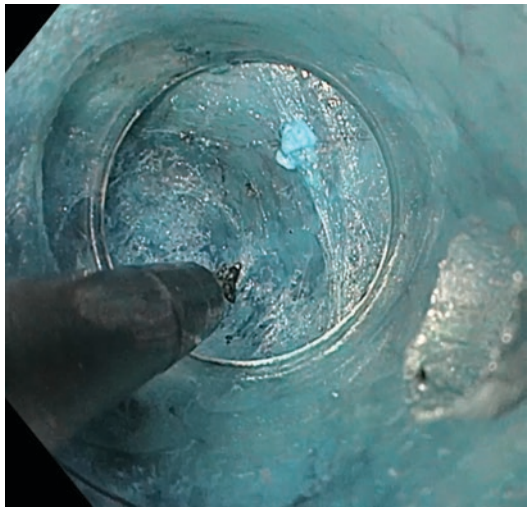

Fig. 11.3 The creation of the submucosal tunnel

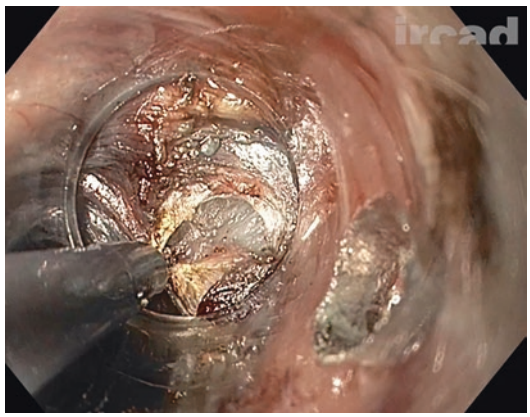

Fig. 11.4 The myotomy of the circular muscular layer

Due to the asymmetric nature of the LES, the myotomy should start 1 cm above the beginning of the high-pressure zone and extend to 2–3 cm distal to the EGJ.

POEM is performed according to the technique previously described by Inoue et al. [1]. In short, a submucosal tunnel is started onto the anterior or posterior esophageal wall (Fig. 11.3) at a distance from the EGJ calculated according to the desired myotomy extent and carried out up to 2–3 cm beyond the EGJ until it meets the prior indigo carmine injection. A selective myotomy of the circular muscular layer is then performed (Fig. 11.4). In patients with distal esophageal spasm and EGJ outflow obstruction (EGJOO), a longer myotomy encompassing the entire spastic segment of the esophagus according to HRM should be performed. Once the myotomy is completed, EndoFLIP™ measurements are repeated in to assess the efficacy of the procedure (Fig. 11.5). At the end of the intervention, the mucosal incision is closed using multiple endoscopic clips.

11.3 Current Evidence

Currently, the quality of the myotomy after POEM is assessed empirically through visual inspection of the EGJ at the end of the procedure. Obviously, this subjective evaluation is not quantitative and does not allow any standardization of the technique.

The ease of use and interpretation of EndoFLIP™ measurements in real time make it a powerful tool to be used as a guide and for quality-control assessment during the myotomy.

Based on the above concept, several studies have demonstrated that intraoperative EGJ evaluation using the EndoFLIP™ system is useful both to calibrate the myotomy and predict patient outcomes [23–27]. Low postoperative DI results in persistent achalasia symptoms, whereas a high final value predisposes toward postoperative iatrogenic GERD. Teitelbaum et al. [26] proposed an ideal range of EGJ DI between 4.5 and 8.5 mm^2/mmHg, with 40 mL balloon fill, to predict 6-month efficacy of POEM with a sensitivity of 68% and a specificity of 80%. Patients with a final distensibility in this range had better outcomes (i.e., Eckardt score $\leq$1 and GerdQ score $\leq$7) than those outside that window. The validity of this range is supported by two studies that showed healthy controls to have a mean distensibility ranging from 5 to 8 mm^2/mmHg [25, 28]. In a recent multicentric study by Ngamruengphong et al. [24], the authors evaluated intraoperative EndoFLIP™ data in 63 patients with achalasia treated with POEM. They concluded that a lower final CSA (using a 30 mL balloon volume) resulted in persistent symptoms, while a higher final CSA was associated with a new onset of reflux esophagitis. In 2020, Su et al.

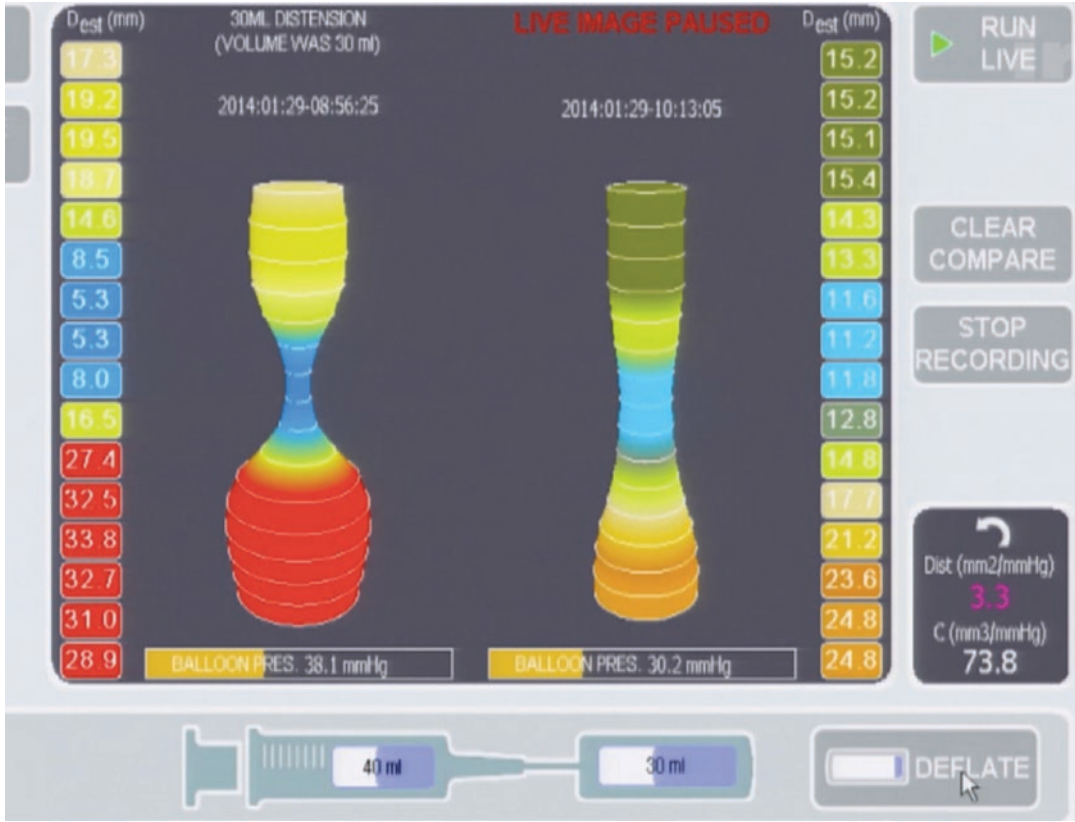

Fig. 11.5 EndoFLIP™ measurements before and after POEM

[21] conducted a retrospective single-center study of 77 patients who underwent LHM or POEM concluding that using a 30 mL volume fill, a final DI >3.1 mm^2/mmHg, or change in DI >3.0 mm^2/mmHg resulted in the best treatment outcomes. Additionally, a final CSA > 96 mm^2 was predictive of long-term reflux based on Reflux Symptom Index scores and could potentially be used as a guideline to tailor myotomy in the operating room and to identify a cohort of patients at high risk for post-myotomy reflux who will require a close follow-up with an objective reflux evaluation. All these results are unfortunately difficult to compare as the EndoFLIP™ protocol has not been standardized yet.

Recently Sloan et al. [29] published the first multicenter study using a new EndoFLIP™ device, called the EsoFLIP 330, to perform hydrostatic dilation of the EGJ in patients with achalasia and EGJOO. Clinical success was achieved in 60% of the patients (achalasia vs EGJOO: 68.4% vs 33.3% $p = 0.18$), and the median Eckardt score decreased from 5 (3–8) to 1.5 (1–4.75) ($p < 0.001$) in achalasia patients, while those with EGJOO had no significant change.

11.4 Conclusion

The EndoFLIP™ technology is the only objective tool that provides accurate functional and geometrical reconstruction of the gastrointestinal lumen allowing real-time assessment of the EGJ before and after POEM procedure. Its application is particularly useful in difficult situations such as redo myotomies in patients presenting with symptom recurrence. Due to a paucity of data on long-term outcomes and to discrepancies between studies, there is currently no standardized

protocol for EndoFLIP™ use during POEM. Nevertheless, all the studies reported in the literature suggest a beneficial impact of using EndoFLIP™ to tailor the myotomy and on predicting or improving patients' outcomes.

According to our personal experience, which accounts for more than 100 EndoFLIP™-guided POEM performed so far, we strongly encourage the routine application of this "smart" calibration catheter intraoperatively. EndoFLIP™ pre- and post-myotomy assessment represents a reliable "quality control" tool to ensure a precise patient-specific intervention to reduce the risk of persisting or recurrent dysphagia and to prevent the onset of GERD.

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12 G-POEM, A Minimally Invasive Endoscopic Technique for Gastroparesis

Caroline Saleh, Paul Fockens, and Bas Weusten

12.1 Introduction

Within the wide range of GI motility disorders, gastroparesis is known as a chronic, debilitating, and difficult to treat condition. Gastroparesis is defined as a syndrome of severely delayed gastric emptying in the absence of a mechanical obstruction, caused by dysfunction of gastric motility [1, 2]. The gold standard to objectively identify gastroparesis is nuclear scintigraphy, which defines gastroparesis as more than 35% retention at 4 hours and more than 60% at 2 hours when using a standard low-fat meal [2].

Though overall not common with 37.8 affected individuals per 100,000 in women and 9.6 per 100,000 in men, the prevalence of gastroparesis is rising substantially [1, 3–5]. In the United States, the number of emergency department visits and charges for a primary diagnosis of gastroparesis increased significantly from 2006 to 2013, with an increase in hospitalizations from approximately 900 in 1994 to 16,440 in 2014 [4–8].

Gastroparesis has a heterogeneous pathogenesis in which loss of interstitial cells of Cajal (ICC) and vagal and sympathetic nerve dysfunction seem to play an important role [1, 6, 9–12]. As a result, impaired fundic accommodation, antral hypomotility, gastric dysrhythmias, and pylorospasm may occur, all of which might contribute to the delayed gastric emptying [1, 11, 12].

Available treatment options for gastroparesis are directed at improving gastric motility and/or pyloric function [1, 4, 12]. Unfortunately, conservative options such as dietary modification and prokinetic medical treatment have limited effect and poor tolerability [1, 12, 13]. Given their low therapeutic efficacy, other more invasive treatment options became available, such as gastric electrical stimulation, endoscopic botulinum toxin intramuscular pyloric injections, endoscopic pyloric dilation, and surgical options including pyloromyotomy, pyloroplasty, and even gastrectomy for patients with severe refractory symptoms, of which the surgical options and endoscopic botulinum toxin intramuscular pyloric injections are most frequently used [1, 9,

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14, 15]. However, studies have shown that endoscopic botulinum toxin intramuscular pyloric injections are only effective for a short period of time, whereas surgical interventions have long-term effect in 70% of patients [15].

In the past two decades, there has been an emergence of minimally invasive endoscopic treatments. With the positive results of the peroral endoscopic myotomy (POEM) in patients with achalasia, other minimally invasive techniques, such as the endoscopic pyloromyotomy or gastric peroral endoscopic myotomy (G-POEM), have been introduced as a treatment option for gastroparesis. This chapter provides an overview on G-POEM, including the indications, technique, and clinical results.

12.2 Technique, Indications, and Work-Up

The technique of G-POEM is based on POEM, which is currently considered one of the established treatment options for achalasia [16]. The G-POEM procedure was first described by *Khasab* et al. in 2013, after which multiple studies followed, reporting G-POEM techniques with slight inter-technique variations [9, 17]. In essence, the G-POEM technique consists of the following essential technical steps: (1) establishment of a submucosal tunnel in the gastric antrum, (2) identification of the pyloric muscular ring, (3) myotomy, and (4) closure of the entrance of the submucosal tunnel [18]. Before giving an in-depth description of the technical G-POEM procedure, an overview is given of the indications and work-up of patients.

12.2.1 Indications and Treatment Eligibility

Gastroparesis has a diverse etiology, the root of the cause being either diabetes mellitus or non-diabetic [6]. The latter includes idiopathic, post-surgical (e.g., iatrogenic vagal nerve injury or due to esophagectomy with gastric tube reconstruction), drug-induced gastroparesis, connective tissue diseases, and neuromuscular diseases; an overview of the etiologies is provided in Fig. 12.1 [3, 6, 8]. Most commonly, gastroparesis originates from diabetes mellitus or idiopathic causes [3, 6, 10]. A meta-regression analysis by *Spadaccini* et al. determined that the etiology of gastroparesis did not appear to be a major determinant for the clinical efficacy of G-POEM [13]. However, taking into account the nature of the included studies, this statement should be taken lightly, and further research has yet to determine whether or not certain etiologies are better treated by G-POEM. For now, patients seem to be eligible for the treatment irrespective of the cause. It is recommended to consider G-POEM based on symptomology and diagnostic measurements. Moreover, given the invasive nature of G-POEM, it should only be considered after conservative measures have failed [16].

Gastroparesis can present with a wide array of symptoms, predominantly including early satiety, nausea, and vomiting [3, 6, 10]. The most common symptoms have been transformed into a validated scoring system, the gastric cardinal symptom score (GCSI), with a GCSI score $\geq$20 indicating the presence of gastroparesis [19]. Moreover, diagnostic measurements, with nuclear scintigraphy as the golden standard, can be performed to objectify the presence of gastroparesis; if nuclear scintigraphy is not available, a timed barium swallow could be considered as an alternative, although no standardized outcome measurements are available [16].

Although both antral hypomotility and pyloric dysfunction are believed to play a role in gastroparesis, the latter is thought to be the dominant factor [3, 6, 8, 10]. An established tool for assessing pyloric function, however, is lacking. Recently, an endoluminal functional lumen imaging probe (EndoFlip®, Medtronic, Dublin, Ireland) has been developed, allowing for the assessment of sphincter pressure, cross-sectional area (CSA), and the distensibility (DI) of the pylorus [10, 20]. Several studies using the EndoFlip® system showed that an increase in CSA and DI after endoscopic pyloromyotomy correlated significantly with favorable clinical outcome of G-POEM [20–22]. However, the

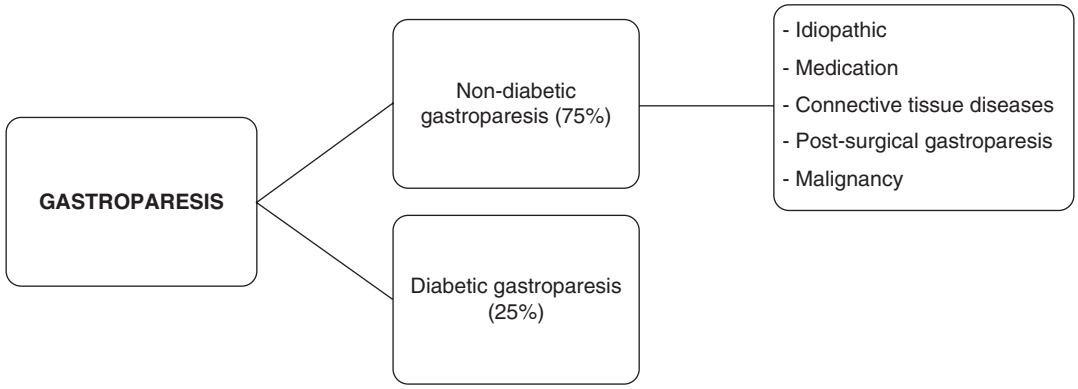

Fig. 12.1 Overview *of gastroparesis etiologies*

usefulness of the EndoFlip® system in the selection of patients who will benefit from endoscopic myotomy is hitherto uncertain since studies on the predictive value of EndoFlip® measurements pre-myotomy reveal conflicting results [23, 24]. Hence, further research is necessary to determine the role of EndoFlip® in the selection of patients for G-POEM [10, 20].

Lastly, some studies show that an initial positive response to intra-pyloric botulinum toxin injection predicts a positive outcome for G-POEM; however, a pooled analysis did not corroborate these results. Furthermore, there is a concern that repeated injections of the toxin might cause pyloric fibrosis making future interventions more difficult [10]. Therefore, if G-POEM is considered, it is advisable to proceed with a more definitive endoscopic intervention such as G-POEM rather than repeated botulinum toxin injections into the pylorus [10].

In summary, at present time, it is recommended to consider G-POEM for the treatment of gastroparesis only in patients with symptoms suggestive for gastroparesis, with evidence of gastroparesis on a validated diagnostic test, where medical therapy has failed [16].

12.2.2 Preoperative Preparation

Before the start of the procedure, the stomach should be empty. This can be challenging given the underlying impaired gastric emptying. Therefore, a rigorous preprocedural diet is mandatory. As preparation, we instruct our patients to follow a liquid diet for at least 3 days before the procedure, followed by clear liquids for 1 day and nil per mouth for 12 hours before the procedure, to avoid food retention in the stomach [18]. Even then, remnants of food are not uncommon, necessitating removal during the G-POEM procedure, before the mucosal incision is made (Fig. 12.2, panel **a**).

Before the start of G-POEM, experts recommend the administration of a systemic prophylactic antibiotic with adequate abdominal coverage, which should be in accordance with national or local protocol [7, 16, 18]. Even though there is no evidence suggesting beneficial use of prophylactic antibiotics, experts base the recommendation on the theoretical plausibility that G-POEM could induce translocation of bacteria from the digestive tract into the peritoneal space, especially if serosal perforation occurs [16, 25].

All patients are treated under general anesthesia with tracheal intubation, usually in supine position.

12.2.3 Equipment

To adequately perform an endoscopic pyloromyotomy, several tools should be readily available.

For the mucosal incision, the creation of the submucosal tunnel, and the final myotomy, different knives can be used. Most series report on

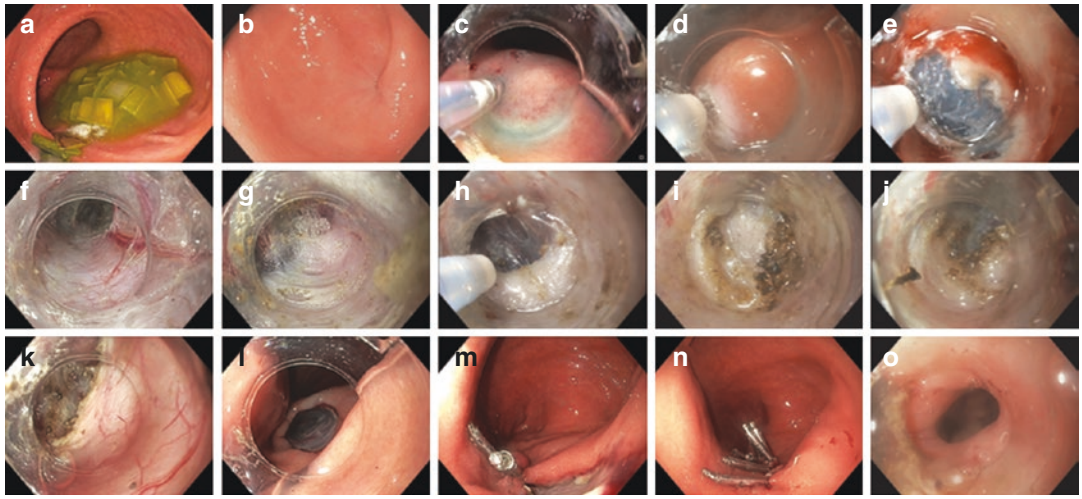

Fig. 12.2 G-POEM: (**a**) Food retention despite preparation; (**b**) closed pylorus; (**c**) creation of submucosal cushion; (**d**) mucosal incision; (**e**) creation of submucosal tunnel entrance; (**f**) submucosal tunnel – attempting to preserve blood vessels as much as possible; (**g**) pay attention to the direction of circular muscle fibers – tunnel should be perpendicular to the circular muscle fibers; (**h**) pyloric arch; (**i**) partial myotomy; (**j**) complete myotomy; (**k**) extension of myotomy toward the antrum (ca. 2 cm); (**l**) mucosal tunnel opening before closure; (**m**) closure in progress; (**n**) closed submucosal tunnel; (**o**) open pylorus

the use of the TT-knife (Triangular Tip, Olympus, Hamburg, Germany), HookKnife (Olympus, Hamburg, Germany), I- or T-Type HybridKnife (ERBE Elektromedizin GmbH, Tuebingen, Germany), or the IT-knife (Insulated Tip, Olympus, Hamburg, Germany) [7, 16–18, 26]. In addition, a device for submucosal injection is needed. Conventionally, a spray catheter (single use, Olympus, Hamburg, Germany) is used for this purpose during the phase of submucosal tunneling instead of an injection needle, to lower the risk of accidental damage of the overlying mucosa by a sharp and long needle. However, newer knives include a fluid injection modality within the accessory, such as the HybridKnife (ERBE Elektromedizin GmbH, Tuebingen, Germany), TT-J knife (Triangle Tip with integrated water-jet function, Olympus, Hamburg, Germany), and HookKnife with integrated water-jet function (Olympus, Hamburg Germany) [16]. As a lifting fluid, normal saline is generally used, with the addition of a small amount of indigo carmine to establish a light-blue color.

All kinds of electrosurgical generators can be used. The settings for the electrosurgical generator vary between the different brands and models, as well as between the various knives. Therefore, the specific electrosurgical generator settings should be manufacturer and knife specific. In the published studies, the vast majority of authors used an ERBE (Tuebingen, Germany) electrosurgical generator, the most commonly used being the VIO300D: when creating the mucosal incision either *Endo Cut Q mode effect 2*, *Dry Cut mode 50 W effect 3,* or *Endo Cut I mode effect 2* is used. During tunneling and myotomy, the preferred setting for most experts is spray coagulation 50 W effect 2 in case a TT-knife is used, whereas for the HybridKnife the preferred settings are either *spray coagulation mode 50 W effect 2*, *swift coagulation mode 35–50 W effect 3–5,* or *Endo Cut Q effect 2* [16]. When encountering a (bleeding) vessel with a diameter equal to or greater than 5 mm, a coagulation forceps (e.g., Coagrasper, Olympus, Hamburg, Germany) with *soft coagulation mode 80 W effect 5* can be used to achieve hemostasis [16, 18].

Both a single-channel and a dual-channel endoscope can be used. In our practice, we prefer a single-channel diagnostic endoscope with a water-jet function because of its flexibility and limited outer diameter. The upper digestive tract

is insufflated using carbon dioxide (CO_2) with the lowest possible insufflation force in order to prevent air-related adverse events, such as capnoperitoneum [16, 18, 26].

12.2.4 Mucosal Incision and Submucosal Tunneling

Before mucosal incision, submucosal injection of either a premixed 0.9% saline with indigo carmine or methylene blue solution is used to create a submucosal cushion where a 1.5–2 cm longitudinal or transverse mucosal incision can be made (Fig. 12.2c). The mucosal incision is made to establish access to the submucosal space (Fig. 12.2d) [17, 18, 26]. Most studies describe a longitudinal incision approximately 5 cm proximal to the pylorus along the great curvature [16, 18, 26]. Though the aforementioned shape and location are often described for the tunnel entry, there is no data on the advantages and disadvantages of different locations (greater curvature versus the posterior wall, or even lesser curvature) and shapes (transverse versus longitudinal) [16]. In our experience, the transversal shaped mucosal incision facilitates easy access to the submucosal space, but closure with hemoclips might be more challenging than for a longitudinal incision. To gain a better view of the submucosal layer, it is advised to attach a transparent cap to the tip of the endoscope [7, 17, 18, 26].

Subsequently, the submucosal tunnel is created by dissecting submucosal fibers from the mucosal entry site until the pyloric ring (Fig. 12.2e) [7, 17, 18]. In order to maintain orientation, it is important to dissect very close to the muscularis propria. This enables the visualization of the smooth muscle fibers. While performing the submucosal dissection, it is of utmost importance to follow a line perpendicular to the direction of the muscle fibers; otherwise, the pylorus might, unfortunately, be missed (Fig. 12.2g). The direction of the submucosal tunnel can be checked by a view from the luminal side. The dissection should be alternated by the injection of a blue saline solution into the submucosal space. This can be done by exchange of the knife for a spray catheter or by using newer knives, which include a spraying function. Moreover, it is important to identify and safeguard the vascularization during tunneling in order to preserve the integrity of the overlying mucosa (Fig. 12.2f). If needed, coagulation is used to ensure hemostasis in the submucosal plane.

Finally, while creating the submucosal tunnel, it is essential to prevent a too narrow tunnel, as this might act as an air valve and might result in a capnoperitoneum, a capnomediastinum, and subcutaneous emphysema.

12.2.5 Myotomy

The identification of the pyloric ring is a crucial step because the duodenum can be easily damaged if submucosal dissection is extended too far beyond the pyloric ring. The pyloric ring is identified by direct visualization of the so-called pyloric arch (Fig. 12.2h), a semicircular rim of muscle fibers as seen from the submucosal tunnel, but also by the bluish color of the stomach and duodenal mucosa near the pylorus when viewing from the luminal side [7, 10, 18, 26]. A complete myotomy of the pyloric circular muscle is performed, and experts recommend that the myotomy is extended for not more than 2–3 cm proximally into the antrum (Fig. 12.2i–k) [7, 10, 18, 26]. However, there is no data assessing the effectiveness and safety of G-POEM with regard to the length of the myotomy; no studies have been performed where different myotomy lengths were compared [16]. Nonetheless, experts assume that a longer myotomy (more than 3 cm) might lead to a worsening of antral hypomotility, and a shorter myotomy (less than 2 cm) might not be sufficient for adequate treatment of pyloric dysmotility [16].

12.2.6 Closure of Mucosal Entry

After myotomy, the tunnel is reinspected for possible bleeding, after which the tunnel entry is closed (Fig. 12.2l–m). In the available research,

closure of the tunnel entry has been described with hemostatic endoclips, the Over-The-Scoop-Clip (OTSC®, Ovesco Endoscopy AG, Tuebingen, Germany), or a suturing device, without any major difficulties [7, 10, 18, 26, 27]. At present, the choice of closure technique should depend on the experience of the endoscopist as there are no published studies comparing different closure methods [16]. Insecure closure of the tunnel might lead to leakage and infectious complications. However, in practice, postoperative leakage through an insufficiently closed or reopened tunnel entry is highly uncommon [16].

12.2.7 Postoperative Care

After the procedure, patients are admitted for 1–2 days, as the risk of severe complications cannot be ruled out. Additionally, patients should be kept nil per mouth for another 24 hours postoperatively; if no complications occur, it can thereafter gradually be expanded to a normal diet. Although some experts advise discharging patients only after a barium swallow (with a water-soluble contrast) or an endoscopy to exclude a possible leak, such an advert event is very rare and, if it does occur, will unlikely be asymptomatic [16]. We, in our practice, therefore, abandoned these postoperative examinations and allow for resumption of oral intake the day after the procedure when symptoms of abdominal pain and fever are absent.

In order to prevent ulceration, patients should be treated with a PPI, starting before the G-POEM extending to at least 4 weeks postoperatively. Prior to G-POEM and during the procedure, the PPI should be administered intravenously as the patient has no oral intake [16].

12.2.8 Postoperative Complications

Regarding safety, overall data are encouraging. The most common adverse events are immediate and postprocedural bleeding in 1.9% and 2.6%, respectively, followed by the formation of gastric ulcers in 2.3% [13]. Intraoperative capnoperitoneum occurs in a minority of patients and is easily treated by needle decompression [9]. Fortunately, there is also a low rate of serious adverse events, which include perforations and peritoneal abscess, with an overall rate of approximately 1% [13, 20, 28]. Late adverse events, such as pyloric strictures due to fibrosis, are reported in 1% of cases [13, 26, 28].

12.2.9 Treatment Evaluation

Symptoms of gastroparesis should be carefully evaluated before and after G-POEM. As briefly mentioned above, symptoms can be assessed using a validated symptom score, such as the GCSI [16, 29].

Additionally, experts recommend to assess gastric emptying with a validated objective tool, such as nuclear scintigraphy, approximately 3–6 months after G-POEM, to evaluate gastric emptying time [16].

12.3 Efficacy of G-POEM

G-POEM is a promising and exciting endoscopic therapy to emerge for gastroparesis. Endoscopic myotomy has already been pioneered for the treatment of achalasia and has been proven effective [9]. The first published case of G-POEM reported by *Khashab* et al. dates back to 2013 [17]. Since then, the number of publications has been growing rapidly [7, 9, 20, 21, 27, 28, 30, 31]. A recent systematic review published by *Spadaccini* et al. provides an overview of the most studies and a meta-analysis regarding clinical efficacy [13]. G-POEM was technically feasible in all patients. Significant symptomatic improvement was achieved after 83.9% of procedures, with a mean follow-up time of 7.8 ± 5.5 months [13]. When comparing the mean values of pre- and postprocedural nuclear gastric emptying, there was a significant decrease in retention at 2 hours from 74.9% ± 5.2% to 52.5% ± 10.8% ($P < 0.001$) and 4 hours from 44.1% ± 13.0% to 20.6% ± 9.5% ($P < 0.001$). Three recent studies by *Jacques* et al.,

Mekaroonkamol et al., and *Rodriguez* et al. all included a larger number of patients and showed clinical efficacy rates ranging from 80% to 90% [7, 20, 31]. Interestingly, the result of a meta-regression analysis showed no significant relationships between clinical success rate and patient characteristics such as gender, age, gastroparesis etiology, preprocedural GCSI score, gastric emptying scintigraphy evaluation, and previous pylorus-directed treatment.

It is important to realize, however, that there is still need for further research to determine the value of this minimally invasive technique. Up until now, *Kahaleh* et al. have been the only study group that followed patients for longer than 2 years, with a follow-up time ranging from 2 to 31 months [30]. Furthermore, most of the studies were of retrospective or uncontrolled prospective nature, and a direct comparison with other therapeutic modalities such as surgical pyloromyotomy, endoscopic balloon dilation, or endoscopic botulinum toxin injection is lacking. Therefore, controlled prospective, preferably randomized studies should be conducted with a long follow-up time to determine the actual benefits of G-POEM as treatment for patients with refractory gastroparesis. Moreover, more studies are needed on possible predictors of treatment success to improve patient selection.

12.4 Conclusion

G-POEM is a minimally invasive treatment option for patients suffering from refractory gastroparesis symptoms. Available data on efficacy and safety are encouraging, but long-term follow-up data are largely lacking, as are comparative (randomized) studies with alternative treatment options such as surgical pyloromyotomy or endoscopic balloon dilation of the pylorus. Finally, since both pyloric dysfunction and antral hypomotility are involved in gastroparesis and G-POEM only targets the pylorus, a combination of pyloric myotomy and gastric pacing is appealing. Future studies should evaluate this intriguing approach.

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13 Intraluminal Endoscopic Suturing System in the Esophagus with Separate Instruments

Karl-Hermann Fuchs, Kai Neki, Arielle M. Lee, Rebeca Dominguez, Brian Sandler, and Santiago Horgan

13.1 Introduction

One of the most challenging maneuvers in the early days of minimal invasive surgery was suturing for safe closure of the gut [1, 2]. Even in open surgery, the precise placement of a suture to stop a bleeding or to close a perforated gastroduodenal ulcer with its fragile inflammatory borders requires complex handling of the needle holder to achieve a "good bite" that is necessary for the patient in this moment. The level of complexity rises substantially with the attempt to suture with flexible endoscopic technology especially in a narrow lumen [3–6]. The latter has been aimed for since many years. Early flexible endoscopic technology such as the EndoCinch was lacking the deep bite to reach the muscularis of the gut wall [5–7]. The plicator was quite successful in creating deep sutures to perform an antireflux plication of the gastric wall [7]. The current version of this technique is used for antireflux procedures and gastric procedures [7, 8].

One of the main challenges during the NOTES hype was the safe closure of the stomach after transgastric procedures [9–12]. At the time the most favored solutions were multitasking platforms developed by several companies such as the EndoSamurai, the Anubis scope, and the Boston Direct Drive system [13–15]. However, none of these complex platforms really made it into routine clinical practice with the exception of the Overstitch system originating from the Eagle Claw device (Apollo Endosurgery, Austin, Texas) [16–18].

Robotic technology has been introduced into gastrointestinal surgery with promising potential also for suturing within a limited space [19–21]. Currently several robotic systems are developed with all the known advantages of being able to

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perform complex maneuvers in a small available space using all the degrees of freedom in robotic joints to perform suturing [22–31].

We have discussed the development of a rather simple mechanical technology, which enables the endoscopists in cooperation with surgeons to perform sutures in the esophagus and stomach, based on established minimal invasive technological principles and experience. We wanted to base our technique on commercially available flexible endoscopes, which would not require a major investment. The suturing system would be a needle holder, grasper, and knot pusher following the laparoscopic paradigm, again using basic mechanical technology with modified laparoscopic instruments.

Exploring the market for tools that would fulfill our aims and requirements for the project, we came across the instrument development of Fortimedix Surgical BV, Geleen, the Netherlands, with a new system of single port technology and flexible hand instruments [32, 33].

Some members of our working group at the Center for the Future of Surgery (UC San Diego) have used this new technology of small flexible instruments originally dedicated to be used in single port procedures [32, 33]. Subsequently, we have developed a flexible needle holder with a similar technology, which can be introduced into the esophagus and stomach alongside any flexible endoscope allowing for movement within the limited diameter of the esophagus without major friction. The idea was to perform a suture with the needle holder under flexible endoscopic guidance and assistance.

13.2 Development of Prototypes

Initially we used a semiflexible grasper from the Fortimedix Surgical™ instrument program for testing the limitations of the diameters of the necessary instruments. For this purpose standard flexible endoscopes (Olympus Corp., Tokyo) were used with a diameter of 10 mm and 6 mm. The diameter of the grasper was 5 mm. Fortimedix Surgical™ provided an initial prototype of a needle holder, which had flexible shaft connected to a handle following a laparoscopic paradigm

Fig. 13.1 Handle of the Fortimedix Surgical™ needle holder following the laparoscopic paradigm. It is used to grasp the needle and also by angulation and turning to steer the end effector

Fig. 13.2 End effector of the prototype needle holder for endoscopic procedures

(Fig. 13.1). The instrument can be rotated via the handle. In addition, the end effector of the instrument such as a needle holder can be manipulated in different directions via the position of the handle toward the shaft, thus allowing differentiated maneuvers in the target area (Fig. 13.2).

Discussing the possible future clinical application, it became evident that an easy and repetitive passage of the pharynx in the clinical situation would be a prerequisite in the future. Therefore, we looked for a commercially available overtube for the pharynx and found a Guardus™ overtube (US Endoscopy, USA; outer diameter: 18.5 mm, inner diameter 17.5 mm), which we used subsequently in all test series (Fig. 13.3). The instruments were placed in a Guardus™ overtube as well as in a porcine esophagogastric explant, fixed on an operating table. The tests showed no friction with the pediatric scope and the grasper, but also in another initial series with a standard gastroscope (10 mm) and the grasper, only minor friction was noticed.

Fig. 13.3 Top entrance of the Guardus™ overtube to insert in the esophagus to facilitate the passage of different instruments, which are needed for the process of suturing and knot tying together with a flexible endoscope

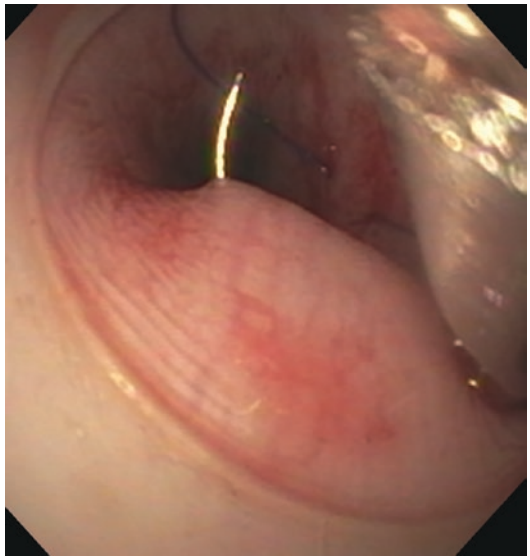

Fig. 13.4 The needle is driven with force into the esophageal wall and tissue to perform a substantial "bite" with the needle (3/0 Prolene), driven by the needle holder prototype (diameter 5 mm) with flexible shaft

Regarding the necessary force to drive a needle through the test material, the following series showed a sufficient grip and force of the initial prototypes (Fig. 13.4). Also, knots could be performed outside the Guardus overtube and pushed inside without problems. An important issue was the grasping and regrasping ability and force of the needle during the process of driving the needle through test tissue (Fig. 13.5).

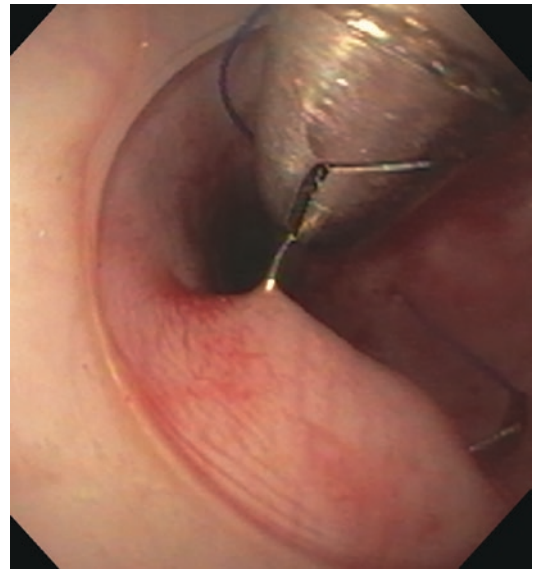

Fig. 13.5 The needle is regrasped with the Fortimedix Surgical™ needle holder after having been driven through the tissue, to complete the "bite"

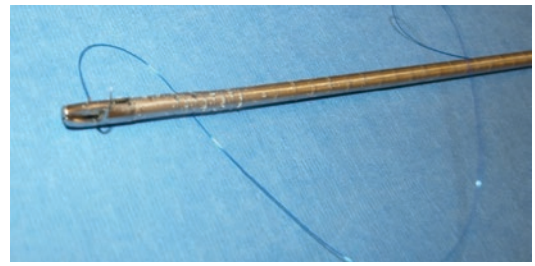

Fig. 13.6 Several test series were done to look for an optimal suture material, which turned out to be a (3/0) Prolene suture material, which is a good compromise between size of needle, tissue abilities of the suture material, and the handling especially for extracorporeal knot tying

After initial test series experience showed that a 3/0 suture material with a RB-1 needle size and shape 3-0 Prolene (Ethicon, Cincinnati, OH, USA) would best fulfill the requirements regarding the suture work, the necessary manipulations in the narrow lumen of the Guardus™ and later the esophageal explant as well as the length of the thread in order to perform extracorporeal knotting (Fig. 13.6).

In a second series of the initial test phase, we explored the actual performance of the system using the esophagogastric explant and the suturing abilities of the system with newly produced

prototype of a needle holder with a diameter of 5 mm. In addition, we had to find optimal suture material, which would fit in size and shape of the needle and also would be sufficient long enough to be able to perform extracorporeal knotting. A 5-mm knot pusher was also provided by Fortimedix Surgical™ with the same flexible technology as the needle holder (Fig. 13.7). Usually three knots would be added after the suture to secure the stitch.

Fig. 13.7 With the flexible Fortimedix Surgical™ knot pusher, the knots can be quite easily pushed downward to complete a closure of the tissue

The important features for a needle holder are the direct transformation of force from the manipulating hand via the needle holder to the needle in the mouth to the tissue. Since the needle holder should be at the same time flexible to follow the flexible scope and preferably steerable to a certain extent, the mechanical solution to fulfill these wishes has to be special, which is solved by the unique technology, provided here. The 5-mm EndoSuture needle holder (Fortimedix Surgical BV, Geleen, the Netherlands) followed the established laparoscopic principles. The shaft was flexible and articulating in all directions by moving the handle outside the "body."

More test series were added. Again, the grip of the needle holder mouth on the needle could be tested and modified. The complete process of grasping the needle before passing the Guardus and driving it through the overtube to the lumen of the explant, followed by a bite with the needle through the esophageal wall, was tested. Regrasping the needle tip, after it was pushed through the first layer, turned out to be quite cumbersome in the beginning. With training the force of turning the needle, the process could be opti-

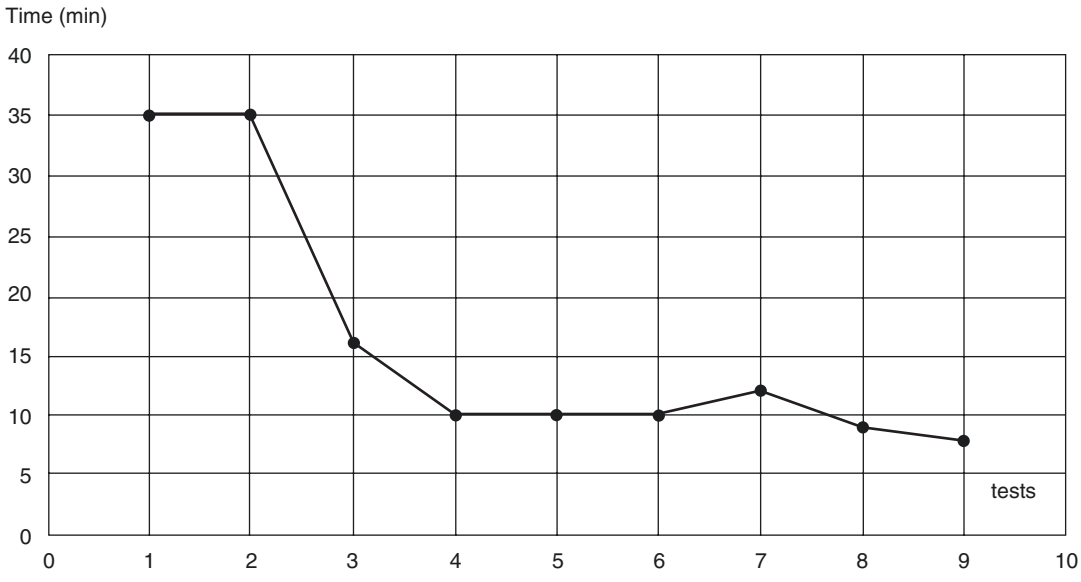

Fig. 13.8 Time consumption of the initial process of performing a suture through the esophageal wall by different surgeons with different levels of experience. In total, the process of learning leads quickly to a shorter duration of the procedure

mized. Finally, a test series with several participants was organized showing an acceptable learning curve regarding duration of the procedure in the first test series with one bite (Fig. 13.8).

Again, the mouth of the needle holder was finally modified to a new prototype with a small groove in the lower branch of the mouth in order to have a rest for the needle bow and a better grip in the needle holder.

13.3 The Final Tests in Porcine Model

The final test series were performed in a porcine model. All necessary requirements for animal testing were requested and granted by the University of California San Diego (UCSD). After permission was obtained, the training was performed at UCSD, the Center for the Future of Surgery, animal training facility in La Jolla, CA, USA. Care was taken to follow strictly the rules for Good Laboratory Practice. The animals were under continuous monitoring and observation by trained personnel during the complete procedure.

The animals were under general anesthesia in supine position on the operating table (Fig. 13.9). In order to provide a stable platform for the needle holder system, the holding structure was anchored on the side rail of an operating table by fixing it to a StrongArm™ Surgical Holder (Mediflex) (Fig. 13.10). The end effector could be turned using the triangulation under camera vision provided by the flexible endoscope. Since the needle holder was not attached to the scope, it could be maneuvered in and out of the esophagus without limitations. Again, an overtube (Guardus™, US Endoscopy, USA; outer diameter: 18.5 mm, inner diameter 17.5 mm) was routinely used. The latter made repetitive passages through the pharynx possible without problems.

By moving the handle of the needle holder in different directions, the tip of the needle holder could be steered in different directions according to the necessities of the suturing process (Fig. 13.10). For knot tying a 5 mm EndoSuture knot pusher with a similar flexible, articulating shaft (Fortimedix Surgical BV, Geleen, the

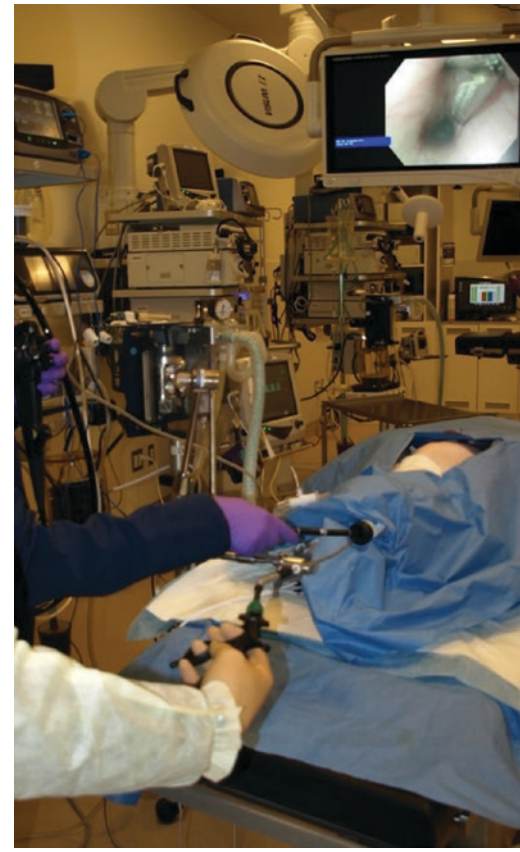

Fig. 13.9 Experimental setup in a porcine model to simulate and train the closure of an esophageal perforation. The subject is in general anesthesia supine on the operating table. One operator is managing the flexible endoscope, while the second operator is handling the needle holder to perform the suturing

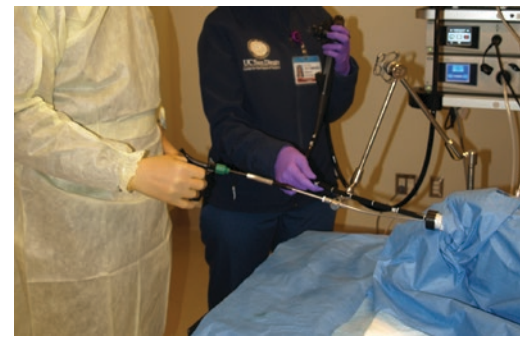

Fig. 13.10 The needle holder is fixed in a StrongArm™ surgical holder (Mediflex) to provide stability to the needle holder shaft. This allows for manipulation of the handle of the needle holder, which is transferred into the steerable end effectors

Netherlands) was used to advance the knots to the suture site. For the actual approximation of the tissue and knot tying, extracorporeal tying just like in laparoscopic surgery was performed.

A standard flexible pediatric endoscope and a standard gastroscope were used for testing. Since the overtube had an inner diameter of 17.5 mm, either a regular gastroscope (diameter 10.5 mm) or the needle holder (diameter 5 mm) could be used, or, as an alternative, we also tested the application of a pediatric gastroscope (diameter 5.5 mm) and the needle holder (diameter 5 mm) together with an additional 5-mm EndoSuture grasper (Fortimedix Surgical BV, Geleen, the Netherlands) to assist the needle holder maneuvers.

During the test phase, suture training was performed in the proximal and distal esophagus and, due to the length of the instruments, also in the proximal stomach. It was also tested transanally in the rectum and sigmoid. Experience showed that suturing was easier in the gastric lumen due to the available space to perform the necessary suture movements and handle the needle. Surgeons from several levels of experience participated in this study in order to gain a representative picture from novices to experts. The shape of the needle holder mouth was changed and adjusted from one training series to the next one based on the experience and the information given by the participants (Fig. 13.11). It also improved the ability of the needle holder to more easily regrasp the needle during the procedure.

Once the esophageal lumen was reached, the surgeon could turn the needle holder to drive the tip of the needle through the esophageal wall in order to get a "good bite" (Fig. 13.12). The necessary force was quite remarkable, since the mucosa was flexible and would hardly allow the needle to penetrate. This could only be overcome by a determined and quick movement to drive the needle tip into the mucosa and subsequently turn the needle sharply (Fig. 13.4). Then, the needle tip was regrasped with the needle holder and pulled out of the tissue (Fig. 13.5). Furthermore, the needle with the thread was pulled back outside of the overtube (Fig. 13.13). An extracorporeal knot was placed and then pushed with the knot pusher to the esophageal site (Fig. 13.14). This was repeated to secure the suture with three knots. The thread was cut with endoscopic scissors.

Another test series included an incision in the esophagus, which was performed of the esophageal wall into the muscle using a TT-knife and monopolar current. Care was taken on the one hand to make a deep enough cut to divide a good portion of the esophageal wall and on the other hand to not completely perforate the esophagus to avoid a pneumothorax. If there was an active

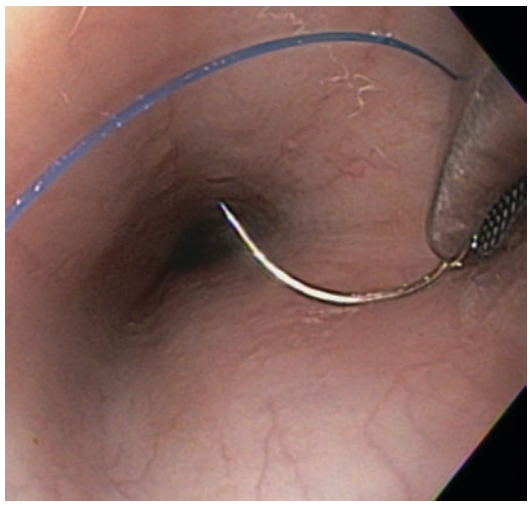

Fig. 13.11 The suture needle is grasped with the needle holder outside the body and advanced through the overtube into the esophageal lumen. It is turned and regrasped to perform a suture

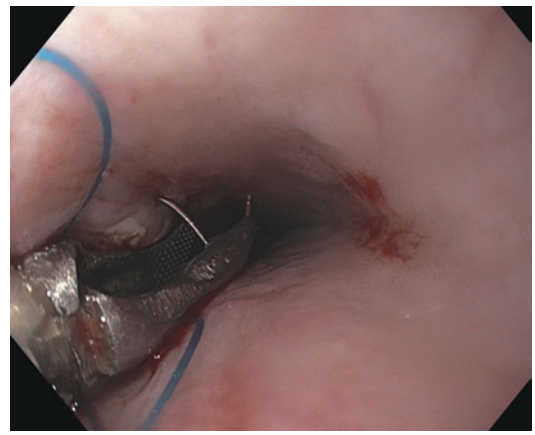

Fig. 13.12 With the flexible shaft of the needle holder a suture site can be performed with sufficient force using the rotating ability of the instrument

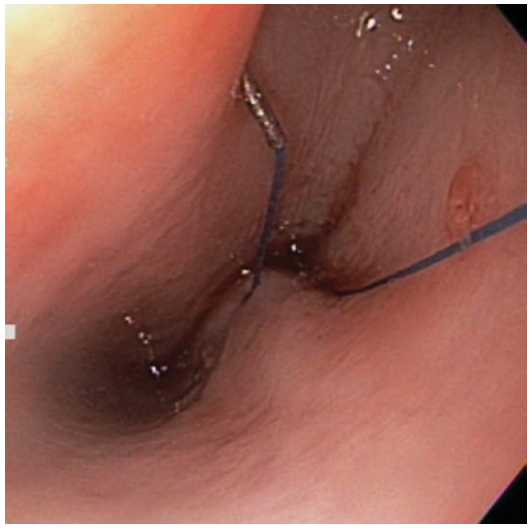

Fig. 13.13 After the needle is pulled out of the tissue, it is withdrawn out of the esophagus outside, thus running the Prolene suture through the suture site. Subsequently, knot tying can be performed extracorporeally

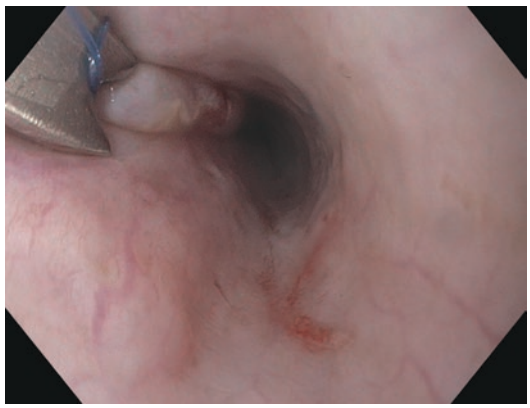

Fig. 13.14 After knot tying extracorporeally, the knot can be pushed and advanced into the esophagus and further distally with the flexible knot pusher

bleeding visible, it was stopped by coagulation with the TT-knife.

Then the needle holder was inserted with the mounted needle under endoscopic vision and advanced to the incision site. Now the wound edges of the incision site were inspected, and the closure was started by driving the needle through one side of the wound opening. The needle tip was regrasped and pulled through the tissue. Then the needle was again regrasped with the needle holder, and the next bite was performed on the corresponding side of the wound. Care was taken to include in the bite as much muscle layer as possible to simulate the "real clinical" situation of closing a perforation. After pulling needle and thread back to the outside, three extracorporeal knots could be tied and pushed down with the flexible knot pusher and thus complete the closure of the esophageal wound.

Each participant performed sutures on the esophagogastric explant in the box model as well as in the porcine esophagus in the different series. Feasibility, duration of the procedure, and handling problems were documented. After each session a debriefing with the engineers was performed to transfer the information and experiences into possible technical improvements of the used devices. Then in the subsequent series the surgeons could experience the benefits or disadvantages of the changes following this iterative process to create improvements.

13.4 Results of Esophageal Closure

The initial series showed that the median duration for the single bite suturing and knot tying was 10 min [8–35]. The process of extracorporeal knot tying was rather easy to handle with the flexible knot pusher and the duration was only median 5 min [2–8]. The duration of the double bite suturing and approximation of the incision and esophageal closure took in the median 20 min [14–45] [34]. The time-consuming part in this series was the suturing segment, since it was sometimes difficult to penetrate the mobile wound border at the incision site and grab as much muscle as possible on the needle. However, the suturing could be finalized with the improved needle holder in all attempts.

13.5 Comments

Nowadays, the trend of minimal invasive therapeutic concepts moves not only from open surgery to minimal invasive surgery but also from

laparoscopic procedures to flexible endoscopic and/or transluminal techniques, for example, from laparoscopic Heller myotomy to flexible peroral endoscopic myotomy (POEM) or from laparoscopic colon resection to transanal, transluminal colon resection [35–39]. If this trend is continuing, endoscopists and surgeons need a dependable and "easy to apply" gut-closure technique [40–44]. However, this is quite challenging and still faces many difficulties.

Currently, extensive experience is gathered in several centers with the over-the-scope clip application for safe closure of perforations [45–46]. The Ovesco clip has also been used to assist in endoscopic full-thickness resections (EFTR) [45–47]. There is a growing number of data for this technique with a good safety record [45–47]. This technique is also used for tumor resection after previous isolation of the tumor by wall inversion [47, 48].

Another option is the Apollo Overstitch system, which is used by a few experienced centers [18, 49, 50]. Other users report on cumbersome and quite time-consuming experience [51–54].

The narrow space in the gut lumen and the limited degrees of freedom in some instruments make it very difficult to manipulate and maneuver endoscopic platforms with therapeutic suturing features [4, 10, 13, 14, 55]. Robotic systems would provide multiple degrees of freedom and could be applied in areas with limited space due to their maneuverability. However, robotic systems are expensive and many are only available as prototypes still under development [56]. The downside of robotic technology is the complexity and the associated costs and necessary investments for the payers. Different robotic systems are competing on the market [22–30]. A major potential advantage is the rather convenient application of robotic technology within a narrow space. However, a challenge could be the application within the gut lumen. For the past 10 years, gastroenterologists and GI surgeons have been awaiting reports on these prototypes, but progress toward widespread clinical applicability is rather slow [13, 14].

As a consequence, our group was searching for a solution of flexible endoscopic closure and suturing, which would combine easy clinical application relying on the existing endoscopic and laparoscopic experience in centers and on a platform with flexible, articulating suturing instruments, which would not require a major investment for the hospital administration.

First, the necessity for such instruments should be discussed to explore the unmet needs. Perforations in the GI tract still belong to medical conditions, which need immediate attention, diagnostic involvement, and potentially immediate subsequent therapeutic action, which should be preferably performed via minimal access techniques. In this situation, one would wish for an endoscopic device or system, which would reach rather easily the site of perforation and close it by rather simple (and inexpensive) methods of suturing. Indications for endoscopic suturing can be widely identified for all perforations in the gut, for anastomotic insufficiencies, possibly also for longer-term fistulas after endoscopic cleaning and conditioning of the fistulas and tissue, as well as for gut closure after elective full-thickness resections [10, 11, 18].

Of course, once such an endoscopic suturing technique is established, it could also be indicated in cases with a therapeutic need for any kind of suturing such as narrowing a wide anastomosis after gastric bypass for obesity or for endoscopic gastric sleeve formation [57]. In addition, other endoscopic suturing techniques have been evaluated and published, however the diameter of these instruments is small; thus rotation force and direct transfer of mechanical manipulations may be limited [58].

Discussions about the technical features of the system must be started with the applicability of the instruments next to an endoscope in the upper GI tract, which will have limitations due to the diameter of the scope and the flexible instruments. The maximum luminal diameter in the esophagus of most human beings is around 20 mm. As clinical experience has shown with stapling devices, this will already be somewhat too large for smaller, thinner individuals [59]. Therefore, it is very helpful that the Fortimedix Surgical EndoSuture system allows for the use of standard 10 mm endoscopes and even 5 mm

endoscopes. It was no problem in terms of friction or sizing to use a pediatric endoscope together with the EndoSuture needle holder and an additional EndoSuture grasper. In this series we used an overtube with 18.5 mm outer diameter, because it was easily commercially available. One could increase the possibilities to use a 20 mm size overtube, if it were available. The main advantage is in this context the system does not need special designed complex endoscopes.

Another advantage of the system is use of regular suture material, which can be made available in any operating room. No complex suturing machinery is necessary, because the actual suturing is performed following the traditional and well-experienced laparoscopic paradigm. The latter, however, may be suspicious to the gastroenterologic endoscopist, who may be not familiar with the suturing process. The results of the study show an acceptable learning curve for this technique. Therefore, one should not be hesitant to use the system for this reason. In addition, it could be advisable not only for the technical steps of suturing but also for the overall management of the patients with perforations to establish a cooperation between the endoscopist and GI surgeon.

13.6 Conclusions

The Fortimedix Surgical™ EndoSuture flexible, articulating instruments are feasible to use and perform dependable intraluminal sutures. The training period and learning curve is short, and the future perspective is to apply this system clinically for closure of perforations and fistulas.

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14 Endoscopic Suturing Platforms for Bariatric Procedures

Margherita Pizzicannella, María Rita Rodríguez-Luna, and Silvana Perretta

14.1 Introduction

Morbid obesity is a growing public health threat across the world [1]. In addition to causing an objective reduction in patient quality of life, obesity should be considered as a health emergency since it is associated with many serious comorbidities reducing life expectancy [2]. Dietary restrictions and lifestyle modifications, including pharmacological therapy, have a limited benefit. Bariatric surgery is the only gold standard treatment, which has been proven to be associated with the best long-term weight reduction and control of comorbidities [3, 4]. However, due to a burden of cost and healthcare resources, related risks, and poor patient acceptance, only 1% of the obese population benefits from a surgical bariatric intervention [5]. The endoscopic procedures for morbid obesity fill the gap between the large number of obese patients and the small number of surgical interventions. Indeed, bariatric endoscopy has proven to be effective in reducing morbidity and achieving weight loss, as it is less invasive and better tolerated. In the vast panorama of endoscopic treatments, the use of endoluminal suturing systems to achieve gastric restriction is certainly the approach which is gaining the highest popularity over the last few years.

Durability is the major challenge of endoscopic sutures, which requires transmural serosa-to-serosa apposition [6]. Currently, three suturing devices are clinically available to create endoscopic gastric restriction with full-thickness sutures, namely, the Incisionless Operating Platform™ (IOP, USGI Medical, San Clemente, CA), the OverStitch™ (Apollo Endosurgery, Austin, TX), and the Endomina™ endoluminal suturing device (Endo Tools Therapeutics (ETT), Gosselies, Belgium).

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14.2 Incisionless Operating Platform™ (IOP, USGI Medical, San Clemente, CA) for Primary Obesity Surgery Endoluminal (POSE™)

POSE™ uses an Incisionless Operating Platform™ (IOP, USGI Medical, San Clemente, CA) [7] (Fig. 14.1).

Fig. 14.1 The IOP™ system. (Courtesy of Doctor Manoel Galvao-Neto)

Fig. 14.2 Detail of the distal tip of the IOP™ system. (Courtesy of Doctor Manoel Galvao-Neto)

The IOP™ system is composed of an overtube with a control handle and four operative channels which suit different devices: a 4.9 mm scope for visualization purposes; the g-Prox™, a grasper with a jawed gripper for tissue grasping and mobilization; the g-Lix™, a tissue anchor catheter with a helical distal end used for anchoring and bringing the tissue inside the g-Prox™; and the g-Cath™, a catheter with a needle at its distal tip which penetrates the grasped tissue, installs two preloaded suture anchors, and cinches them to form a plication (Fig. 14.2).

The IOP™ system was approved for gastrointestinal tissue apposition by the Food and Drug Administration (FDA) in 2006, and in 2010, the system was upgraded to the current configuration. The POSE™ procedure consists of the application of eight to nine suture anchors in the gastric fundus in retroversion until the apex of the fundus is lowered at the gastroesophageal junction (Fig. 14.3).

Once the fundus has been restricted, three to four additional suture anchors are placed in the distal body near the proximal antral inlet (Fig. 14.4).

Espinos et al. published the first in-human study of POSE™ in 2013, showing a 15.5% TWL at 6 months [8]. Subsequently, Lopez-Nava et al. observed an average %EWL of 44.9 ± 24.4% (and %TWL of 15.1 ± 7.8%) in 116 patients available for follow-up at 1 year [7]. In 2016, a multicentered randomized sham-controlled trial (ESSENTIAL trial) was conducted revealing a technical success rate for POSE™ of 99.5% and a mean TWL at 12 months of 4.95 ± 7.04% versus 1.38 ± 5.58% in the control group [9]. The

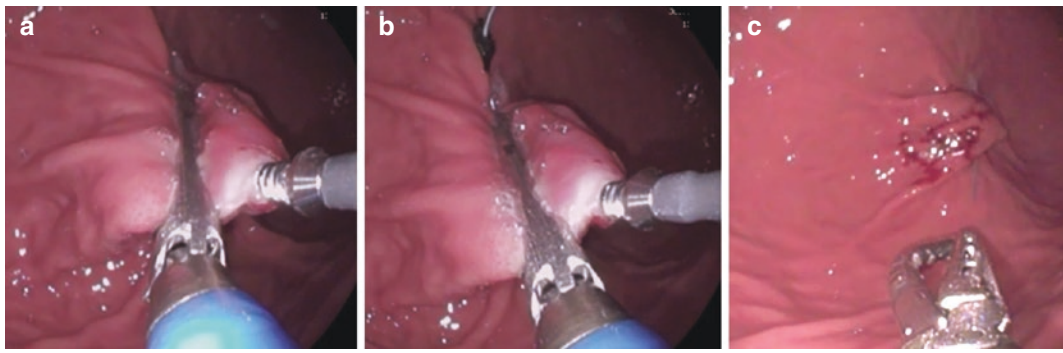

Fig. 14.3 The POSE™ procedure: (**a**) The g-Lix™ anchors the tissue and brings it inside the g-Prox™. (**b**) The g-Cath™ penetrates the grasped tissue with the needle and installs the first preloaded suture anchor. (**c**) The second preloaded suture anchor is released and cinched forming the plication

poor outcome of this large controlled study questioned the efficacy of the technique and reduced its spread. However in 2020, Lopez-Nava et al. proposed a new suturing pattern named POSE™ 2.0 targeting the gastric body and sparing the fundus, making the procedure more similar to the OverStitch™ and Endomina™ gastroplasty techniques [10]. In the preliminary results with 73 obese patients treated, no adverse events were reported after POSE™ 2.0, and a TWL of 15.7% was obtained at 6 months.

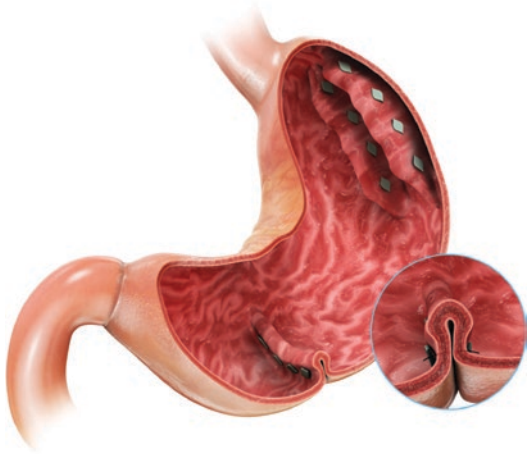

Fig. 14.4 Reconstruction of the POSE™ procedure. (Courtesy of Doctor Manoel Galvao-Neto)

14.3 Endomina™ System

Endomina™ is a suturing system relatively new on the marketplace [11]. The device is CE marked in Europe. It is made of a triangulation platform assembled to a forward-viewing scope in the stomach. A 5 French needle preloaded with sutures (Transmural Anterio-Posterior Endoscopic Suture, TAPES, SA-ETT) is accommodated in its flexible arm. The gastric restriction starts at the level of the distal body, going backward to the fundus, which is spared. The Endomina™ system is advanced into the stomach over two guidewires. A standard gastroscope is then pushed into the system in between its arms once guidewires have been retrieved. The TAPES is then introduced into the flexible arm of the platform. A large forceps (Raptor, US Endoscopy, Mentor, Ohio, USA) is introduced through the channel of the endoscope and is used to grab the tissue and pull it back into the two arms (Fig. 14.5). The needle is passed full-thickness through the gastric wall and a first

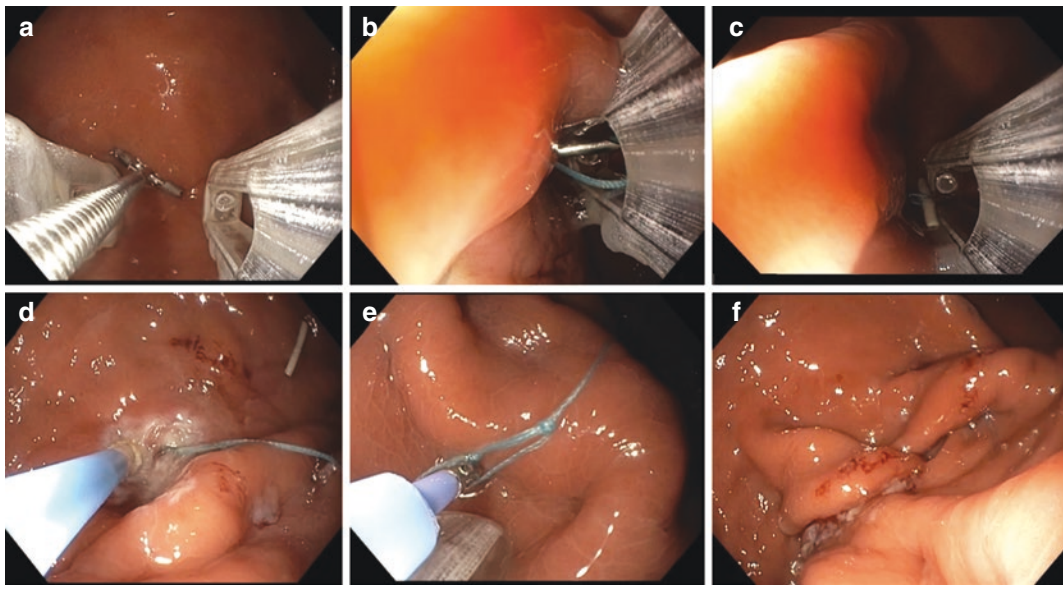

Fig. 14.5 Gastric plication steps using the Endomina™ system: (**a**) A large forceps is used to grab the tissue into the system. (**b**) The needle is passed full-thickness through the wall. (**c**) A first tag attached to the suture is released. (**d**) After releasing the second tag on the opposite wall, the entry points of the two sutures are coagulated with a bipolar probe. (**e**) A hook is used to pull on the suture. (**f**) The plication is created

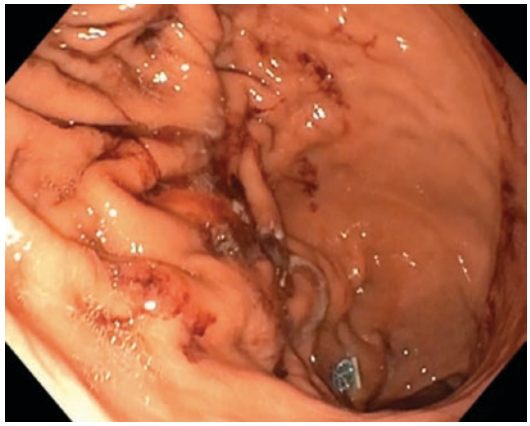

Fig. 14.6 Final aspect of the gastric plication using the Endomina™ system

tag, attached to the suture, is released. A second plication is made in a similar fashion on the opposite wall of the stomach, and a second tag, attached to the same suture, is released. Bipolar coagulation (Gold Probe, Boston Scientific, Marlborough, Massachusetts, USA) is then applied around the entry points of the two sutures to facilitate the mucosa-mucosa apposition. A hook is passed through the endoscopic channel and is used to pull on the suture to achieve suture tightening (Fig. 14.6).

Due to the novelty of the procedure but above all because of its technical demand, Endomina™ has not known a great spread and only few studies have been published in literature [11, 12]. In a multicenter prospective study, at 12 months of follow-up, 45 patients showed a TWL of 7.4 ± 7% and no severe adverse events [12].

14.4 OverStitch™

Among the endoscopic suturing devices used for obesity, the FDA-approved OverStitch™ system is the one that is most popular and widely used. The key of its success is probably related to its ease of use and to the promising clinical results obtained so far. Since its first use in the bariatric field by Abu Dayyeh et al. in 2013 [13], this over-the-scope suturing platform has gained a certain popularity.

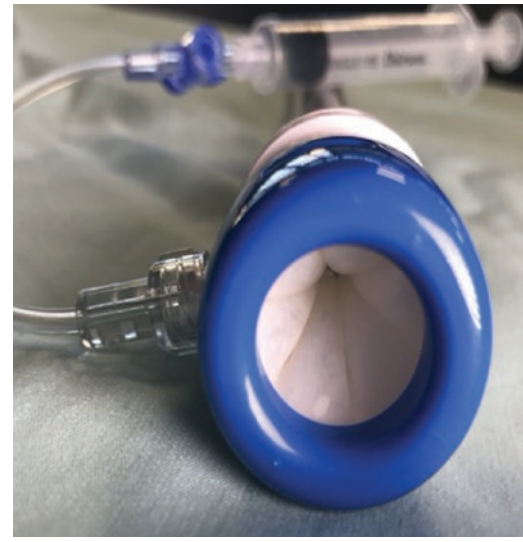

Fig. 14.7 Overtube® (Apollo Endosurgery, Austin, Texas, USA)

Fig. 14.8 The OverStitch™ Sx™. (Courtesy of Apollo Endosurgery)

The procedure is performed under general anesthesia with the patient lying supine. An Overtube® (Apollo Endosurgery, Austin, Texas, USA) is placed to protect the esophagus and the airways. The Overtube® has a peculiar inflatable cuff at its proximal tip designed to ensure an appropriate insufflation for a safe access to the gastric cavity (Fig. 14.7). Two are the suturing systems currently available on the market: the classic OverStitch™ and the OverStitch™ Sx™ (Fig. 14.8). The latter is compatible with several single-channel endoscope and has been recently introduced to overcome the disadvantage of the OverStitch™ to be suitable only for dual-channel endoscopes [14].

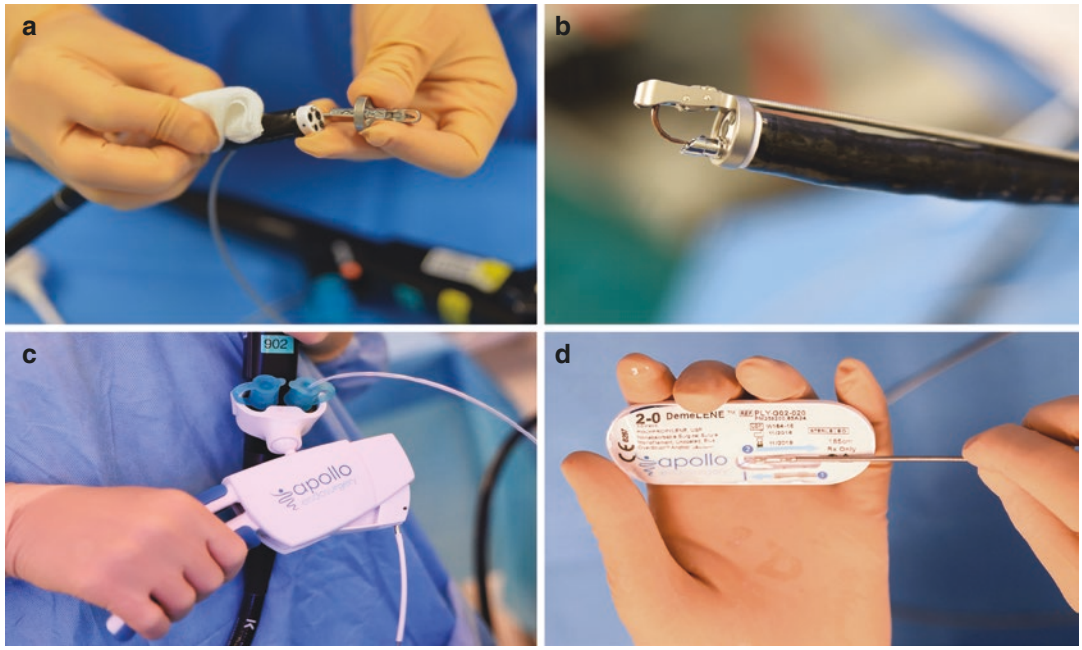

Fig. 14.9 The OverStitch™ system in detail

The gastroplasty is created using the OverStitch™ system mounted on a double or single scope under carbon dioxide insufflation. The over-the-scope platform is composed of an OverStitch™ handle, fixed to the endoscope control handle, and a needle driver attached at the distal tip of the scope (Fig. 14.9). The operator can activate a 15-mm curved needle by pressing and releasing the OverStitch™ handle. A specific polypropylene 2/0 suture is mounted on the anchor exchange catheter and inserted into the right channel of the endoscope. Following a precise sequence of movements, the anchor exchange secures the suture to the curved needle. The helix device is passed through the left channel and turned clockwise to grasp and pull the tissue back to the system.

The OverStitch™ handle is pressed and the stitch is passed full-thickness through the gastric wall. The gastroplasty is constructed in a distal-to-proximal fashion with the application of several full-thickness sutures, from the incisura angularis to the gastric fundus, which is preserved (Fig. 14.10). The first stitch of the purse string suture is placed at the level of the first gastric folds next to the incisura angularis, on the anterior gastric wall. The greater curvature and the posterior wall are then taken before completing the purse string in the opposite direction so that the final configuration of the suture is U-shaped. A Cinch® device (Apollo Endosurgery, Austin, Texas, USA) is used at the end of each suture to cut the thread and tighten the suture (Fig. 14.11).

Interrupted sutures are easy to place, possess a greater tensile strength, and have less potential to cause wound edema and impaired circulation [15]. With each grab, the helix device brings tissue into the over-the-scope suturing system, pulling it away from the surrounding extraluminal structures, hence reducing the risk of injury. To complete the gastroplasty,three to five sutures are usually required depending on the dimension of the stomach (Fig. 14.12). After each plication, a cinching device is used to secure the suture. Different techniques and suture shapes have been described in the literature according to the operator's preferences [16–19]. However, no comparative studies to define the best pattern are available at present.

To reduce the risk of pneumoperitoneum and pneumothorax, as suggested by previous

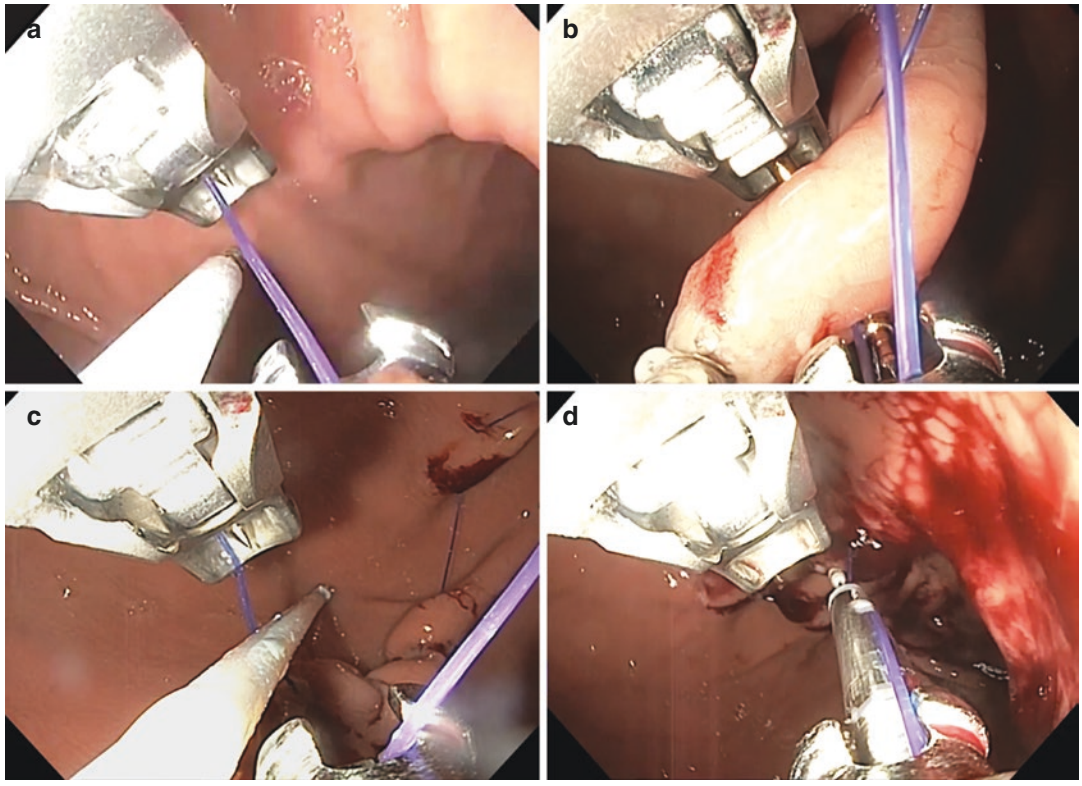

Fig. 14.10 Steps of the ESG procedure: (**a**) Starting at the level of the incisura angularis on the anterior wall, the helix device is used to grab the tissue and pull it back inside the suturing platform. (**b**) The needle is passed full-thickness through the wall. (**c**) The suture is completed in a U-shaped fashion. (**d**) A Cinch® device is used to complete the plication

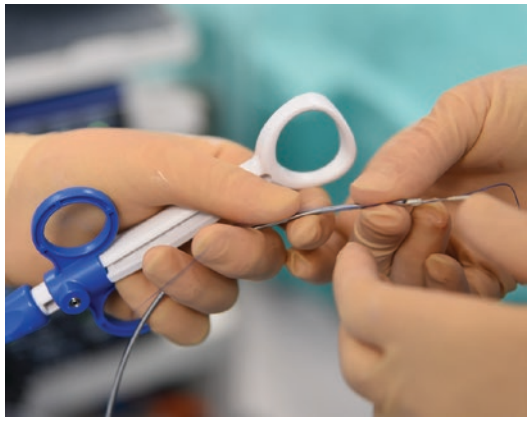

Fig. 14.11 Insertion of the thread into the Cinch® device

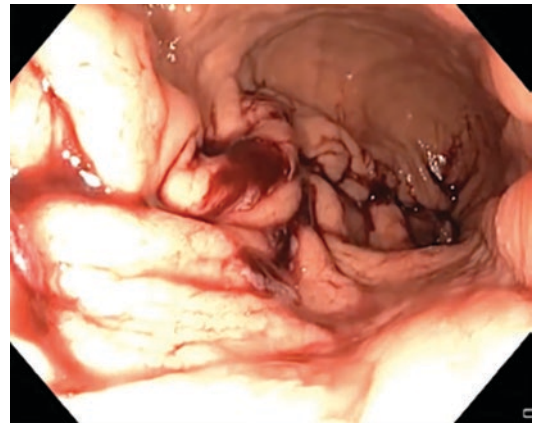

Fig. 14.12 Final appearance of the gastroplasty using the Apollo OverStitch™ system

authors [16–19], carbon dioxide insufflation has to be minimized during suture placement and the abdomen closely monitored for distention during the procedure.

ESG is effective, well tolerated by patients, and has extremely low complication rates (1–2.2%), thus having the advantage of being often performed in outpatient setting [16–19]. Weight loss outcomes after ESG using OverStitch™ are substantial and the procedure is gaining in popularity worldwide.

A recent meta-analysis, reporting data from eight original studies, including a total of 1772 patients, found the following: mean 6 months TWL of 15.1% (95% CI, 14.3–16.0), mean decrease in body mass index of 5.65 kg/m^2 (95% CI, 5.07–6.22), and mean EWL of 57.7% (95% CI, 52.0–63.4) [20]. At 12 months and 18–24 months, the authors reported a TWL of 16.5% (95% CI, 15.2–17.8) and 17.2% (95% CI, 14.6–19.7), respectively. Despite the good results and the success of the technique, there is currently lack of strong evidence comparing ESG to other therapeutic options. Only one study compared ESG with dietary and lifestyle changes and there are a few reports comparing ESG to surgical therapy [21–23].

The long-term weight loss data are still scarce but seem to be encouraging. At 5 years, Hajifathalian et al. showed a TWL of 14.5% with more than 69% of the patients achieving a TWL > 10% [24]. Interestingly, the endoscopic gastroplasty appearance might undergo changes overtime. As recently published, an efficacious weight loss following ESG seems to correlate with the sutures' integrity at follow-up [25]. Accordingly, Lopez-Nava et al. assessed the technical feasibility and safety of Redo-ESG after previous ESG. Moreover, the authors showed that 90% of the patients with weight loss failure (failure to achieve ≥10% TWL at 6 months) or weight regain (recover of 50% of the maximum weight loss at or after 12 months post ESG) had an open gastroplasty at the endoscopic control, resulting in a near-normal gastric luminal volume [26].

In addition, in case of insufficient weight loss, ESG does not prevent patients from undergoing subsequent bariatric surgery, such as Roux-en-Y gastric bypass (RYGB) or laparoscopic sleeve gastrectomy (LSG). Conversion of ESG to LSG or RYGB is feasible using a combined laparoscopic-endoscopic technique to identify plication orientation and ensure safe stapling and avoidance of sutures, anchors, and cinches [19, 27, 28].

Furthermore, unlike other suture systems, which might only be utilized to achieve gastric reduction, OverStitch™ has versatile application portfolio. For instance, the OverStitch™ platform has been employed to close gastrointestinal wall's defects or to secure self-expandable metal stents [29]. In addition, it has been used to resize dilated gastrojejunal anastomosis (GJA) after Roux-en-Y gastric bypass (transoral outlet reduction (TORe) procedure) [30]. The reduction of GJA size using OverStitch™ has demonstrated to be effective, safe, and durable in arresting weight regain with a reported 8.8 ± 12.5% TWL at 5-year follow-up [31].

14.5 Conclusion

The limited penetration of bariatric surgery and the scarce outcome of pharmacological options created a very favorable space for less morbid alternative treatments such as primary bariatric endoscopic suturing techniques. Endoscopic suturing systems offer the possibility to perform an effective and durable gastric volume reduction similar to that of achieved surgically by full-thickness tissue apposition yet via an incisionless approach. Several endoscopic gastric reduction techniques are currently available for the treatment of obesity. Among those, the ESG using the OverStitch™ is the most popular and fastest growing technique with more than 100 studies published to date. Current data demonstrate that ESG is safe, with a much lower complication rate when compared to surgical therapies, while still resulting effective in terms of weight loss. Nevertheless, ESG, as the other existing endoscopic suturing procedures, is technically challenging and difficult to standardize and requires a high level of training and expertise. Currently,

few endoscopists focus on obese patients and they are often not fully trained for it. To overcome the challenges and pitfalls of the existing techniques and training, novel automated endoscopic suturing devices operator-independent are being developed such as the EndoZip™ (NitiNotes Surgical, Caesarea, Israel). This platform has been designed to be operator-independent, fully automated, and showing promising results in a first in-human study [32].

Given the global dimension of the obesity pandemic and the limited penetration rate of surgery in the eligible patient population, there is indeed room for novel less invasive endoscopic alternatives. The development of such new technologies ushers a new era in the treatment of obesity where endoluminal suturing approaches will play a central role also in the management of bariatric surgery failure and complications. The future should envisage hybrid bariatric approaches and specialists able to manage obese patients through surgery or endoscopy. This would ensure that each patient receives the best treatment available, consequently securing the best outcomes.

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15 Transgastric Endoscopic Interventions at the Pancreas

Hans Seifert

15.1 Indication for Intervention, Timing of Intervention

In the case of undoubtedly infected necroses or acute fluid collections, i.e., septic lesions with typical biochemical markers (CRP increase, leukocytosis), beginning organ failure, fever, and gas formation in the necroses, evacuation of the infected area should be performed. Basically, the surgical principle applies: "ubi pus, ibi evacua." Already the suspicion of an infected closed lesion with or without solid contents is a possible indication for intervention. In elderly and multimorbid patients, we have in the first few years occasionally waited too long until a manifest septic picture had developed, even under antibiotic treatment. Thus, a "point of no return" may be reached and the risk of the intervention be increased significantly. In tertiary referral centers, this typically affects patients referred because of clinical deterioration [17] after peripancreatic lesions have been infected spontaneously or by EUS-directed puncture with insufficient pigtail insertion or by ERCP. They are often under antibiotic therapy with a carbapenem. In these patients, a state of contamination can remain relatively stable for some time.

It is generally agreed that a debridement procedure should, if possible, only be performed at the stage of demarcated fluid accumulation or necrosis, i.e., at least 3 or 4 weeks after the onset of the disease. These original surgical principles are also widely accepted for minimally invasive and endoscopic interventions. However, extensive necroses are sometimes not anatomically delineated even after weeks. It is also difficult to define "infected necrosis" in the frequent symptomatic cases with pain, fullness, nausea, and compression of the stomach, duodenum, or bile duct without unequivocal signs of infection, with normal or moderately increased inflammatory parameters (Table 15.1). The chance of healing under conservative therapy speaks against and the threatening septic derailment with organ complications speaks pro intervention. The inclusion criteria of guidelines and the larger studies take this into account and accept the suspicion of infected necrosis and clinical deterioration or symptomatic sterile necrosis as indication for intervention. It should be considered that in individual cases infected necrosis can also heal under antibiotic therapy, so that the clinical condition of the patient is a decisive criterion. Sterile asymptomatic necrosis should always be treated conservatively, since even large necroses can be spontaneously resorbed. However, it is not clear what conservative treatment consists of, especially for large necrotic masses.

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Table 15.1 The indication to intervene is based on various criteria of different categories

Not indicated	Intervention?		Indicated
Liquid	Mixed		Solid
Sterile	Contaminated		Infection, sepsis
Clear	Cloudy		Pus
CRP, Leukocytes			
Normal	+		+++
Early, postacute Weeks 1–2	Persisting, increasing		
	>3		>6 (?)
EUS, MRI, CT: lesions of the pancreas (duct ± parenchyma)			
None	Fistulas, leaks (always?)	Strictures	Defects, necroses
Asymptomatic	Complaints		Severe symptoms

Often, patients can not be easily categorized to the left or the right column. In the typical case of a mixed pattern, e.g., liquid lesion with solid components, rising CRP, and no symptoms, the therapeutic strategy follows a clinical and day-by-day team decision

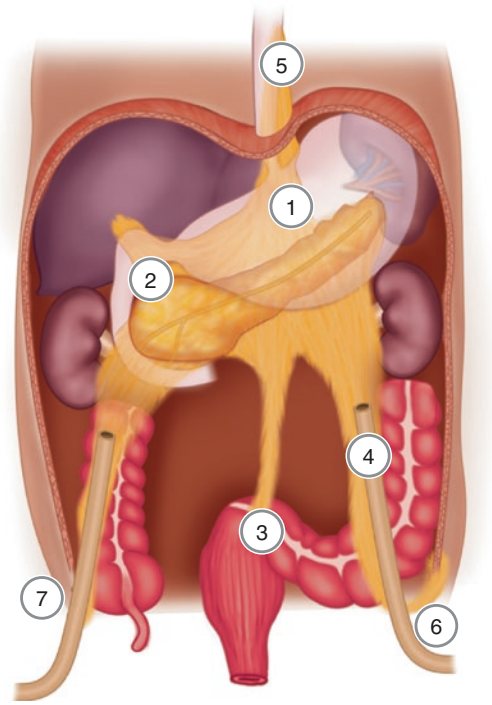

Fig. 15.1 Schematic depiction of the peripancreatic retroperitoneal space and its extensions (*yellow*) that must be accounted for. Endoscopic transmural interventions can address the peripancreatic *1*, paraduodenal *2*, pararectal *3,* parasigmoidal *4*, and mediastinal paraesophageal *5* lesions. Retrosigmoidal *6* and retrocecal *7* extensions can be drained via percutaneous tracts (modified from Seifert 2002). LAMS can be used for all transmural fenestrations

As a guideline for the team decision for or against the intervention, the following principle applies in the first 4–6 weeks: "postpone the intervention as long as possible, do not come too early" and afterward rather: "do not wait for the septic complication, don't come too late." The therapeutic goal is drainage and the complete removal of all infected material.

Prior to the intervention, a current sectional imaging (CT or better MRI [18]) should be available giving an overview of the extent of the necroses and the suitable accesses for the intervention. The transluminal interventions are then performed under EUS control, transcutaneous ones under sonographic guidance.

15.2 Pathological Anatomy

Peripancreatic fluid accumulations as a complication of acute pancreatitis usually contain high concentrations of amylase or lipase. They result from lesions of the pancreatic organ with defects of the pancreatic ductal system. Typically, the ductal defects are in the genu or in the cauda pancreatis. Defects in the genu or pancreatic head area are more likely to lead to right-sided paraduodenal necroses and in the area of the liver hilum. Lesions in the cauda cause fat necroses on the left side in the area of the splenic hilum and the retrocolic gutter. In severe cases necroses can also be bilateral and very extensive. In extreme cases, they can follow the interfascial planes [19, 20] around the pancreas and the anterior perirenal space retrocolically into the pelvis, rarely also beyond the hiatus cranially into the mediastinum (Fig. 15.1). While the necroses of the pancreatic parenchyma (Fig. 15.2) presumably develop as ischemic lesions in the context of acute pancreatitis [21, 22], the extensive necroses of the peripancreatic fat are to a large extent also consequences of the leaked pancreatic secretion. The immediate peripancreatic region including the V. lienalis is always affected. Frequently, thrombosis of the V. lienalis occurs, which after some time leads to typical varices restricted to the gastric fundus. These do not usu-

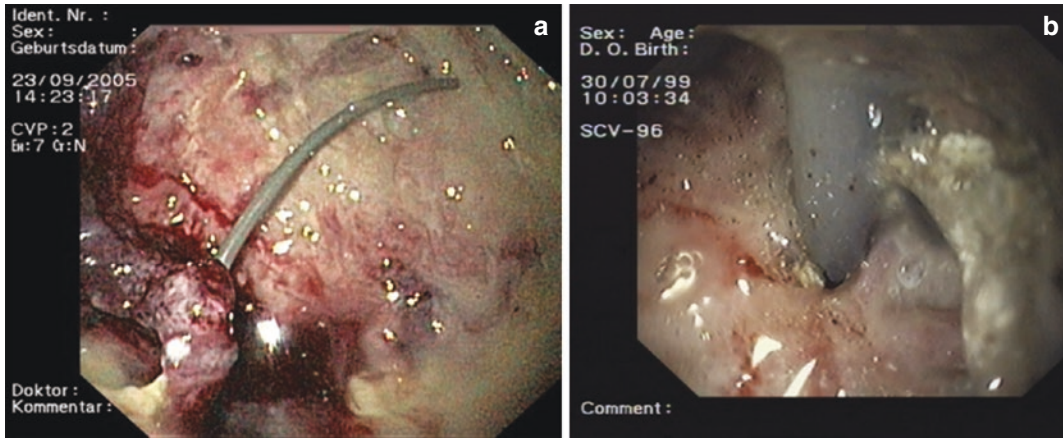

Fig. 15.2 Transpapillary pancreatic plastic stents visible after debridement in giant cavities: (**a**) The stent was meant to be in the pancreatic tail region, which is completely lost. (**b**) Duodenal wall seen from the cavity with 7F plastic stent: loss of the pancreatic head in a patient with acute necrotizing pancreatitis and pancreas divisum

ally lead to variceal bleeding but must be considered in transgastromural procedures. In some patients, the retroperitoneal cavity containing liquid and solid masses after 4–6 weeks or even months has a well-defined shape with a strong fibrous wall. In these lesions that are "walled off necroses" (WON) sensu strictu, transgastric interventional therapy is a straightforward procedure, usually requiring less than five sessions. However, in others, the cavity is complex and extensive and not really "walled off." The deep recessus seem somehow defined because they follow preformed anatomic structures [20]. The terminus "WON" does not correctly characterize these lesions. The well-demarcated and anatomically defined "WON," which are mostly mentioned in the literature, are to be distinguished from the infected necroses with extensive retroperitoneal extensions. Endoscopic access can be transgastric, if necessary, also transduodenal, transesophageal, transrectal, transcolonic, or through the abdominal wall (Figs. 15.1 and 15.3).

15.3 Diagnosis

For the classification of the pathological anatomy of the target structures, see the revised Atlanta Classification of 2013 [23] and, better still, newer guidelines, which summarize the problem very well at the current state of the art [24–26].

The reliable diagnosis of an infected lesion is not without problems in imaging. In case of a septic clinical picture, purulent contents proven by puncture or imaging (gas inclusions, liquid portions changing from echo-free to echogenic, spontaneous perforations with pus discharge, etc.) and increase of CRP or procalcitonin in serum, the indication is clear. In case of doubt, sonographically guided diagnostic puncture under sterile conditions can provide information about ambiguous findings, also for differentiating bleeding from purulent findings. However, the sensitivity of such punctures is limited.

15.3.1 Abdominal Sonography

Abdominal ultrasound is the initial examination for major diagnoses and differential diagnoses: free fluid, pleural effusions, venous (varicose veins, splenic or portal vein thrombosis) or arterial lesions (pseudoaneurysm), retroperitoneal necrosis, pancreatic pathology. Contrast enhanced ultrasound (CEUS) allows identification of non-perfused regions.

15.3.2 Endoscopic Ultrasound (EUS)

EUS allows precise visualization of the retroperitoneal structures, liquid and solid (non-perfused,

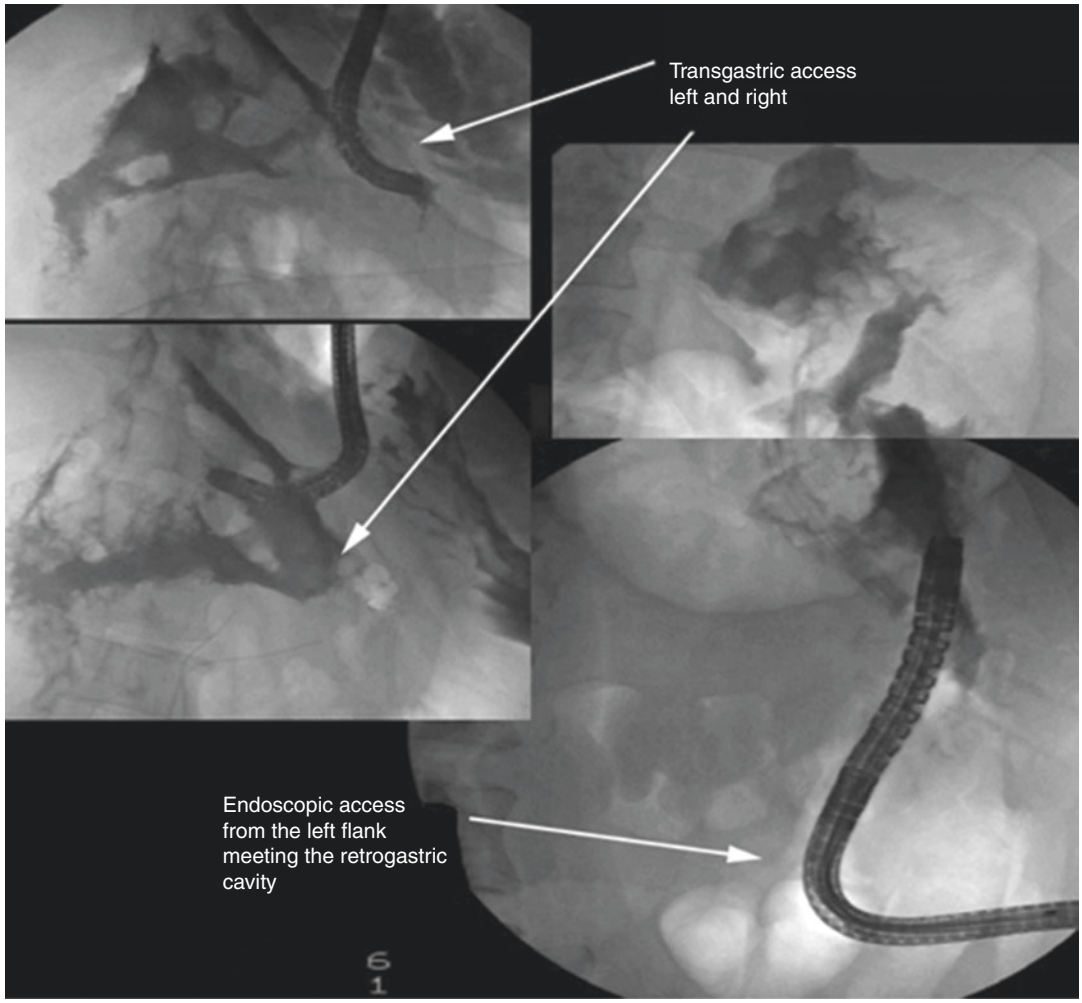

Fig. 15.3 Extensive cavity with endoscopic rendezvous of the transgastric and left percutaneous approach. Endoscopic treatment was successful

floating, echogenic) lesions and vessels, and defines the appropriate window for transmural intervention. EUS allows highest reproducibility of fluid-to-debris component estimation with the added advantage of being a single stage procedure for both diagnosis (solid debris delineation) and management (puncture and drainage) in the same sitting. Contrast-enhanced EUS identifies non-perfused tissue.

15.3.3 Computed Tomography (CT)

Ct gives a good overview of the extent of pathological findings. It is not necessary in the first week [23]. There is no reliable differentiation of solid and liquid findings, and estimation of the extent of necroses is unreliable. Radiation exposure, a possible worsening of pancreatitis or kidney function, as well as possible contrast agent

reactions must be considered. Classification of acute pancreatitis based on CT-determined retroperitoneal extension is a useful indicator of the disease severity and prognosis without the need for contrast-medium-enhanced CT [19].

15.3.4 Magnetic Resonance Imaging (MRI)

MRI distinguishes well between fluid and necroses. MRI performs better than CT in characterization of pancreatic/peripancreatic fluid collections especially for quantification of solid debris and fat necrosis (seen as fat density globules). Also, MRI is highly sensitive for detecting pancreatic duct disruption and choledocholithiasis. Recent advances, including significantly better soft-tissue contrast, favor multiparametric MRI for a more comprehensive assessment of acute pancreatitis pathology, particularly for small necrotic/fat debris within a collection. In addition, a MRI severity index (MRSI) has been validated for the initial evaluation, staging, and prognosis of acute pancreatitis [18, 27–29].

15.3.5 ERCP

An early ERCP is only indicated in exceptional cases with therapeutic intent. The visualization of the pancreatic duct always contaminates it and is the way from the sterile to the infected lesion, so it is always contraindicated in sterile lesions. Combined with transmural interventions ERP reconstruction of the pancreatic duct via plastic prosthesis may be helpful to prevent the disconnected duct syndrome. Even in severe acute pancreatitis (SAP) with extensive infected necrosis, the leak of the duct may be hard to detect without complete contrast filling (Fig. 15.4).

15.4 Infection, Antibiotics

Infectious complications have a decisive influence on the morbidity and mortality of severe acute pancreatitis. Traditionally, prophylactic antibiotic administration has not been recommended. However, recent data promise a reduced mortality and a lower incidence of infected necroses for early antibiotic treatment in severe acute pancreatitis with extensive fluid accumulation and/or necrosis [30]. This corresponds to common clinical practice and to recent guidelines [24]. Candida infections are also common in SAP; invasive candidiasis is associated with increased mortality. The indication for antimycotic treatment should be generously provided. In critically ill patients, prophylaxis with fluconazole, ketoconazole, or caspofungin may significantly reduce invasive fungal infections and mortality [31, 32]. Antimicrobial treatment of infected pancreatic necrosis becomes more challenging over time, owing to a change in spectrum favoring difficult-to-treat pathogens and an increase in multiresistant bacteria and from *Candida albicans* to non-*Candida albicans* spp. associated with worse clinical outcomes [33, 34].

15.5 Practical Approach

Due to small case numbers and variable expertise of different clinics – most of them are still in the learning curve – there is no standardized procedure. The basic principles of the transgastric intervention have not changed since their first description [2]: EUS-guided puncture, plastic stent, dilation with a 16-mm balloon through the scope, and retroperitoneal debridement with a therapeutic gastroscope, plastic stent as placeholder. Different techniques are used for transmural access. Many authors follow a step-by-step approach, initially with catheter drainage and transnasal irrigation catheters followed by endoscopic debridement only if there is no success. We avoid transnasal and other catheters and follow the extensive debridement through a transmural window dilated to 15–18 mm in the first session. Access through the gastric and the often tough fibrous wall of the lesion can best be performed with a ring knife. In complicated patients needing several transgastric interventions, the rapid spontaneous closure of the transgastric windows requires repeated balloon dilations with

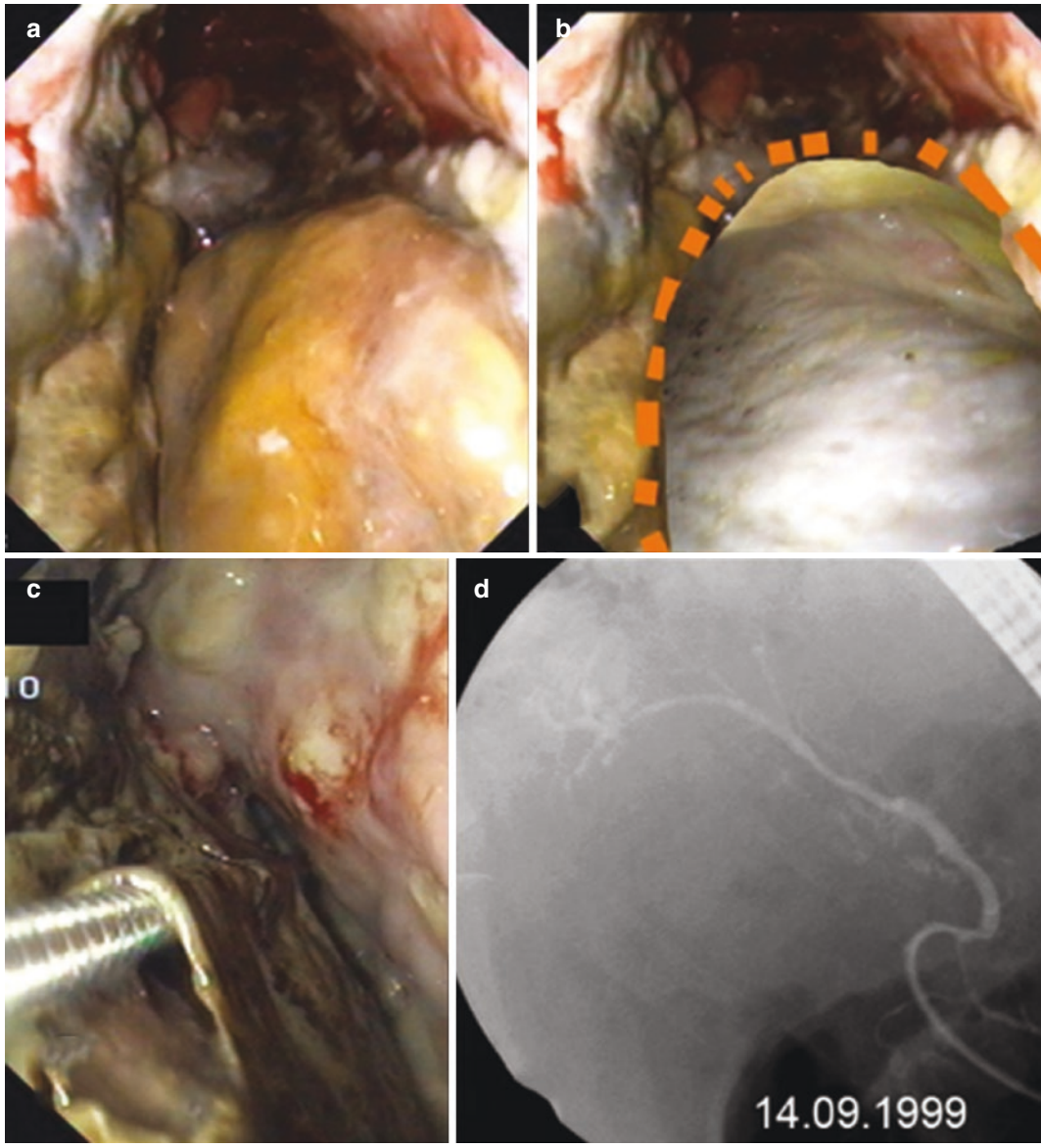

Fig. 15.4 Severe acute pancreatitis with extensive necrosis and occlusion of the A. lienalis. The ischemic necrosis of the posterior gastric wall (**a**) was resected using a needle knife (**b**) giving view of the ischemic spleen. Endoscopic subtotal snare resection of the spleen was performed. Opening of the splenic capsule with a forceps (**c**). The peripheral defect of the pancreatic duct was small and easily overlooked (**d**)

removal and reinsertion of silicone drainages or stents as placeholders.

Transmural interventions should be endosonographically controlled, as this is the only way to ensure low-risk puncture, considering the often-complicated pathological anatomy. Not infrequently, even extensive necroses hardly cause bulging of the gastric wall and almost always arteries of the stomach and pancreas, and – due to splenic vein thrombosis – dilated veins must be avoided.

The gastric transmural window is typically at 45–50 cm from incisors in the posterior gastric wall. Windows close to the cardia can be problematic because of the proximity to the mediastinum, those at 55–60 cm in the antrum because of

the difficult access in retroflexion. In rare cases, the primary access is in the bulbus or the descending duodenum.

As a standard, puncture with a 19G needle is performed directed at a liquid and avascular area, to allow the placement of a balloon and then a LAMS under EUS control. In the case of predominantly or exclusively solid lesions, orientation is much more difficult. Therefore, drains and pigtail inserts should not be performed by preliminary examiners as diagnostic or even therapeutic attempts. Diagnostic aspirate can better be obtained by external sterile puncture or after the EUS-guided primary therapeutic puncture before insertion of a wire. It has proven to be a good idea to visualize the retroperitoneal space with contrast medium after aspiration of some material for diagnostics to get an idea about possible fistulas, deep recessus, and the communication between different retroperitoneal spaces. The placement of the LAMS is done under endosonographic (the extragastral part) and direct endoscopic (the intragastral part) control. After placement, the LAMS can be expanded to its maximum diameter with a balloon to allow immediate endoscopic intervention. Alternatively, after placement of the LAMS and discharge of pus, the intervention is terminated to allow the LAMS to expand. The follow-up intervention with debridement of the necroses follows 2–3 days later.

The size of the transmural access depends on the composition and consistency of the infected material (mainly solid or liquid). As a rule, in infected necroses, multiple entry into the retroperitoneal cavity should be possible with a therapeutic endoscope. When using LAMS with an integrated application set (Axios, Boston Scientific), puncture, dilation of the access, and stent placement are performed in one step. Otherwise, it is sufficient to dilate the window to 4–8 mm before LAMS insertion. If the infected cavity has already spontaneously ruptured into the stomach or duodenum [35], this access can first be used for debridement. Additional nasocystic drains annoy patients and restrict their mobility. A benefit has not been proven. The transmural window can be secured primarily or after extraction of a LAMS by inserting a soft silicone drainage (Fig. 15.5).

In case of extensive infected areas, the transgastric approach must sometimes be combined with a percutaneous (retrocolic lesions) or transesophageal (mediastinal lesions) approach (Fig. 15.1). Appropriate therapy planning before the start of the interventional procedure is required. A minimally invasive procedure with multiple accesses is preferable to open surgery. Endoscopically inaccessible procedures can be reached by sonography- or CT-guided [36, 37] punctures. They can then also be cleared out endoscopically after dilatation of the puncture channel with different dilators from 3 up to 10 mm, to allow passage of regular endoscopes (Fig. 15.2).

In mediastinal lesions, the endoscopic intervention can be restricted to balloon dilation and silicone drainage [own experience (Fig. 15.6)] or combined with LAMS [38–40]. In extensive necroses, multiple accesses may be advantageous or even necessary to reach all extensions of the necrotic cavity. LAMS have been described in this respect for "single-step endoscopic ultrasound-guided multiple gateway drainage of complex walled-off necrosis" [41].

15.6 SEMS/LAMS Versus Plastic

In recent years, self-expanding metal stents (SEMS) in various forms specially adapted to the transmural procedure as "lumen-apposing metal stents" (LAMS) have facilitated endoscopic retroperitoneal access for repeated interventions [15, 16]. A recent systematic review and a meta-analysis of metal versus plastic stents for drainage of pancreatic fluid collections found that the use of metal stents for drainage of pancreatic fluid collections is associated with improved clinical success, fewer adverse events, and reduced bleeding compared to plastic stents [42, 43]. However, while enabling easy endoscopic access through the gastric window, LAMS may prevent endoscopic maneuvering in the retroperioneal cavity. Shrinking of the cavity and proliferating granulation tissue may impede the endoscopic passage,

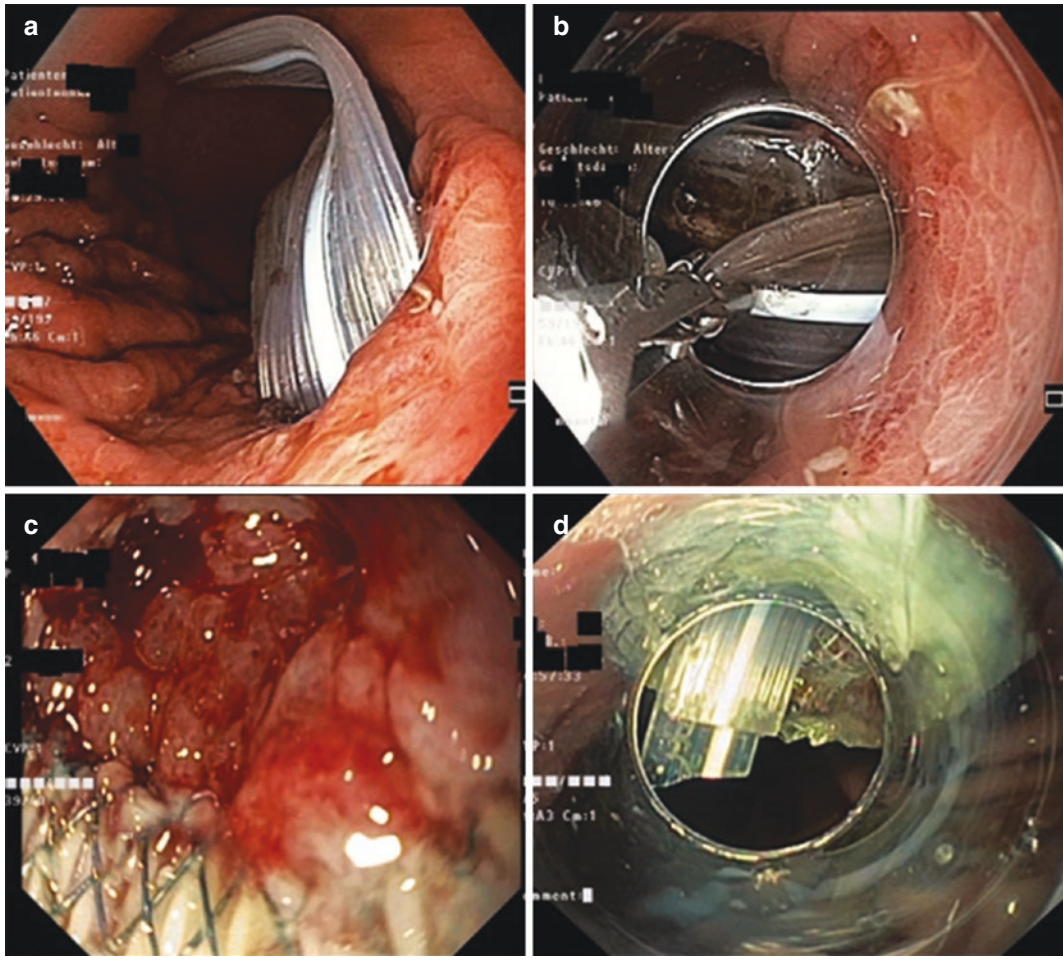

Fig. 15.5 (**a**) Soft silicone drainage in the transgastric window. (**b**) Placement of the silicone drainage through cap-fitted gastroscope. (**c**) Overgrowth of a LAMS by granulation tissue. The LAMS was removed. (**d**) Combination of LAMS with silicone drainage keeping the access to the deeper recessus open

and the retroperitoneal flange of the stent may itself occlude deep purulent recessus originating just behind the gastric wall (Fig. 15.5c). Typically, this pertains to the extension to the splenic hilum.

In these situations, we routinely remove the stents using a forceps through a gastroscope armed with a hood. After stent extraction often pus spontaneously evacuates from the formerly inaccessible recessus. After the now easier endoscopic debridement and flushing all extensions of the cavity, the same LAMS can be gently managed into the working channel of the gastroscope and reinserted by pushing it with forceps under endoscopic control through the hood.

The correlation of possible complications like bleeding or overgrowth with the duration of LAMS placement is not clear [44, 45].

Some problems of longtime LAMS placement can be overcome by combination of LAMS with silicone drainages (Fig. 15.5). These atraumatic and inexpensive drainages come in different sizes. Trimmed as needed and inserted into the deepest recessus, they prevent their premature closure with abscesses or sequesters as consequence. The cavities should granulate like deep wounds and close from the deepest ground to the gastric opening. Usually in extensive cavities, we start with LAMS, followed by LAMS plus sili-

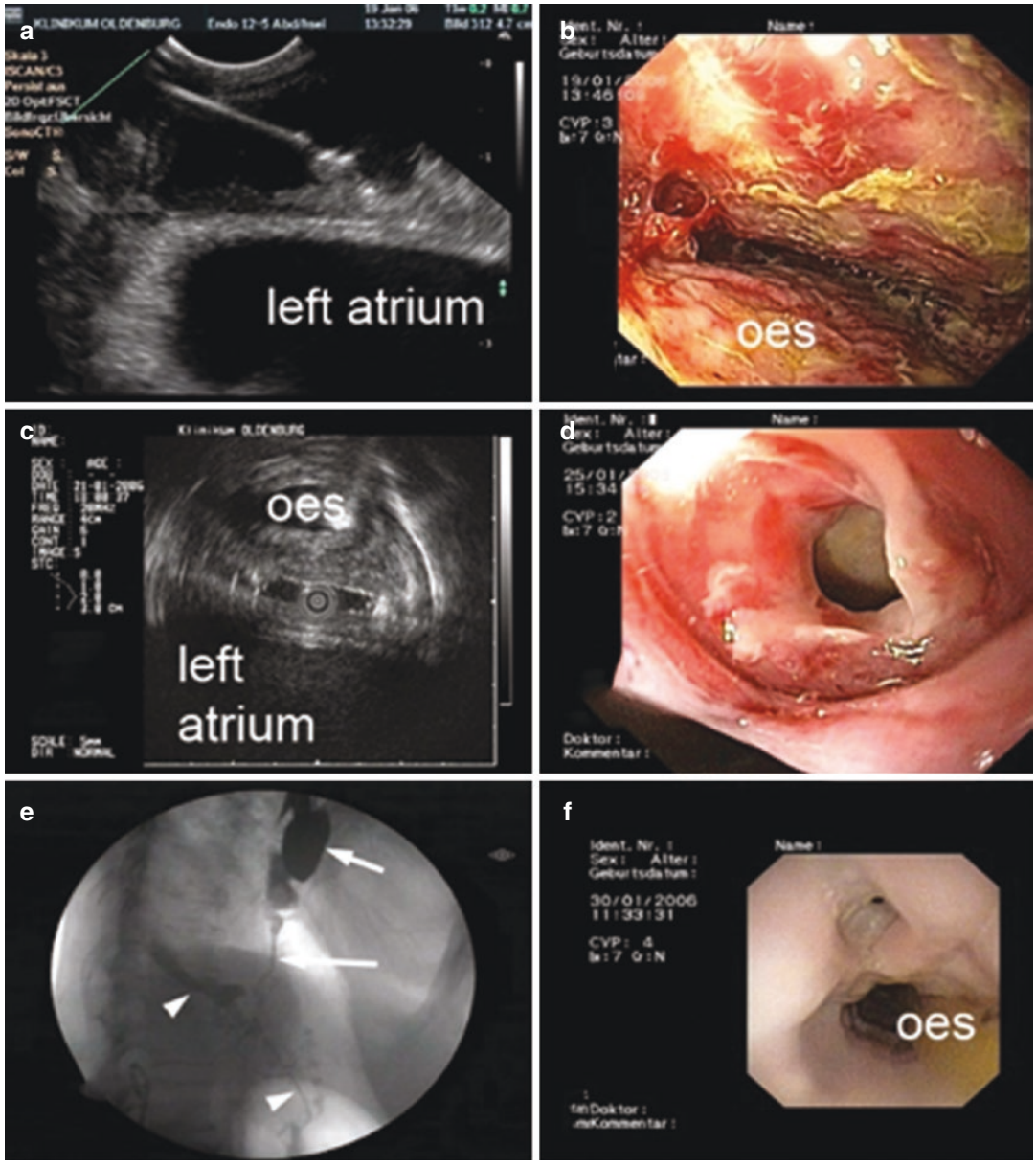

Fig. 15.6 (**a**) The mediastinal extension of a peripancreatic infected lesion is punctured under EUS guidance. (**b**) After drainage and aspiration of pus, the cavity sitting between the esophageal wall and the heart is clean. (**c**) Miniprobe EUS in the cavity shows close proximity of the left atrium. Therefore, in this case, no stent was used. (**d**) The transesophageal window on day 6 and (**f**) almost closed on day 11. (**e**) Contrast injected through the endoscope in the esophageal window shows the mediastinal cavity and connection (*arrows*) to the abdominal retroperitoneal space and the damaged pancreatic duct (*arrowheads*)

cone drainage, and finally silicone drainage alone, when the cavity is small and retroperitoneal endoscopy no longer needed. Regular, e.g., weekly, flushing and cleaning of the shrinking cavities is then done in parallel to the drainages. In cases of disconnected pancreatic tail, the transmural fistula may need to be kept open to allow appropriate drainage.

15.7 Pancreatic Duct Defects

Necrotizing pancreatitis is always associated with a defect in the pancreatic duct. Such damage with leaks, fistula connections, strictures, or loss of whole parts of the pancreatic organ (Fig. 15.2) are of great importance for the further course and the therapeutic procedure. They can be detected primarily by MR-cholangiopancreaticography (MRCP) or EUS. Endoscopic transpapillary pancreaticography (ERP) may be performed if an infection is already present or a draining intervention is directly intended or has already been performed (Fig. 15.4).

Frequently, the ductal defect is in the pancreatic corpus or in the genu. In the course of healing of the necrotic cavity, the duct often becomes strictured just at its defect, while the periphery of the pancreas is drained into the stomach via the necrotic cavity without any problems as long as the transmural window is still open. After obliteration, the syndrome of a disconnected or lost pancreatic tail develops with recurrent pseudocysts, fistulas, and troublesome symptoms. Reconnection to the duct system via a transpapillary drainage is rarely successful on the long. Endoscopic alternatives are the permanent maintenance of the transmural window by pigtail catheter and the targeted transmural drainage of the disconnected duct system [46–48]. In addition to the resection of the "lost" pancreas, surgery offers the possibility of drainage using a Roux-Y-loop. Probably, the preservation of the lost cauda is recommendable to avoid pancreatic diabetes mellitus.

15.8 Transgastric Pancreaticoscopy

In the context of innovative endoscopic technology for transgastric pancreatic intervention, SEMS-based therapy of calcifying chronic pancreatitis and of postoperative strictures of pancreatic anastomoses deserves to be mentioned [49–54]. The EUS-guided access in combination with covered SEMS and pancreaticoscopy with the new small through-the-scope endoscopes (SpyScope, Boston Scientific) renders the pancreatic duct accessible for electrohydraulic lithotripsy, biopsy, and efficient recanalization and drainage (Figs. 15.7 and 15.8). While resection of neoplastic or inflammatory tissue remains in the domain of surgery, drainage of the pancreatic duct may soon be endoscopic terrain.

15.9 Possible Complications

Bleeding (gastric wall arteries, retroperitoneal portal vessels, sometimes eroded by LAMS – caution!!!) during or after the intervention is the most common complication. It often stops spontaneously or can be handled endoscopically, but besides sepsis it is one of the most common reasons for surgical intervention.

Air embolisms with fatal outcome have been described. Therefore, retroperitoneal interventions should be performed under CO_2 insufflation.

Abdominal pain after the intervention may be the expression of a (micro-) perforation from the infected into sterile peritoneal compartments. These can usually be treated conservatively, just as fistula connections to hollow organs usually close spontaneously.

Sequestered infected material as septic foci (inconsistent approach, too long intervention intervals, lack of experience) can lead to therapy failure.

15.10 Material Required

Different sizes of clips for hemostasis, adrenaline 1:20000, and possibly dilatation balloon for compression of bleeding from arteries in the gastric wall.

Overtube (US Endoscopy) for "inverse intubation" protected endoscopic access to prevent aspiration if large amounts of purulent discharge after opening the retroperitoneum are expected. Water-soluble contrast agent, Nacl 0.9%.

For transmural interventional therapy:

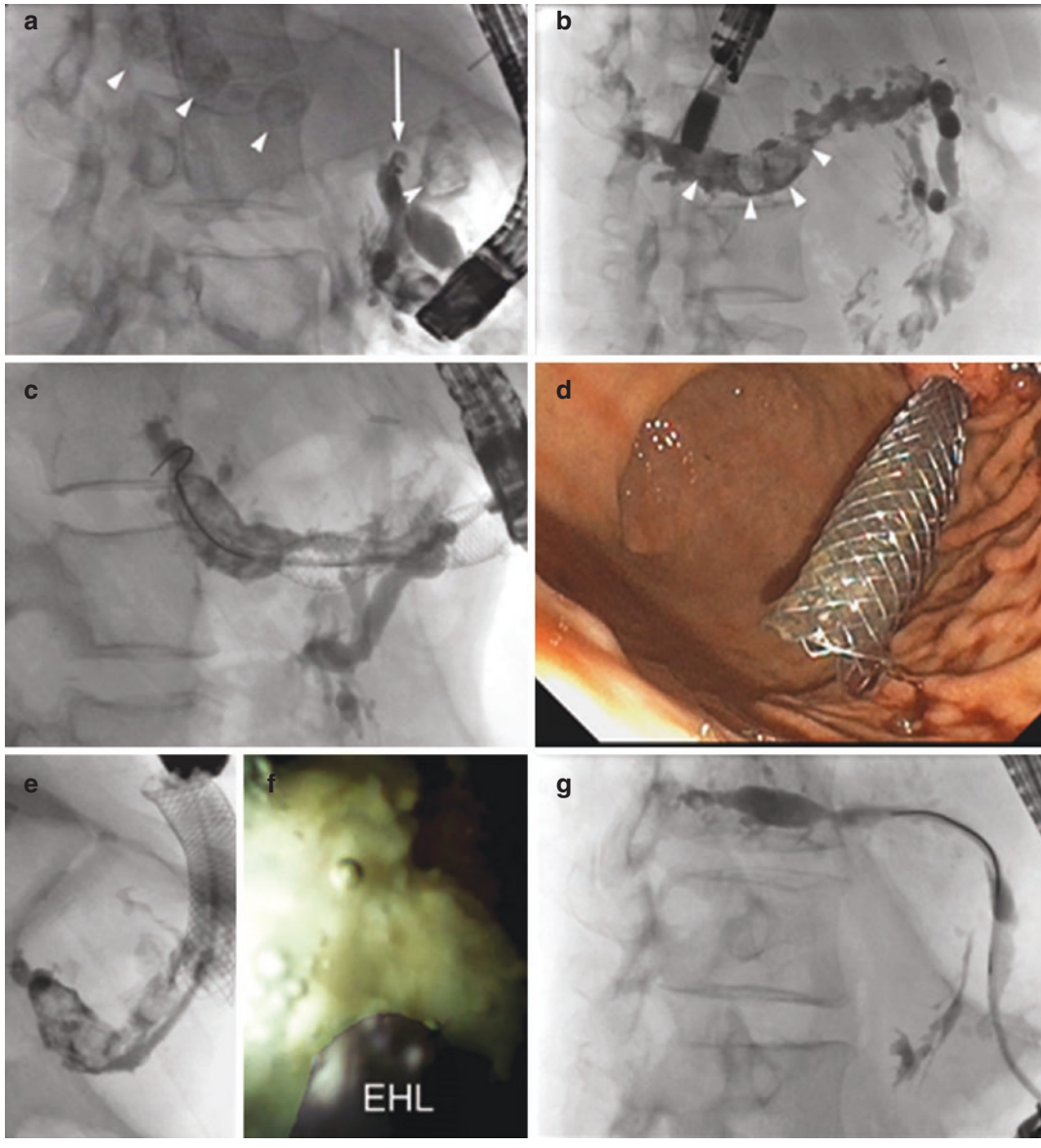

Fig. 15.7 A 45-year-old female patient with a chronic hereditary pancreatitis (SPINK 1 mutation) was referred in 2015 after 5 years of combined endoscopic and ESWL therapy because of severe attacks of abdominal pain. Primarily this strategy had been successful with multiple stone extractions, recently however given up because of giant obstructing stones. Pancreatic head resection or pancreatectomy had been recommended. She had neither endocrine nor exocrine insufficiency. (**a**) There was a dominant stricture in the pancreatic genu (*arrow*) and large stones in the pancreatic head as well in the periphery (*arrowheads*). After clearance of most of the stones in the pancreatic head and (**b**) EUS-guided visualization of the periphery transgastric SEMS insertion (**c**, **d**, **e**) enabled endoscopic access to the pancreatic tail. Pancreatoscopy using a SpyScope (Boston Scientific) allowed EHL (**f**) of the big peripheral stones and finally led to a stone-free open duct (**g**). Since the decompression of the duct, the patient is free of pain

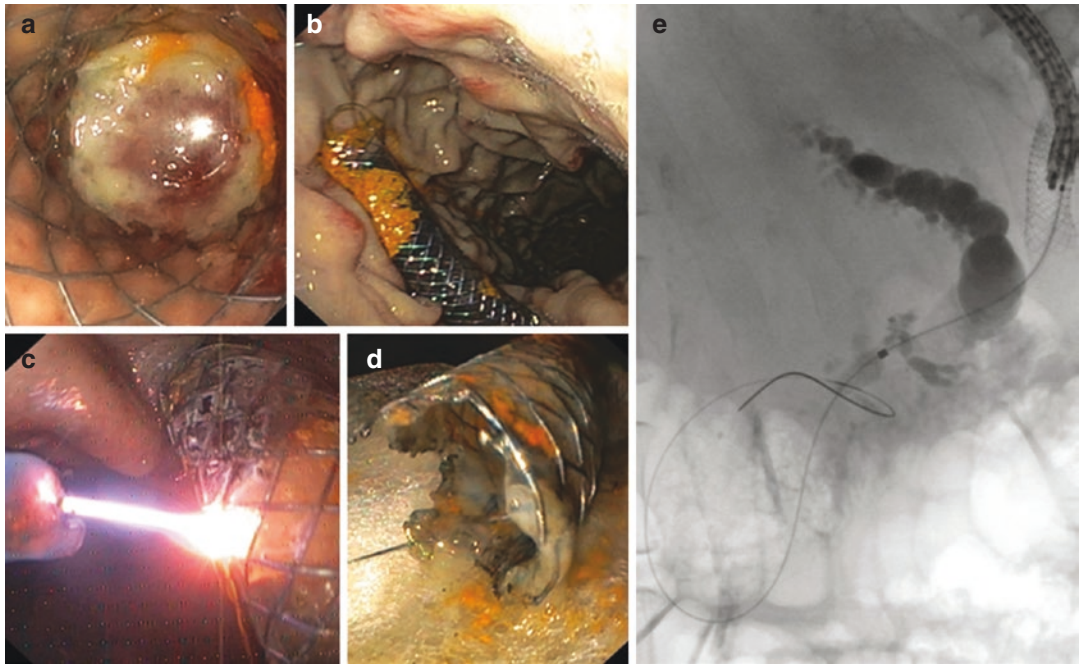

Fig. 15.8 Chronic pancreatitis with inaccessible pancreatic duct because of impacted prepapillary stone. (**a**) A transgastric SEMS (8 × 60 mm biliary wall stent, fully covered, Boston Scientific) was inserted into the pancreatic duct. Sitting against the opposite wall of the duct, it did not allow endoscopic passage. (**b**) After retraction of the SEMS by around 15 mm, the gastric part was too long for easy endoscopic passage. (**c**, **d**) After trimming the SEMS with argon-plasma-coagulation (ERBE VIO 3, 60 W) passage through the SEMS into the pancreatic duct was accomplished. (**e**) Using a 6 mm gastroscope, EHL, transpapillary passage of a guide wire, balloon dilation, and stent placement through the papilla were accomplished

- EUS device: Longitudinal scanner, therapeutic gastroscope (large working channel), and diagnostic gastroscope (small diameter) with matching spacer caps (hoods).
- 19G EUS puncture needle, 0.025 guide wire 4500 mm long, cystotome or ring knife, and dilatation balloon for metal stent placement maximum diameter 10 mm (6–10 mm).
- LAMS with at least 15 mm lumen, length depending on puncture distance.
- Alternatively complete application set with needle, diathermy, and LAMS all in one (Axios, Boston Scientific).
- Easy flow silicone drainage as placeholder (6–12 mm width, 30 cm length, scissors for trimming as needed) and grasping forceps.
- For debridement and flushing, Nacl 0.9%, soft braided snares of various sizes (10, 15, 25 mm), and stone extraction balloon for over-the-wire debridement from foxhole fistula ducts and recessus.

For percutaneous interventions:

- Abdominal ultrasound, puncture set (needle combined with dilators), and guide wire, e.g., Amplatz Super Stiff (Boston Scientific) which can be shortened as needed with pliers.
- Fluoroscopy for wire control and orientation over communicating cavities.
- Dilators or pneumatic balloons (depending on length of tract) up to 10–12 mm diameter.
- 24F silicone drainage (Ecolab) as routinely used in open surgery as placeholder and drainage.
- 6 mm gastroscope for direct endoscopic access (after forming of tract after 5 days).
- Gastroscope for rendezvous with transgastric access, if possible – can sometimes help pulling percutaneous silicone drainage into place.

15.11 Conclusion

The endoscopic treatment approach, as compared to minimally invasive surgery, significantly reduces complications and length of hospital stay in patients with infected necrotizing pancreatitis. In the most challenging patients with extensive necroses, maximally invasive endoscopy comes close to minimally invasive surgery. If the therapeutic goal of drainage and debridement of all infected material without leaving any purulent sequesters is reached with the least traumatic approach, the differentiation of surgical from endoscopic interventions seems somehow artificial. Significant differences in mortality were only to be expected between open surgery and less traumatic approaches. Infected necrotizing pancreatitis is quite a heterogeneous and relatively uncommon entity. Consequently, the interventional techniques are not standardized even among expert groups. Following initial EUS-guided drainage, additional interventions varied between the studies. Minimally invasive surgical treatment and interventional endoscopic treatment were highly variable among different centers/studies [7, 9, 11, 14]. In our hands, after treating the first severely ill patients that were considered inoperable in 1999, more and more patients were referred for the transluminal-transmural therapy. Randomization to open surgery in these patients was considered inacceptable by patients, surgeons, and gastroenterologists. Since pooled data from meta-analyses included only 184 [14] and 641 [13]patients, respectively, who were treated over many years with variable surgical or endoscopic techniques by centers with more or less experience, interpretation even of these high-quality data is difficult. Nevertheless, there recently is general acceptance of endoscopic debridement as default therapy of infected peripancreatic necrosis, as mirrored by guidelines [26, 48, 55–58] and even surgical experts [59–61]. Future investigations must focus on optimizing the procedural techniques and developing new devices to further the advancement of interventional endoscopy [14].

15.12 Open Questions

- Which patients can be treated conservatively, for which is the intervention urgent?
- Which patients benefit more from simple drainage (with or without irrigation, endoscopic or radiological) than from endoscopic debridement?
- Is a step-by-step procedure – first drainage and irrigation, then debridement, and retroperitoneal endoscopic intervention – preferable to immediate consistent intervention?
- Is antibiotic treatment indicated for very large and questionably contaminated patients? And how long should this treatment be given? And with which antibiotics/antimycotics?
- Is an increase in CRP or a slight symptomatic deterioration below or after discontinuation of antibiotic treatment already an indication for intervention?
- When is the persistence of large necrotic masses without signs of organization or resorption in itself a reason for intervention?
- How can the high mortality of severe courses – infections and sepsis – be controlled despite a minimally invasive and consistent approach?

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16 Endoscopic Ultrasound-Guided Interventions

U. Will

16.1 Endoscopic Ultrasound-Guided Interventions on the Biliary System (EUS-BD)

16.1.1 Introduction, Indications, Requirements for the EUS-BD

Endoscopic retrograde cholangiography with intervention (ERC) is the standard method in the treatment of biliary obstruction caused by stones or tumors. The selective transpapillary cannulation and drainage of the bile duct is successful in almost 90–95% of cases. In patients with previous surgery (Billroth-II (BII) anatomy, Roux-en-Y anastomosis, hepaticojejunostomy, gastroenteroanastomosis), tumorous gastric outlet obstruction or duodenal stenosis, an inflammatory or tumorous destructed papilla, or complete obstruction of the bile duct, primary internal endoscopic drainage is only possible in 15–40% of cases [1–3].

Percutaneous transhepatic cholangiodrainage (PTCD) and palliative surgical cholangiodrainage are currently used after these frustrating ERC interventions. With PTCD, successful bile drainage is achieved in 87–100% of cases, but with complication rates of 9–33% and a mortality rate of 2–10% [4–7]. In 5–10% of cases, PTCD can not be completed as an external-internal drainage, but remains in an external drainage alone. In addition to the bile loss syndrome, this drainage technique carries the risk of bile leakage as well as secondary inflammatory complications. In patients with malignant, incurable underlying conditions and limited life expectancy, external drainage also poses a noteworthy psychological problem, as physical integrity is disturbed and the drainage visible to the patient is a constant reminder of the incurability of the tumor disease. This is a problem not to be underestimated, especially in palliative treatment, where the maintenance or improvement of quality of life is required.

With EUS-guided biliary drainage (EUS-BD), a method is available that can achieve internal bile drainage in patients with failed ERC and, especially, in patients with malignant incurable obstruction. EUS-BD can fulfill the therapeutic goal of permanent internal bile drainage as the main goal of palliation [8–15]. Patients with benign cholestatic diseases and frustrated ERC can also be treated by an EUS-guided intervention (stone extraction in push technique; transhepatic balloon dilatation of anastomoses with drainage, etc.). Table 16.1 summarizes the indications for EUS-BD.

In recent years, the techniques of EUS-supported biliary drainage have been further refined and considerably expanded. Today, at

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least six different internal drainage techniques are distinguished, which are used solitary or combined, depending on the anatomy and type of congestion. Table 16.2 shows the different drainage techniques, which can essentially be divided into antegrade and retrograde drainages, whereby the transhepatic or extrahepatic route to the bile ducts can be considered. The success and complication rates of the different techniques vary considerably and depend primarily on the expertise of the endoscopist and the competence of the team.

Note: The EUS-BD is a complex and technically demanding intervention whose success depends to a large extent on the understanding of the anatomy, a high level of experience in interventional EUS, and in particular an optimal coordination between the endoscopist and the team. The examination should be reserved for specialized centers.

Table 16.1 Indications for EUS intervention on the biliary system in cholestasis and frustrated ERC

Multiple failed ERC
Papilla or anastomosis after hepatic jejunostomy with single- or double-balloon enteroscope in case of previous surgery (BII, gastrectomy or Roux-en-Y hepaticojejunostomy) not available
Malignant non-passable gastric outlet or bulbus stenosis
Obstructed left ductus hepaticus with cholangitis in hilar tumor
Acute cholecystitis and co- or multimorbidity (ASA III, IV)
Afferent loop syndrome with cholestasis in peritoneal carcinomatosis
Cholangiolithiasis in patients undergoing surgery (BII, gastrectomy, Roux-en-Y) and frustrated ERC
Suspicion of benign or malignant anastomotic stenosis after hepaticojejunostomy
Pat. with PTCD problems (leakage, infection, pain, only external drainage)
Frustrated PTCD or rejection of PTCD or surgical intervention

16.1.2 Basic Principles and Technical Requirements for EUS-Supported Cholangiodrainage

Decision-making for the optimal choice of the various drainage techniques should be based on a planning sonography or planning computed tomography. These planning investigations provide the nature of the cholestasis, the location and type of obstruction, and the individual anatomical situation with assessment of the relationship between the bile ducts and the intestine (condition after gastrectomy, condition after Roux-en-Y, ascites, gastric or small intestinal obstruction). From surgical reports and preliminary findings of CT, ERCP, etc., valuable information can be obtained, which determines the preferred procedure for EUS cholangiodrainage.

Table 16.2 EUS-supported biliary drainage techniques

Type of EUS drainage, EUS-BD	Abbreviation	Drainage direction
Transhepatic access after FNP of the intrahepatic bile duct		
EUS-ERCP – rendezvous	EUS-RV	Antegrade – anatomically correct
Transhepatic internal antegrad	EUS-AD	Antegrade – anatomically correct
Hepaticogastrostomy	EUS-HG	Retrograde
Hepaticoesophagostomy	EUS-HE	Retrograde
Hepaticojejunostomy	EUS-HJ	Retrograde
Extrahepatic access after FNP of the extrahepatic bile duct		
EUS-ERCP – rendezvous	EUS-RV	Antegrade – anatomically correct
Choledochogastrostomy	EUS-CG	Antegrade – neo-ostium
Choledochoduodenostomy	EUS-CD	Antegrade – neo-ostium
Choledochojejunostomy	EUS-CJ	Antegrade – neo-ostium
Drainage of gallbladder	EUS-GBD	
Cholecysto-duodenostomy/-gastrostomy	EUS-CCD EUS-CCG	Retrograde

Table 16.3 Obligatory requirements for an EUS-BD

Informed consent for EUS-BD/ERCP and PTCD done and available?
Coagulation status current and in the prescribed range (platelets >50, PT > 50, PTT >50)
Antibiotic prophylaxis received (usually 2 g Ceftriaxone)?
Have anticoagulant drugs (NOAK, LMWH) been discontinued? Is the interval between breaks sufficient? ASS does not have to be paused!
Check ASA criteria (propofol sedation ASA1–2; or ITN anaesthesia with medical supervision (ASA3-4) required)

The EUS-supported cholangiodrainage is performed in the ERCP room under x-ray fluoroscopy. In addition to the longitudinal EUS device, a duodenoscope and a gastroscope must be available. The obligatory requirements for the intervention (listed in Table 16.3) are to be checked as questions in the form of a checklist. Pre-interventional antibiotic administration is always necessary, and the administration of 2 g Ceftriaxone is preferred.

The examination is usually performed in a prone position with propofol sedation. For seriously ill or septic patients or patients with aspiration risk, the examination is carried out under general anaesthesia in the supine position. Table 16.4 lists the technical equipment required for an EUS-BD.

Table 16.4 Technical equipment with intended use

EUS-FNP needle 19G	Transhepatic FNP of intrahepatic bile ducts, direct FNP of extrahepatic bile duct
0.035″ guide wire with Terumo tip	Introduction into the bile duct system and lead to the papilla
HF ring knife n. Will (MTW°) or another cystostome (5 or 6 Fr.)	Transhepatic HF access to the bile duct system before wire manipulation at the stenosis
Various special guide wires	Manipulation of stenoses
Bile duct dilatation balloons 6/8 mm Dilatation balloons 10/15 mm	Balloon dilatation of stenoses of bile duct Balloon dilatation of anastomoses
Stone extraction balloon	Stone removal in push technique
Pigtail catheter 8.5/10 French, 11–14 cm	Installation of ring drains as protection (e.g., jejuno-hepaticogastrostomy) after dilatation of stenoses
SEM 10 mm–6 cm partially covered (e.g., HANAROSTENT, Olympus°)	Internal antegrade drainage Retrograde transhepatic drainage
LAMS (e.g., Hot Axios stent; 8/10/15 mm)	Drainage of extrahepatic bile duct and gallbladder drainage of afferent loop syndrome
Metal clips; OTSC clip	If necessary, closure of the access route

16.1.3 General Information on the Technical Implementation of EUS Cholangiodrainage Regardless of the Specific Technique

After initiation of sedation (propofol) under permanent personal and apparatus monitoring (blood pressure, pulse, SO2) in prone position on the X-ray table, the longitudinal EUS device is introduced and the examination begins, depending on the planned intervention technique, either in the duodenum (planned drainage of the extrahepatic bile ducts or the gallbladder) or subcardially in the stomach (planned antegrade internal or retrograde, transhepatic drainage of the intrahepatic bile ducts). After puncture of the bile ducts with a 19G needle, bile is preserved for microbiological examination and only then is contrast medium instillation performed. After sufficient filling of the bile ducts with presentation of the specific anatomy and in particular of the obstruction localization, a 0.035″ wire is inserted. It should be noted that wire manipulation at the sharp needle should be performed with special care to avoid shearing of the wire coating at the needle. Shearing off the coating is usually caused by rapid forward and backward movement of the wire, as is common when overcoming stenoses in ERCP. If shearing occurs, the wire is no longer removable from the needle. If the wire is removed with coarse force, the coating is torn off, which remains as a foreign body in the bile duct system.

To avoid friction problems between the wire and the needle, there are several possibilities:

1. Puncture the bile duct tangentially to avoid bending the wire behind the needle tip.
2. Avoid forced wire manipulation of stenoses in the sense of rapid pulling and pushing movements; if possible, work should only be carried out with feeling and the definitive wire passage should be made via the inserted HF ring knife or a cystostome.
3. If, after wire insertion into the bile ducts, the constriction cannot be overcome or the position of the wire is unsuitable for further manipulation, the puncture needle should be removed and a HF cystostome (e.g., Will ring knife, MTW°) should be inserted via the wire. The ring knife allows subsequent wire manipulations without friction or shearing problems.

Other working groups gain access to the bile duct system via balloon dilatations of the puncture channel and bougies, although this often causes problems, especially in a coarse liver. Therefore, we prefer the primary use of the HF ring knife, with which we rarely have problems.

Note: The search for the optimal puncture route avoids unnecessary complications. Color Doppler insertion for the verification of interposed vessels is essential. The aspiration of bile for microbiological examination is obligatory. Avoid forced wire manipulation via the needle (Cave: shearing off). If the wire can no longer be moved, the needle with wire should be removed and a new puncture must be performed.

16.1.4 Special EUS Cholangiodrainage Techniques

The transhepatic and extrahepatic cholangiodrainage techniques listed in Table 16.2 should be applied according to a corresponding step-by-step scheme, which is outlined in the following (Fig. 16.1), due to their considerably different complications. The lowest complication rate can be expected from the internally antegrade anatomically correct drainage techniques, followed by the rendezvous techniques and the extrahepatic antegrade drains with the application of a neo-ostium (choledocho-duodenostomy, EUS-CD). Retrograde transhepatic interventions (hepaticogastrostomy, EUS-HG, resp. hepaticojejunostomy, EUS-HJ) have the highest complication rates, since stent dislocations into the free abdominal cavity with deleterious consequences may occur [16–18].

Note: An EUS-BD requires specific preparations. The existing anatomy, previous operations, cause, and localization of the occlusion should be known in advance, as the puncture route and technical procedure are based on this. One should always consider which alternative option is possible if the planned one does not work or if there are problems.

16.1.4.1 EUS-ERC Rendezvous Procedure (EUS-RV)

In 5–10% of ERCP the drainage is not successful. In the case of cholestasis, the cause and location of the obstruction must be checked before an intervention. A rendezvous is certainly advisable in the case of stones in the duct, since the stones are easier to remove by transpapillary means. In case of tumor stenosis with the intention of a palliative drainage, an internal antegrade drainage would be an alternative. The latter would be possible without rendezvous technique and would have a lower complication profile. In cases of a planned EUS-ERC rendezvous, there are basically two possibilities: a transhepatic approach via the stomach or an extrahepatic approach via the duodenum. A transhepatic puncture of the congested intrahepatic bile ducts through the stomach with insertion of a wire over a longer distance has the advantage of a more stable position of the wire and a position more distant from the papilla, so that the placement of prostheses in distal stenoses is possible with an inserted wire. In addition, the transgastric-transhepatic approach has the advantage that no serious complications are to be expected even in the case of frustrated rendezvous attempts, since the bile leakage from the liver via the canal made by the

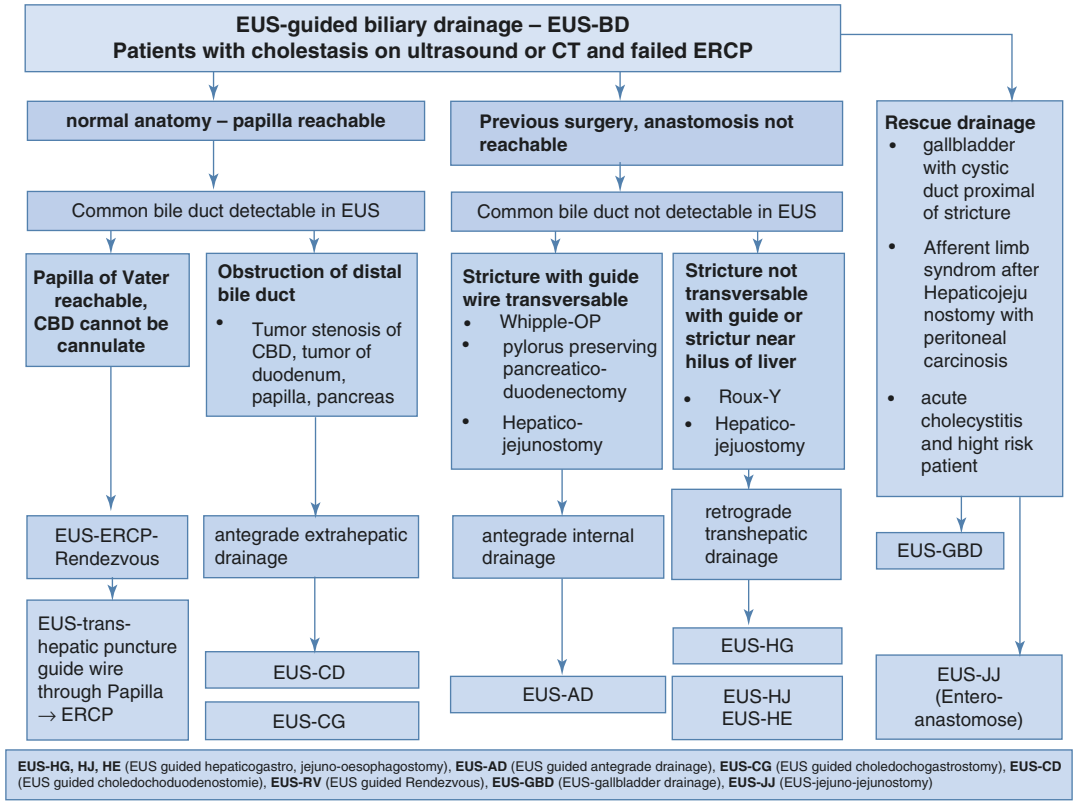

Fig. 16.1 Step diagram of EUS-guided cholangiodrainage depending on anatomy and localization of occlusion

ring knife is usually stopped and the stomach wall is also less at risk of perforation [16–18].

The transgastric-transhepatic puncture with a 19G needle is performed after thorough examination of the anatomy of the bile ducts in the left lobe of the liver. For this purpose, the bile duct in segment 2 or 3 is adjusted, so that the direction of puncture is always directed toward the hilus. In these cases, the bile duct is always hit orthograde, i.e., ultrasound demonstrated transversely, so the duct is shown with the round lumen. In the case of transduodenal puncture of the extrahepatic bile duct, the duct is always punctured tangentially, with the needle pointing toward the papilla. The short path often makes it difficult to overcome the stenosis with the wire. In this position, forced measures such as access with an HF ring knife or balloon dilatation of the access path should be avoided, since the widening of the access path into the bile duct causes retroperitoneal leakage and perforation of the duodenum. The latter leads to serious complications that increase mortality and worsen the prognosis. A lack of wire removal after transduodenal puncture should prompt the endoscopist to choose alternative drainage procedures, such as transhepatic access or PTCD.

With the EUS-RV techniques, after overcoming the obstruction and maximum wire exit from the papilla, the echoendoscope can be removed and a therapeutic duodenoscope can be inserted next to the wire. Special attention should be paid to a dislocation of the wire. The insertion of a duodenoscope next to the EUS device prevents wire dislocation or looping during wire withdrawal (Fig. 16.2).

Via the duodenoscope, the wire is picked up with a special grasping forceps or a sling and led out. The transpapillary interventions can then be performed in the usual manner. The proximal part of the wire is left in place until the stenosis has been overcome. In this way, it is also possible

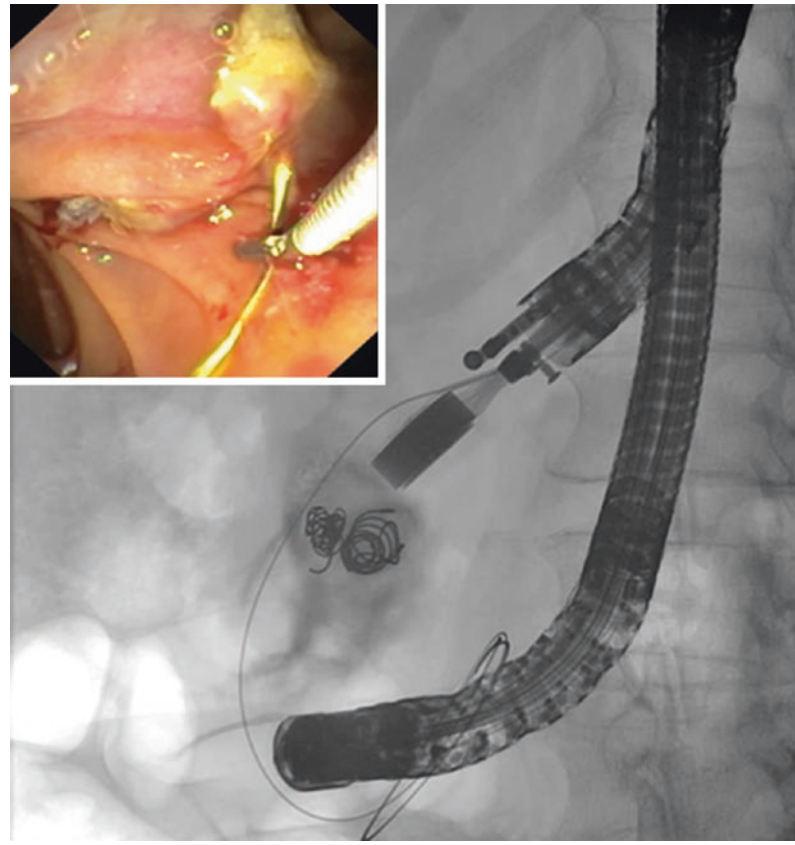

Fig. 16.2 A patient with cholestasis because of pseudoaneurysm of the pancreas with hemobilia. In emergency of bleeding, an EUS coiling was done followed by an EUS-ERC rendezvous after transbulbar EUS-FNP of CBD with wire removal with duodenoscope

to overcome high-seated, coarse stenoses by countertraction of the wire in position. At the end of the examination, the wire is retracted through the duodenoscope. An inspection of the transgastric or transduodenal access route is essential. In case of bleeding, clips should be applied; elective mucosal clip closure of the access route is not necessary.

Note: The EUS-RV is a variant of the access to the biliary system, if the papilla is accessible but not palpable. The transhepatic approach is safer than the transduodenal approach. There is a risk of wire dislocation, when the duodenoscope is inserted.

16.1.4.2 EUS-Guided Transhepatic Internal Antegrade Anatomically Correct Drainage and Stone Extraction in Push Technique

This drainage technique is associated with the least complications of all EUS-BD, which are described with a maximum of 2–5% and are usually of a milder nature (temporary pain, minor bleeding) [6, 7, 18]. In cases of malignant obstruction of the bile duct far from the hilus and endoscopically inaccessible papilla (altered anatomy, tumorous gastric or duodenal stenoses) or malignant anastomotic stenosis after hepaticojejunostomy, the primary aim should be to bridge the stenosis with an EUS-guided internal antegrade luminal drainage. In this case, anatomically correct bile drainage is maintained by bridging the stenosis with a metal stent inserted transhepatically into the bile duct system. After transhepatic puncture of the congested bile ducts in the direction of the hilus with a 19G needle and bridging the biliary duct stenosis with a guide wire, the transhepatic access route is prepared for the insertion of a metal prosthesis. For this purpose, a 6 French HF cystostome (e.g., HF ring knife, MTW°) is inserted over a 0.035″ guidewire. Once the wire has passed through the tumor stenosis, the ring knife can be adjusted under HF

energy application to achieve thermal widening of the tumor stenosis. This enables a prosthesis insertion even without balloon dilatation. If, after RF conditioning of the access route, the ring knife has to be advanced without energy application from the stomach to a position above the tumor, the carrier system of a partially covered metal prosthesis (e.g., Boston° with 6 French carrier system) can be inserted over the lying wire without any further measures. If there are problems with the advancement, a bile duct dilatation balloon (6 mm Boston°) should be used to prestretch the narrowed areas. In contrast to EUS-supported hepaticogastrostomy, the metal prosthesis is advanced completely into the bile duct system, overcoming the stenosis and releasing it internally so that the natural antegrade bile flow is restored (Fig. 16.3).

When choosing the stent, the location of the stenosis must be considered. In case of proximal stenoses with the possibility of occluding secondary ducts, uncovered stents should be preferred. In case of stenoses of the CBD, we prefer partially covered stents. If the carrier system does not pass through the stenosis after access and passage with the ring knife, balloon dilatation (6 mm) must be performed prior to stenosis, whereby the transgastric-transhepatic route through the liver should not be dilated in order not to increase the probability of leakage or perforation. The transgastric access can be closed with clips after removal of the carrier system, especially if extended manipulations such as balloon dilatation, etc. have taken place, in order to avoid secondary complications. In case of HF diathermy alone, the closure can be omitted.

In the case of stones in the common bile duct and anastomotic stenosis or papillary stenosis with an inaccessible papilla, the initial approach is carried out in the same way, but subsequently a balloon dilatation of the stenosis is always performed (rigiflex balloon, Boston°). The width of the balloon should be oriented to the bile duct and should be at least 12–15 (sometimes 20 mm)

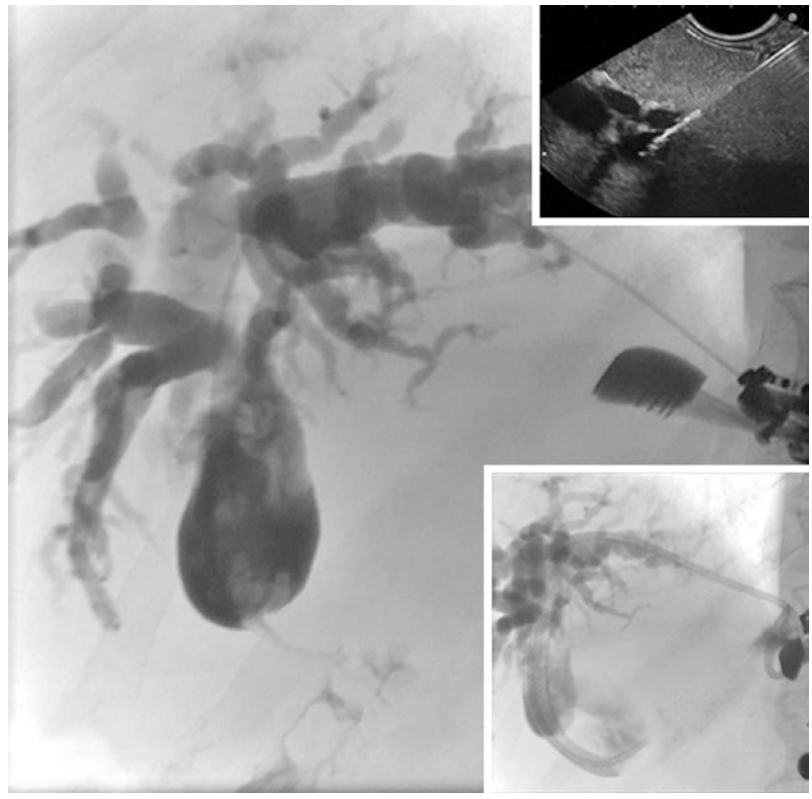

Fig. 16.3 Patient after pancreatic head resection with choledochojejunostomy because of pancreatic cancer local recurrence with jaundice; transhepatic EUS cholangiography shows tumor obstruction at the anastomosis, transhepatic insertion of a cSEM, and a pigtail drainage with bridging of the stenosis and securing the access route

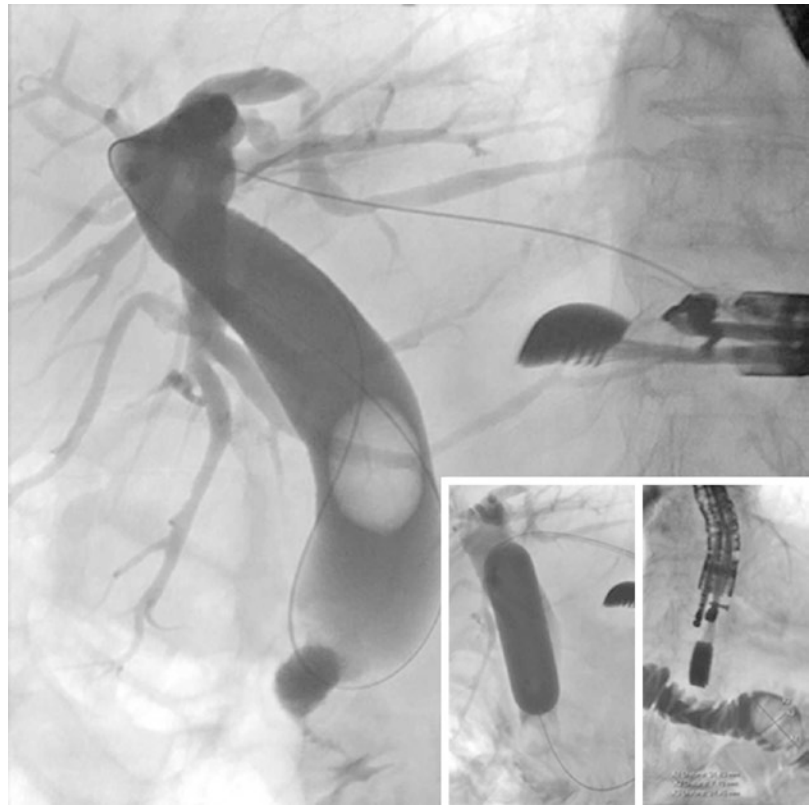

Fig. 16.4 EUS-guided stone extraction in patient after gastrectomy; transhepatic balloon dilatation to 20 mm and stone extraction in push technique

to allow for subsequent stone extraction. A stone extraction balloon is inserted, which is blocked above the stones and then pushed distally (Fig. 16.4).

Technical assistance is particularly important in this case, since a tension must be built up over the wire lying far in the small intestine in order to move the stone distally. Under X-ray view, special attention should be paid to the curved wire in the stomach. The danger of dislocation is particularly high due to the opposing force developments. In our experience, it has also proven to be a good idea to use the slightly deflated dilatation balloon to attempt stone extraction using the push technique. When the balloon is pushed, the material of the deflated balloon wraps smaller stones softly around them, thus facilitating extraction. To secure the papilla or anastomosis after stone extraction, an 8.5 French double pigtail drainage is inserted as a ring drainage (gastro-hepatic jejunostomy), which can be removed after approx. 6–8 weeks.

Note: EUS-AD is the preferred drainage technique for malignant obstruction, since it has the fewest complications. Manipulation with wire on the stenosis should not be performed over a needle. We prefer the HF ring knife. Balloon dilatations should only be performed on the stenoses. Stone extractions in push technique require wide distal dilatations. The insertion of ring drains ensures access and bile flow via the anastomosis.

16.1.4.3 EUS-Assisted Hepaticogastrostomy (EUS-HG), Hepaticojejunostomy (EUS-HJ), and Hepatico-Esophagostomy (EUS-HE)

In patients with previous surgery (gastrectomy, Billroth-II resections, pancreaticoduodenectomy, hepaticojejunostomy) and malignant proximal occlusive jaundice with dilated intrahepatic bile ducts or in patients with completely obturated choledochus, in whom a primarily targeted ante-

grade EUS-BD does not succeed, an EUS-assisted transhepatic retrograde bile drainage is applied. This technique is the most frequently used EUS-BD procedure in our patient population and in the literature [16–18]. The initial procedure corresponds to the internal antegrade drainage technique, with the problem that wire passage of the obstruction is not successful, which excludes EUS-AD and opens up the possibility of EUS-HG as a reserve therapy. As with EUS-AD, it is important that a centrally located duct is punctured so that sufficient liver tissue is available between the bile duct and the capsule to stabilize the prosthesis. A short transhepatic puncture of peripheral bile ducts should be avoided, as the risk of leakage and dislocation is increased. In addition to the access route into the bile duct, the branches of the bile duct that open into this duct should be taken into account in order to determine the required length of the prosthesis and the type of prosthesis. When inserting partially covered metal prostheses, care must be taken to ensure that secondary canals are not cut off from the bile flow after stent release.

The wire that does not pass through the stenosis is advanced as far as possible and access is made with the HF ring knife. Due to the short wire stabilization, the risk of wire dislocation is increased. In general, balloon dilatation of the access route is not necessary if the liver passage is not particularly rough. In case of additional manipulations prior to prosthesis insertion, looping of the wire in the stomach and especially perigastrically, which inevitably leads to wire dislocation, must be avoided. For this reason, all manipulations should be controlled radiologically and endosonographically. A partially covered metal prosthesis is placed over the wire, which should measure at least 6–8 cm and have a special configuration. This consists of a wide tulip-shaped configuration of the stent end in the stomach, which prevents dislocation (e.g., HANAROSTENT from Olympus°). After internal release, there is maximum expansion only in the biliary system, and in the liver to the periphery, the expansion is limited by the maximum 6 French measuring access. The problem with release of the stent is the space between the liver and the stomach in which the prosthesis can expand freely. This has to be considered especially when the stent release is controlled endoscopically alone, as the stabilizing force of the echoendoscope is applied to the left lobe of the liver with pressure from the stomach wall, causing the stomach to deviate from the liver. This can be avoided by performing the release by pressure on the stomach wall under EUS and X-ray control. Here it is important to pay attention to "belly formation" of the stent between the stomach and the liver, which must be avoided at all costs, since dislocation into the free abdominal cavity threatens if the stent is further released. In the case of perigastral "belly formation," the prosthesis must be closed again immediately, and the release must be performed again by means of dosed withdrawal, pressure on the stomach wall, and, if necessary, proximal stent release in the endoscope. After proximal stent release in the endoscope, the stent end can be carefully advanced out of the endoscope with the pusher of the delivery system (Fig. 16.5).

In patients with non-passable unclear anastomotic stenosis, after approx. 3–4 days, a cholangioscopy with biopsy can be performed through the transhepatic stent, and the antegrade passage can be achieved with targeted wire placement and balloon dilatation (Fig. 16.6). In case of postoperative cholestasis with intrahepatic lithiasis, cholangioscopically guided electrohydraulic lithotripsy can be performed through the stent placed in the stomach. For this purpose, the distal stenosis is dilated and the stones are rinsed antegrade or retrograde after defragmentation or removed with a balloon using the push technique.

If there are tumorous constrictions in the right bile duct system at the hilus, these can also be dilated via the transgastric access from the left and supplied with intrahepatic uncovered stents, which divert the bile flow from right to left and via hepatogastrostomy into the stomach (Fig. 16.7).

Note: Sufficient transhepatic wire delivery into the intrahepatic bile duct system is essential prior to further intervention. Loops of the wire in the stomach and perigastrally increase the risk of dislocation and should be corrected. For the

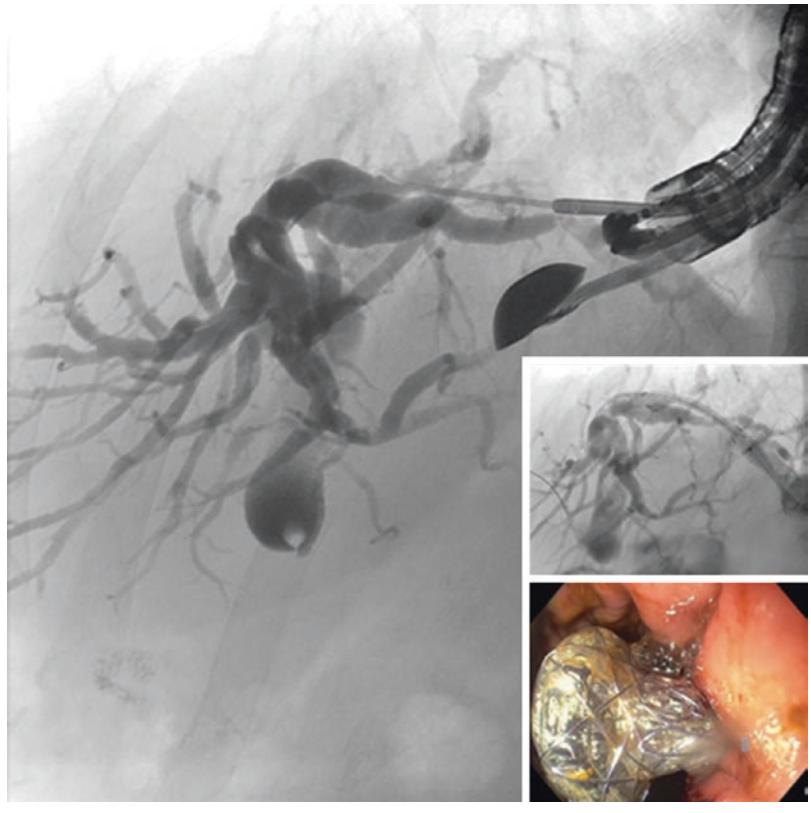

Fig. 16.5 Jaundice after hepaticojejunostomy because of a cholangiocarcinoma. Question: tumor recurrence? EUS-HG with subsequent transhepatic intervention

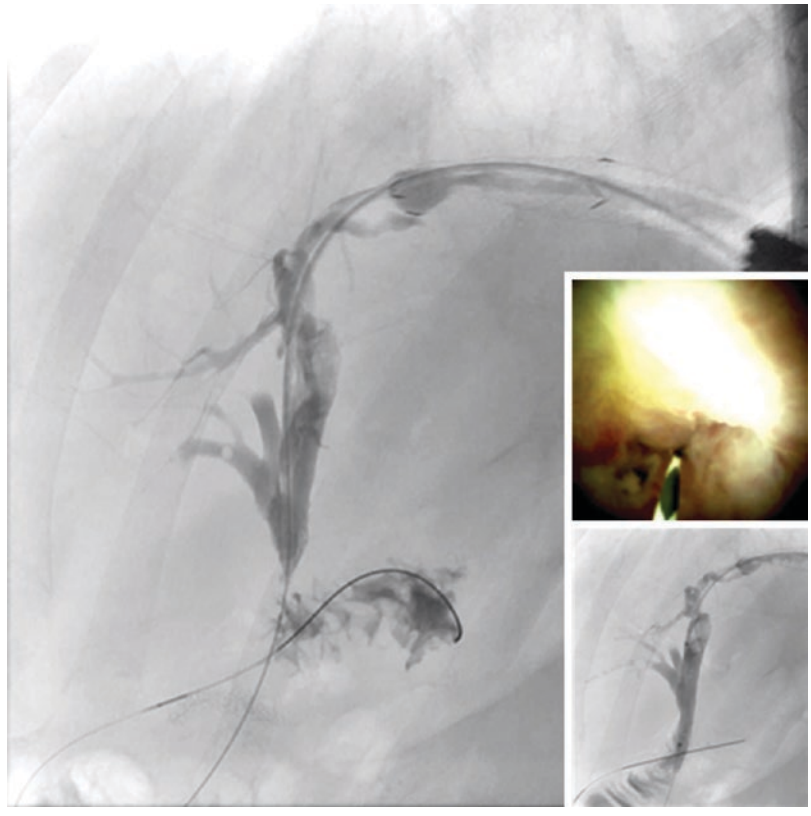

Fig. 16.6 Transhepatic cholangioscopy with SpyGlass: only scarred stenosis; balloon dilatation with subsequent ring drainage

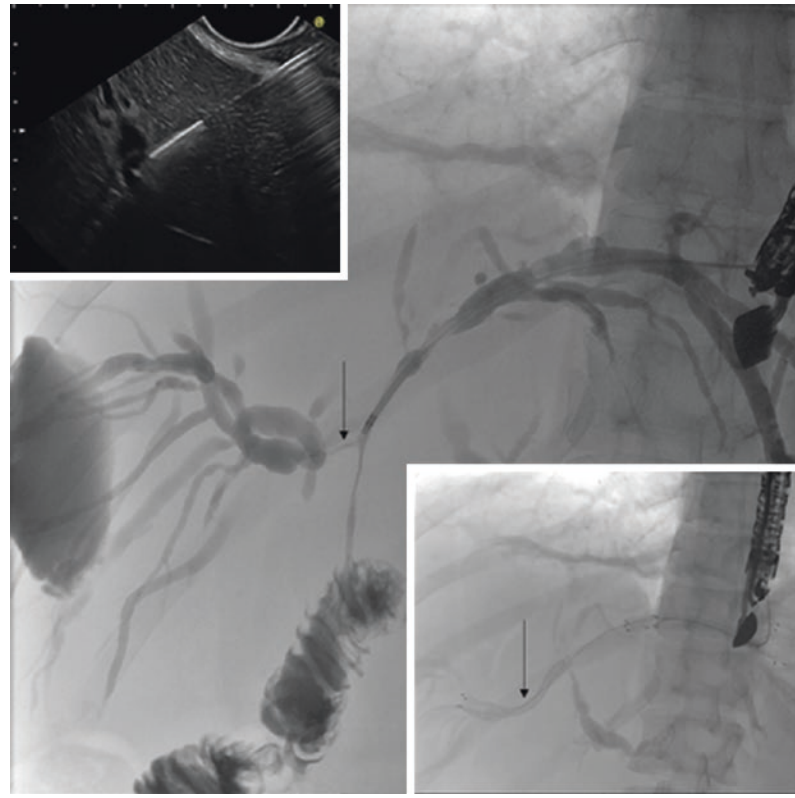

Fig. 16.7 Patient after pancreatic head resection because of pancreatic cancer; local recurrence with liver metastases and cholestasis, cholangiography: stenosis at the anastomosis and the intrahepatic central bile ducts; EUS-HG with balloon dilatation of the right hepatic duct with insertion of a uncovered SEM, thus drainage of the bile of the right hepatic system via the left liver lobe into the stomach

insertion of SEM, access with a ring knife is sufficient. Interventions via the stent (balloon dilatations, stone extractions, interventions on the right bile duct system) are possible in the interval via the transgastric access.

Caution: High risk of dislocation in case of "belly" formation of the self-expanding stent between the stomach and liver – immediate correction required!

16.1.4.4 EUS-Guided Choledochoduodenostomy, Choledochogastrostomy (EUS-CD, EUS-CG)

In patients with distal malignant obstruction of the bile duct or duodenum and dilated intra- and extrahepatic bile ducts, primary transduodenal or transgastric antegrade drainage of the bile ducts should be attempted, if the papilla is not accessible. In contrast to hepatic gastrostomy, this has the advantage of an undisturbed intrahepatic bile duct anatomy. A prerequisite for this is that the choledochus can be adjusted in the bulbus or antrum in a manner suitable for puncture. This technique is increasingly used when primary transpapillary drainage via ERC is not possible. Comparative studies of an EUS-CD with ERC show besides higher success and lower complication rates of the EUS-CD. Therefore, in the palliative setting, a primary EUS-CD has to be considered as well [10, 16, 17].

The echoendoscope is placed in the bulb or antrum on the small curve side so that the direction of the puncture is directed toward the hilus of the liver (unstraightened, pushed on, long way). In the hepatoduodenal ligament, the three leading structures portal vein, hepatic artery, and CBD are easily recognizable, whereby the use of the color Doppler is helpful in differentiating these structures.

After successful puncture of the common bile duct with a 19G needle, preservation of bile, and cholangiography for radiological imaging, the path is secured by insertion of a 0.035″ guide wire. This wire is used to perform an endoscopic choledochostomy. The safest option is by using

the Hot Axios system (Boston). The conical stent carrier system of 10 French is equipped with a small metal ring on the tip, where two metal wires are pulled over the cone proximally. An HF current is applied via the cone and the metal wires so that the preliminary cut can be made without any problems by pulling the wire slightly. The advancement is controlled radiographically and endosonographically, the stent release is under EUS control, and finally the flow of contrast medium or bile into the lumen can be documented radiologically and endoscopically (Fig. 16.8). If the position in the duodenum is secure and stable, the system can also be used to attempt primary access to the bile duct system without wire. In these cases, control fluoroscopy, bile aspiration and wire guidance are not avaiable.

The Axios stents are available in different sizes, for this indication we prefer sizes of 6–8 mm and 10–10 mm. They are very well suited as permanent drainage in palliative settings. The special stent configuration with full coating and a proximal and distal stent flange prevents dislocation. Reinterventions in case of obstruction are possible but very rarely necessary, as bile flow is reliable. In these cases, pigtail stents can be inserted to keep them open. In addition to the Hot Axios stents, the insertion of conventional cSEM or plastic stents is also possible. In these cases, the access must be conditioned to ensure a safe insertion, i.e., contrary to the Axios system, a second step must be performed before the prosthesis is inserted. This can be a sequential bougienage with an initial 5 French and 7 French bougies or primarily the access with the HF ring knife ("Will," MTW°). Any additional intervention performed transduodenally increases the complication rates (wire dislocation, leakage, perforation, bleeding). The author prefers partially covered metal prostheses with a length of 6 cm (Boston°) as the ring knife access is sufficient for the stent insertion. Balloon dilatation is not necessary and the access route is securely closed (Fig. 16.9). A dislocation of these prosthe-

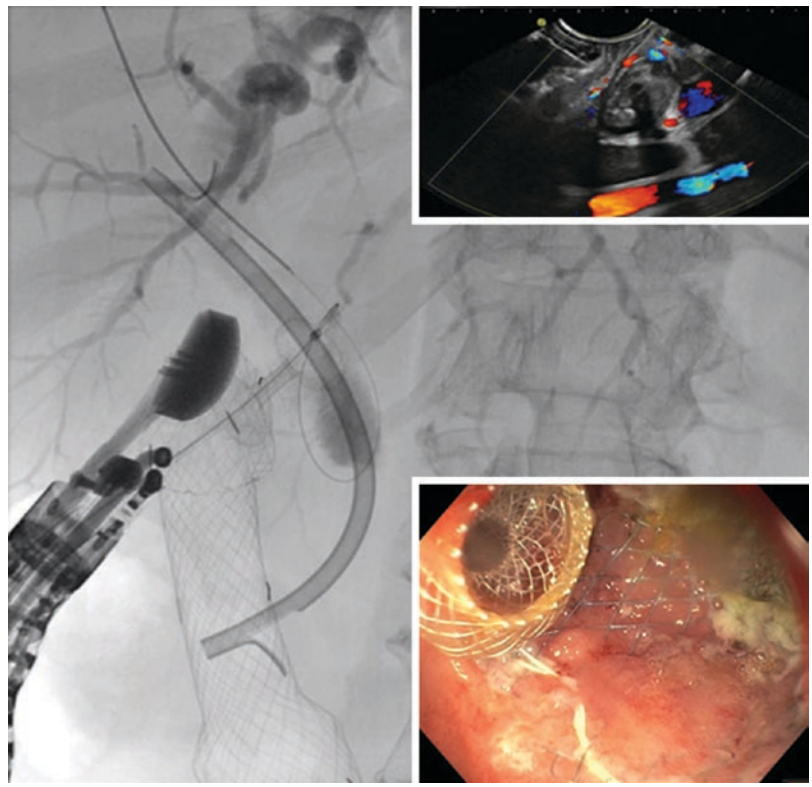

Fig. 16.8 Patient with pancreatic carcinoma and duodenal stenosis with stenting of CBD and duodenum. Cholangitis, ERCP failed. An EUS-guided choledochobulbostomy was performed

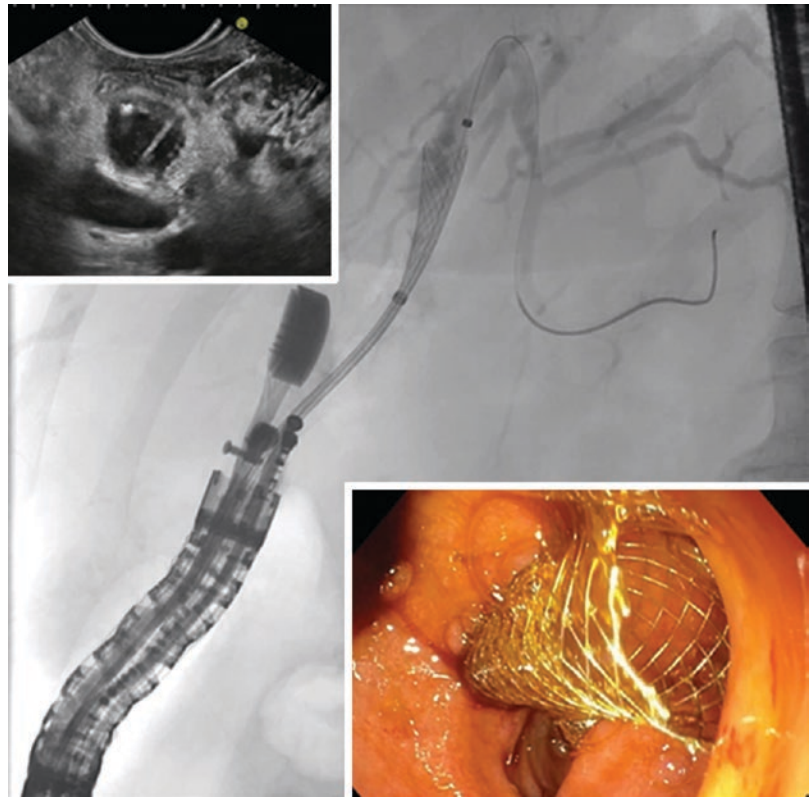

Fig. 16.9 EUS-guided drainage of CBD as choledocho-bulbostomy with partial covered stent – 6 cm (Boston°)

ses is not to be expected with retroperitoneal position and fixation of the duodenum with the bile duct.

In patients with benign distal stenoses and stones in CBD or intrahepatic, antegrade choledocho-duodeno or choledocho-gastrostomy is an ideal technique for permanent bile drainage and reintervention for stone fragmentation and extraction via the neo-ostium.

Note: In the case of EUS-guided antegrade extrahepatic drainage, CBD should be punctured near the hilus of the liver (unstraightened endoscope). LAMS with an HF carrier system are ideally suited, since intermediate steps (HF diathermy; bougienage; balloon dilatation) are not necessary. A choledochotomy with the ring knife is usually sufficient for the insertion of conventional metal prostheses. Balloon dilatations, bougienage, and the insertion of pigtails increase the complication rates.

16.1.4.5 EUS-Guided Drainage of the Gallbladder (EUS-GBD): Cholecysto-Duodenostomy (EUS-CCD), Cholecysto-Gastrostomy (EUS-CCG)

Patients with acute cholecystitis are usually admitted to immediate surgery. Patients with previous stenting (cSEM) of the choledochus with palliative intention may have an obstruction of the cystic duct, which increases the probability of inducing acute cholecystitis. Polymorbid patients or patients with malignant, incurable underlying disease are also burdened with a significantly increased postoperative morbidity and mortality, so that alternative drainage techniques should be favored.

In addition to percutaneous US-guided transhepatic drainage, EUS-guided internal drainage is becoming increasingly important, since the

inflammatory focus can be permanently restored by minimally invasive procedures. The technical and clinical success rates are described with 95–100% and complications with 5–15% [19–22].

The investigation is similar to the EUS-CD. The echoendoscope is positioned in the bulb or antrum, and with further advance of the device in the stomach (unstraightened), the transducer is directed at the hilus. The inflamed gallbladder is usually easily visualized by turning the device slightly to the left. Comparable to the EUS-CD, a Hot Axios stent can now be inserted in direct HF puncture (usually 10 mm), or a puncture with a 19G needle and wire insertion is performed in order to preserve pus and to keep the position more stable in order to avoid a "false cut" with the HF system of the LAMS. The release of the Axios stent is performed as described for EUS-CD. The use of other fully covered double-shielded stents as used for cysts and WON drains is possible as an alternative, but involves greater risks due to the necessary dilatative intermediate steps (perforation of the gallbladder; purulent peritonitis). The procedure should be coordinated with the surgeons in advance in order to be able to react quickly in case of complications. After stent placement, the gallbladder usually collapses quickly, which can lead to mechanical stent closure and block the drainage of the inflammatory secretion. This can lead to a recurrence of the inflammation at interval. To prevent this, the additional insertion of a short 8.5Fr. pigtail drainage has proven to be effective (Fig. 16.10). Stone removal by the LAMS is of course also possible, but clinically it does not make sense.

Note: Internal transduodenal or transgastric drainage of the gallbladder is an alternative therapy option for critically ill polymorbid patients or patients with malignant underlying disease and acute cholecystitis with a high success rate and few complications. The currently safest stent system for such an application is the Hot Axios system.

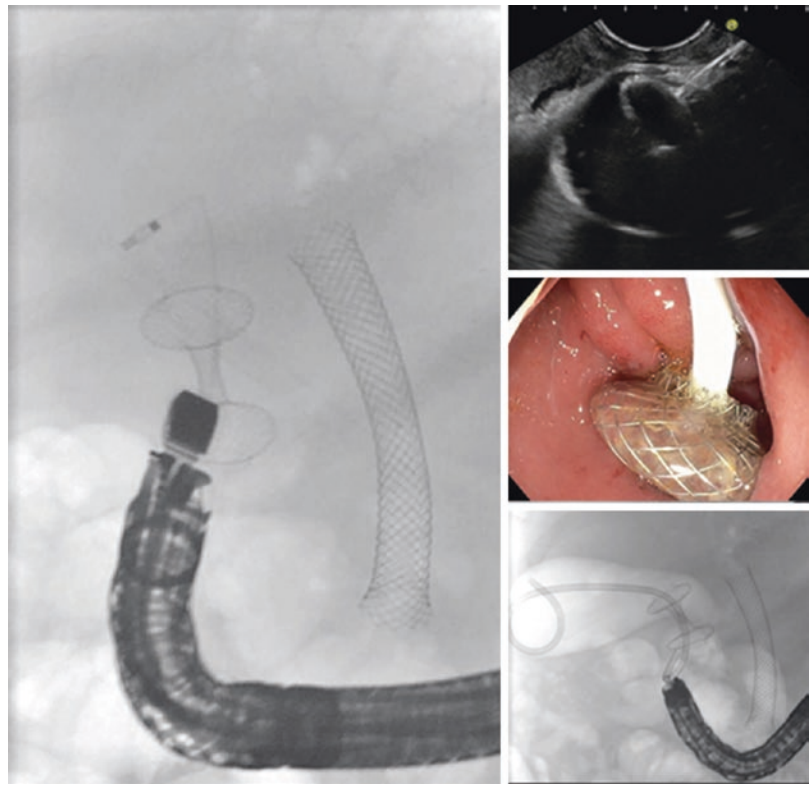

Fig. 16.10 EUS-guided drainage of gallbladder (EUS-GBD) because of cholecystitis only 4 weeks after stenting of CBD with cSEM. The obstruction of the outflow of the gallbladder by the SEM is a risk factor for infection

16.1.4.6 Indirect EUS Cholangiodrainage Through Therapy of Afferent Loop Syndrome (EUS-Gastrojejunostomy (EUS-GJ), Jejunogastrostomy (EUS-JG) or Jejunojejunostomy (EUS-JJ))

In patients with an altered anatomy hepaticojejunostomy with tumorous diseases and a local or peritoneal recurrence, obstruction of the afferent loop may occur in the further course of the disease, which secondarily causes cholestasis due to the disturbed bile outflow [23]. Sonographically, in these cases dilated bile ducts and a dilated loop of small intestine at the hepatic hilum can be recognized. The anastomosis of the hepatic or choledochojejunostomy is usually recognizable in these cases as a broad connection of the bile duct system with the loop of the small intestine and allows the exclusion of a stenosis. If this is not possible in imaging, the patencys of the anastomosis should be documented before performing an EUS-guided enteroanastomosis. This is achieved by initially performing a transgastric, transhepatic puncture of the congested bile duct system with contrast medium instillation in the same session. An enlarged biliary system with immediate filling of the afferent loop without contrast outflow to the distal side is the evidence for an afferent loop syndrome. In this case the needle is removed and the afferent jejunal loop is adjusted endosonographically transgastrically or transjejunally (efferent loop). As described for the drainage of the extrahepatic bile ducts or the gallbladder, the dilated loop of the small intestine can be drained directly with the Hot Axios system through an HF-guided approach. A needle puncture with 19G and wire insertion can be performed upstream for safety if the setting is difficult (Fig. 16.11). Other covered stents can also be inserted via this system, such as those used to supply pancreatic cysts or WON. This requires prior extension of the access with a ring knife or balloon dilatation.

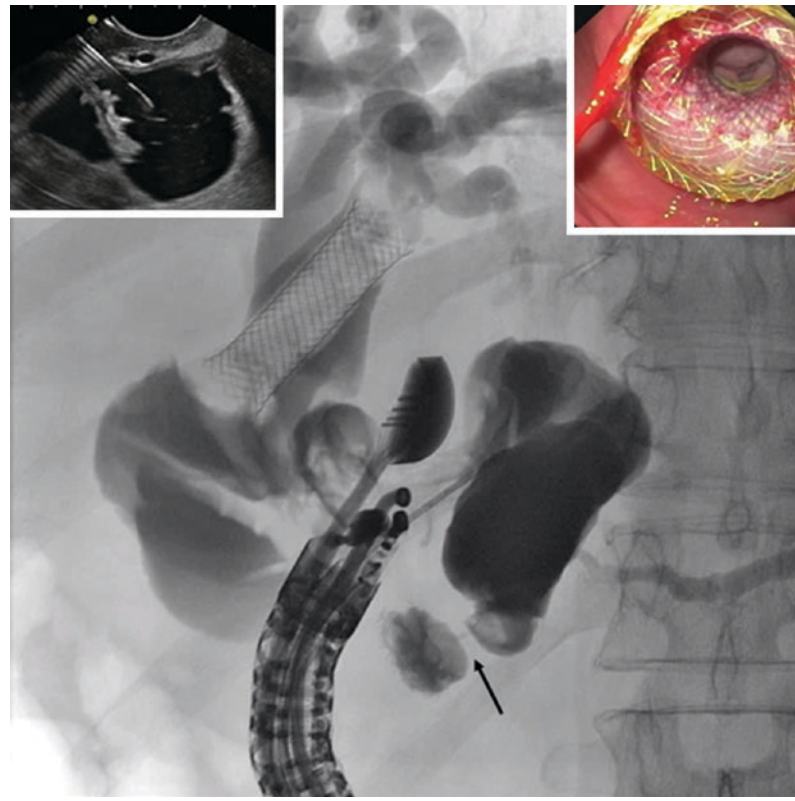

Fig. 16.11 Patient 1 year after surgery for pancreatic cancer with jaundice; cholestasis due to peritoneal carcinomatosis with stenoses of afferent loop (*arrow*), EUS-guided jejunojejunostomy EUS-JJ

16.1.5 Postinterventional Care According to EUS-BD

Patients with EUS-BD should be followed up postinterventionally in the same way as patients with ERCP. Mandatory peri-interventional antibiotic therapy has already been mentioned. This should usually be continued for 3–5 days and must be adjusted according to the germ spectrum after receipt of the antibiogram from the bile aspirate.

During the entire day of intervention, patients remain fasting and receive infusion therapy and, if necessary, pain medication. The first obligatory check of stent function and stent position is performed the following day with percutaneous sonography and laboratory chemistry. Sonographic signs of pneumobilia and decongested bile ducts are to be considered as signs of a functioning drainage system. The stent is displayed in its entire length, in particular the section extending into the intestinal lumen, and the part in the bile duct or liver must be measured exactly in order to obtain signs of dislocations in the further course of the disease if symptoms are present. An asymptomatic pneumoperitoneum after intervention is seen more frequently and is considered harmless if the drainage function is normal and the patient is free of symptoms. Since most patients undergoing EUS-BD suffer from a malignant, incurable underlying disease for which the drainage was designed with palliative aspects in mind, reinterventions are rather rare due to the long openness rate of metal stents. If the stents are closed, an attempt can be made to clean them via the neo-ostium or to insert additional prostheses.

16.1.6 Long-Term Experience and Outlook

Endosonographically assisted biliary drainage (EUS-BD) is considered to be a new possibility of internal bile drainage in cases of obstructive jaundice and failed ERC or PTCD and is mainly used for palliative purposes in cases of malignant underlying disease. The EUS-BD published so far has all been performed in high-volume EUS and endoscopy centers and shows drainage success rates of 70–95%. The complication rates are estimated at 0 and 25% (average 15.7%) and are lower than those described for PTCD, with improved patient comfort [24]. Primarily complications such as cholangitis, stent migration, and biliary leakage due to problems with the prosthesis or at the access route with consecutive peritonitis are reported. Metal stent dislocations and migration, especially in hepaticogastrostomy during release and postinterventional course, have become a rarity with modern stent configurations (stent flange in the stomach).

The advantage of EUS-BD in terms of patient comfort and morbidity compared to PTCD and ERCP (distal tumor stenosis), which is currently being demonstrated in controlled studies, makes EUS-BD the preferred drainage procedure in the palliative setting, at least in centers with high expertise in interventional endosonography [12–15].

16.2 Endoscopic Ultrasound-Guided Interventions on the Pancreatic Duct System

16.2.1 Introduction, Indications, Requirements for the EUS-PD

Endoscopic retrograde pancreaticography with intervention (ERP) is the standard method in the treatment of symptomatic obstructive pancreatitis. Selective transpapillary cannulation and drainage of the pancreatic duct is successful in almost 90–95% of cases. In patients with altered anatomy (Billroth-II anatomy, Roux-en-Y anastomosis, gastric outlet stenosis with gastroenterostomy anastomy), primary internal endoscopic drainage is rarely possible, even with the use of an enteroscope. EUS-PD is indicated for the therapy of patients with symptomatic non-neoplastic pancreatic duct obstruction (especially in the context of obstructive chronic pancreatitis and postoperatively after pancreatic head resection and pancreaticojejunostomy), chronic pancreatic

duct fistulas, in the disconnected pancreatic tail syndrome (DPTS) after a complete rupture of pancreatic duct, if internal drainage is not possible by ERP, and, in an interdisciplinary consensus, a surgical procedure is judged not to be indicated or too risky or is rejected by the patient [25–27]. Patients with an inflammatory destroyed major papilla or suspected pancreas divisum and undetectable or failed cannulation of the minor papilla are further candidates for EUS-guided internal drainage. In patients with chronic pancreatitis and symptomatic retention of pancreatic duct in case of inflammatory head tumor, a surgical procedure has priority in any case, since in these patients a malignoma is to be expected in up to 20% of cases. The decision on EUS-PD should always be made in a surgical-gastroenterological consultation, taking into account the individual anatomy, comorbidities, and complication rates (Table 16.5).

EUS-PD can be performed as a rendezvous procedure if the papilla is accessible, but the cannulation fails (e.g., pancreas divisum) or as primary transmural-antegrade or, more rarely, transmural-retrograde pancreatic duct drainage, if the rendezvous procedure fails or if the papilla is not accessible postoperatively (especially after gastrectomy and/or Roux-en-Y reconstruction). More recent techniques to solve retention of the pancreatic duct after pancreaticojejunostomy include transintestinal-transpancreatic EUS interventions at the anastomosis, if it is possible to pass the narrowed area with a wire. In these cases, temporary ring drains are used after balloon dilatation similar to surgical techniques. If no wire passage is possible in the case of severe stricture of the anastomosis or complete obstruction, transintestinal (mostly transgastric) drainage techniques are used. The technical requirements, endoscopic instruments, preparation, and technical execution are largely the same as for an EUS-BD (see Table in Chap. 16.1.2). The examination technique is difficult and extremely complex and should only be performed in centers with high expertise in EUS intervention and pancreatic surgery including expertise in interventional radiological intervention [27].

Table 16.5 Indications for EUS-guided pancreatic duct drainage

Patients with pain and/ or remitting pancreatitis and/or enlarged pancreatic duct and failed ERP
Pancreas divisum
Failed ERP on major and minor papilla
After operation and not reachable anastomoses (Whipple, duodenum-preserving pancreatic head resection [DPPR])
After operation of pancreas with chronic fistula
Altered anatomy (BII, Roux-en-Y, gastrectomy, gastroenterostomy) and not reachable papilla
After acute pancreatitis with rupture oft the pancreatic duct and remitting pseudocysts and disconnected pancreatic tail
Chronic pancreatitis with not traversable strictures and contraindication for operation or refusal of surgery

Note: For a strictly selected patient clientele, EUS-PD is an effective but technically very sophisticated complementary method to ERP to achieve endoscopic drainage of the pancreatic duct in cases of obstruction, interruption of continuity, and/or chronic fistula. It should be reserved for centers with high expertise in interventional EUS.

16.2.2 Basics and Basic Technical Requirements for EUS-Supported Pancreatic Duct Drainage

The decision, which of the different drainage techniques is to be favored, is made in a planning-sonography or planning-CT. This provides the special anatomy of the pancreas, the location, and type of obstruction, as well as the surrounding area and relationship to the intestine (condition after gastrectomy, condition after Roux-en-Y, ascites, portal hypertension). From surgical reports and preliminary findings of CT, ERCP, etc., valuable information can be obtained which will determine the preferred procedure for EUS pancreatic duct drainage.

The examination is performed in the ERCP room under X-ray fluoroscopy. In addition to the longitudinal EUS device, a duodenoscope and a gastroscope must be available. The obligatory

requirements and the technical equipment necessary for the interventions are comparable to those of an EUS-BD (Tables 16.3 and 16.4). Pre-interventional antibiotic administration is always necessary.

The examination is usually performed in prone position under midazolam/propofol sedation. In critically ill patients or in patients at risk of aspiration, the examination is performed under general anaesthesia in supine position.

Note: The technical requirements of an EUS-PD are similar to those of a complex ERCP or EUS-BD. In patients with chronic pancreatitis and inflammatory head tumor as the cause of retention, EUS-PD is only used if surgery is refused (Cave: high incidence of pancreatic cancer). Pre-interventional antibiotics should be administered as standard.

16.2.3 General Information on the Technical Implementation of EUS Pancreatic Drainage Regardless of the Specific Technique

After initiation of sedation (propofol, midazolam) under permanent personnel and equipment monitoring in prone position on the X-ray table, the longitudinal EUS device is inserted and the examination begins in the stomach with a thorough inspection of the pancreas. In particular, the transition from head to body to pancreas tail is analyzed, the pancreatic duct is followed and measured in its entire extension, and the parenchyma is examined for calcifications, atypical vessels, and venous convolutions. In case of a previous pancreas surgery, the analysis of the anastomosis region is important. Here, special attention should be paid to tumorous structures that are causally responsible for the obstruction. In these cases, the examination would be terminated with an EUS-FNP of the tumorous formation and an internal drainage would be omitted, since the symptoms are mostly caused by tumor recurrence. In this context, it is important to point out that an inspection of the left lobe of the liver and the peripancreatic lymph node stations must be obligatory, especially in the case of post-tumor surgery before a planned EUS-guided drainage, in order not to overlook a metastatic tumor disease. If there is no sign of a malignant tumor, there is no contraindication for a pancreatic duct drainage, the distance of the pancreatic duct to the stomach wall and the vascular structures in and around the stomach are further important parameters for the selection of the access route.

The pancreatic duct is in most cases dilated and easy to follow. In case of pancreatic ruptures or fistulas, the pancreatic duct may have a normal lumen. In these cases, there are usually peripancreatic or perigastric exudations or cysts. The pancreatic duct is adjusted so that the puncture can always be made in the direction of the papilla or anastomosis. After puncture of the pancreatic duct with a 19G needle, which can be difficult with increasing fibrosis or calcification of the pancreatic parenchyma, pancreatic juice is obtained and analyzed (mucin test, microbiology, cytology, CEA, lipase). With a subsequent contrast agent instillation, the anatomy of the pancreatic duct, anastomosis, leakage, fistula to pseudocyst, etc. can be well visualized (Fig. 16.12).

After sufficient filling with view of the special anatomy and especially the localization of the obstruction, a 0.035″ wire is inserted. It should be noted that the wire manipulation on the sharp needle should be carried out with special care in order to avoid a shearing off of the wire coating on the needle. To avoid friction problems between wire and needle, please refer to the tips and tricks mentioned in Chap. 16.1.3 (EUS-BD).

In case of recognizable problems in overcoming stenoses, the wire should primarily be advanced as far as possible. Further wire manipulation of the stenosis should only be carried out after access with the HF ring knife (Cave: wire shearing). Access via bougies is only possible sporadically in the pancreas, as the pancreatic parenchyma is usually very coarse, whereas the

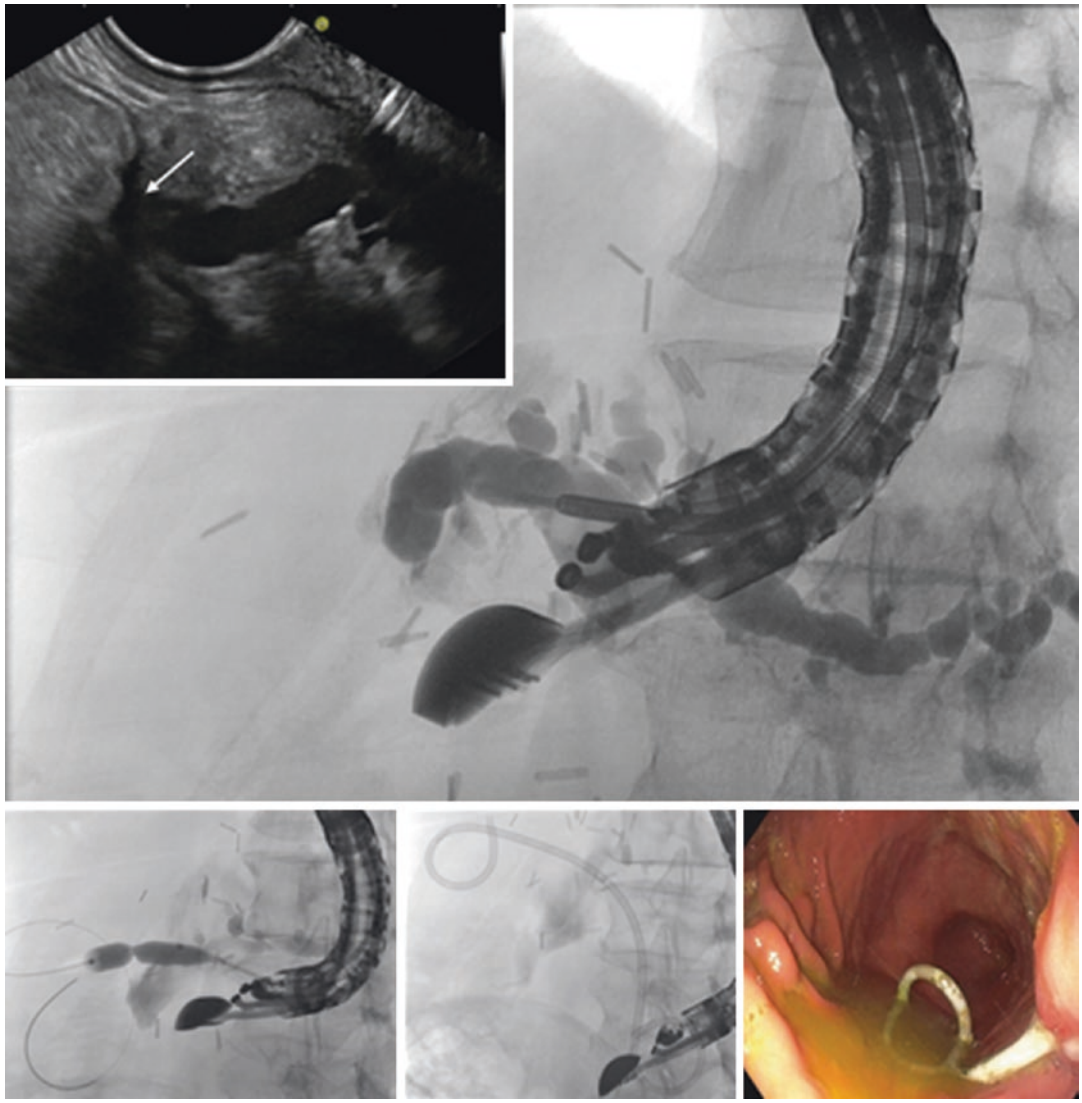

Fig. 16.12 Patient with pain and pancreatitis after pancreas head operation; enlarged pancreatic duct; EUS pancreraticography: stricture of the anastomosis

HF ring knife is used in almost all cases to access the pancreatic duct.

Note: The search for the optimal puncture route avoids unnecessary complications. Color Doppler for the verification of interposed vessels is essential. The preservation of pancreatic juice is mandatory (Cave: IPMN, neoplasia, infection). Avoid extensive wire manipulation via the needle (Cave: shearing off). If the wire can no longer be moved, the needle with wire should be removed and another puncture should be performed.

16.2.4 Special EUS Pancreatic Duct Drainage Techniques

Due to their significantly different complications, the EUS pancreatic duct drainage techniques should be applied according to an appropriate step-by-step scheme, which is outlined below. The lowest complication rate is to be expected from the rendezvous techniques, the highest complication rates are shown by the retrograde transgastric or transjejunal interventions

(pancreaticogastrostomy EUS-PG; pancreaticojejunostomy EUS-PJ), since here bleeding, peripancreatic leakage with formation of pseudocysts, and secondary infections can occur.

The various options for EUS-guided intervention at the pancreatic duct are summarized in Fig. 16.13.

Note: Knowledge of the anatomy and previous operations is essential for planning the EUS-guided access route. If the papilla is accessible, preference should be given to rendezvous with the ERP. Interventions in anastomotic stenoses should be performed with transpancreatic balloon dilatation and ring drains, retrograde drainage should be preferred if the wire systems do not pass the strictures or in the case of DPTS.

16.2.4.1 EUS-ERP Rendezvous Procedure (EUS-RV)

In cases of obstructive chronic pancreatitis with inflammatory involvement of the papilla as well as in symptomatic pancreas divisum with a small papilla, it is often difficult to access the pancreatic duct. In 5–10% of cases, this is not possible and other relief techniques must be used in cases of remittent pancreatitis or chronic pain due to duct obstruction. In case of chronic calcifying pancreatitis, this is primarily the surgical treatment, especially in the case of chronic inflammatory head tumors with the risk of malignant transformation. In case of pancreatic divisum or inflammatory stenosis of papilla, surgical treatment would be considered overtreatment. The

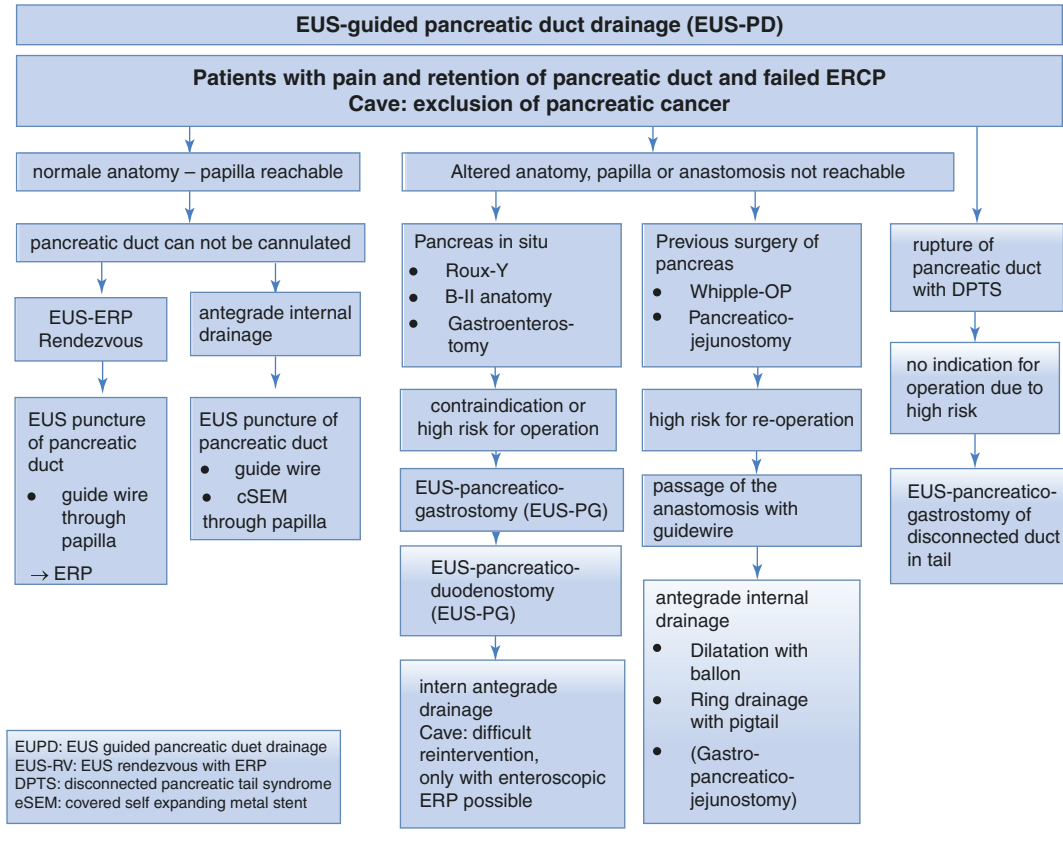

Fig. 16.13 Therapeutic algorithm of an EUS-guided pancreatic duct drainage (EUS-PD) depending on anatomy and obstruction localization

EUS-guided rendezvous technique is an elegant procedure to achieve drainage of the congested pancreatic duct in cases of failed ERP [25].

The pancreatic duct in the corpus head junction is adjusted from the stomach so that it is punctured as tangentially as possible in the direction of the papilla. After successful puncture with a 19-gauge needle and diagnostic aspiration of pancreatic juice, pancreaticography is performed to characterize the anatomical situation. A 4 m long 0,035″ inch guide wire is then inserted and guided out through the narrowing at the papilla with slight forward and backward movements. The wire is then picked up with the duodenoscope and the drainage can be terminated conventionally (Fig. 16.14).

If the wire cannot be led out, the intervention can be extended; however, this should be discussed with the patient in advance, as an extension of therapy can increase the complication rate up to 35%, especially in patients without chronic pancreatitis. Forced therapy involves access via wire with the HF ring knife, which leads to thermal damage to the pancreas, with a higher probability of inducing acute pancreatitis.

Note: The EUS-ERP rendezvous procedure is an elegant method to still achieve transpapillary access to the pancreatic duct in frustrated ERP. An extension of the therapy with a transgastric drainage should only be done in exceptional cases when there are no signs of chronic pancreatitis. This must be discussed with the patient in advance.

16.2.4.2 Transgastric EUS-Guided Drainage as Ring Drainage

Patients with altered anatomy conditions, in which the papilla or anastomosis is no longer accessible or in whom a blocked pancreatic duct is suspected, are potential candidates for reoperation or second pancreatic surgery with surgical drainage in cases of remittent pancreatitis with retention of the pancreatic duct. Especially in patients with retention of the pancreatic duct after surgery, this carries special risks that can be avoided with EUS-PD. In the EUS, the anatomy

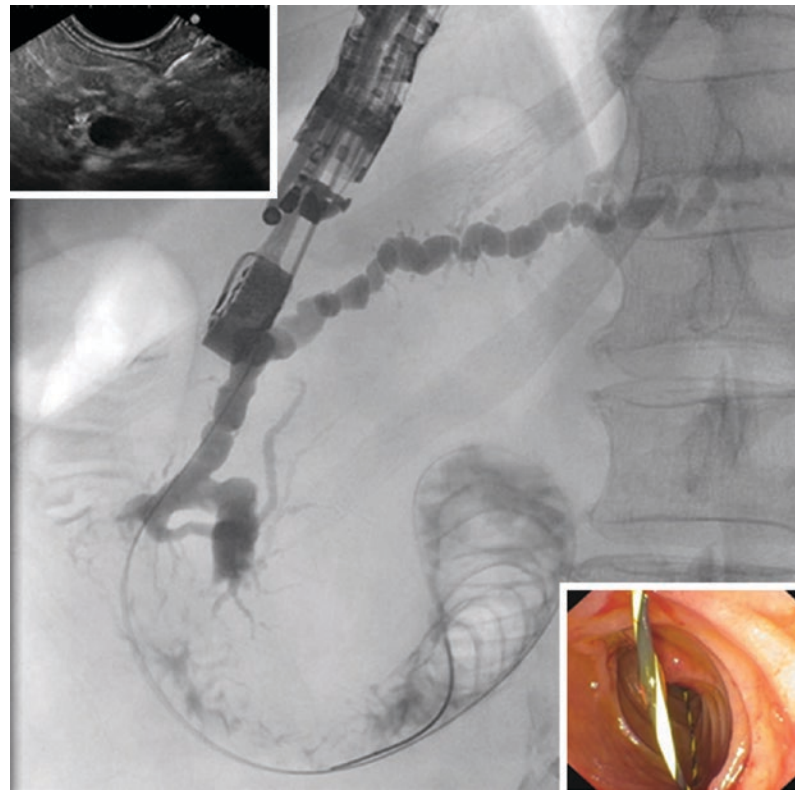

Fig. 16.14 Patient with symptomatic pancreas divisum; puncture of pancreatic duct, pancreaticography and leading out the wire of the minor papilla

of the pancreas can be visualized well. In the case of a previous operation, the anastomosis and the pancreatic duct can be visualized regularly. In the absence of pre-operation and after gastrectomy or Billroth-II resections, at least the proximal pancreatic head with the knee of the pancreatic duct can be seen in its tangential angulation to the papilla. Similar to the rendezvous procedure, the congested pancreatic duct is punctured in the direction of the papilla or anastomosis. After contrast filling, the anatomy can be visualized and the cause of the retention can be identified. In case of a stenosis, one should try to overcome it with the wire system; for this purpose, it is useful to create access with the HF ring knife. If the stenosis can be overcome (anastomosis or papilla), various dilatation balloons (e.g., Rigiflex, Boston) can then be added to expand the narrowed area. The width of the balloon should be measured according to the width of the pancreatic duct. As a rule, balloons with a width of 6–12 mm are sufficient (Fig. 16.12). If there is evidence of concrement in the lumen, after dilatation, an attempt can be made to transport it into the intestinal lumen using the push technique. After balloon dilatation, it makes sense to ensure pancreatic juice flow by inserting a ring drainage for 6–8 weeks. In these cases, we prefer the insertion of long 8.5 French double pigtail stents, which are advanced transpancreatically from the stomach to the small intestine. Before inserting the pigtail, it should be checked whether the transpancreatic approach must be subjected to balloon dilatation to 4–6 mm due to a coarse parenchyma in order to avoid failed stent insertion. This is already indicated by the ring knife, which should be reinserted without current power application after the primary insertion. If this causes difficulties, a balloon dilatation should be performed.

16.2.4.3 Transgastric EUS-Guided Drainage as Pancreaticogastrostomy (EUS-PG) or as Pancreaticoduodenostomy (EUS-PD)

If no wire passage of the stenosis or papilla is possible after pancreaticography or if a complete obstruction is visible, retrograde drainage procedures are used. In this case, the maximum wire length in the pancreatic duct should be placed in order to be able to apply a straight plastic stent or a covered SEM transmural under slight tension on the wire. Compared to EUS-BD, the danger of dislocation of the guidewire is significantly higher in EUS-PD due to the short wire advancement. In any case, the transintestinal-transpancreatic approach should be conditioned by balloon dilatation, since it is usually a coarse pancreatic parenchyma that makes insertion of the prostheses difficult. A balloon dilatation to 6 mm is usually sufficient after a ring knife incision. For retrograde drainage, straight plastic prostheses (10 French, 4–6 cm) as well as covered metal prostheses (e.g., 6 cm Boston) and LAMS (Axios 6–8 mm) are used. The stent application depends on the anatomy, the access route, and the width of the pancreatic duct. A short access path (<1 cm) directly at the level of the closure (no risk of side branches being pinched off) into a wide pancreatic duct (>1 cm) makes a Hot Axios stent 6–8 mm preferable. In this case an SEM can also be chosen for longer access routes. The advantage of the metal stent is, besides a secure closure of the access route, its wide lumen, through which a stable neo-ostium in the stomach can be reached, which also allows reinterventions (EHL with stone extraction). In the case of a central access to the dilated pancreatic duct, one should choose straight 7/10 French plastic stents (Boston°), since the secretion can drain from both sides (Fig. 16.15).

The complication rates of EUS-guided retrograde pancreatic drainage are increased (10–40%) compared to internal antegrade and rendezvous techniques. In addition to perforations of the stomach wall, an increased rate of bleeding, pancreatitis, and the development of peripancreatic fluid sequestration is to be expected [25–27].

Note: A EUS-guided retrograde pancreatic duct drainage is a complication-prone and technically demanding procedure. With short wire advancement, wire dislocations and thus failed drainage attempts must be expected in many cases. A balloon dilatation of the access route before stenting seems to be reasonable.

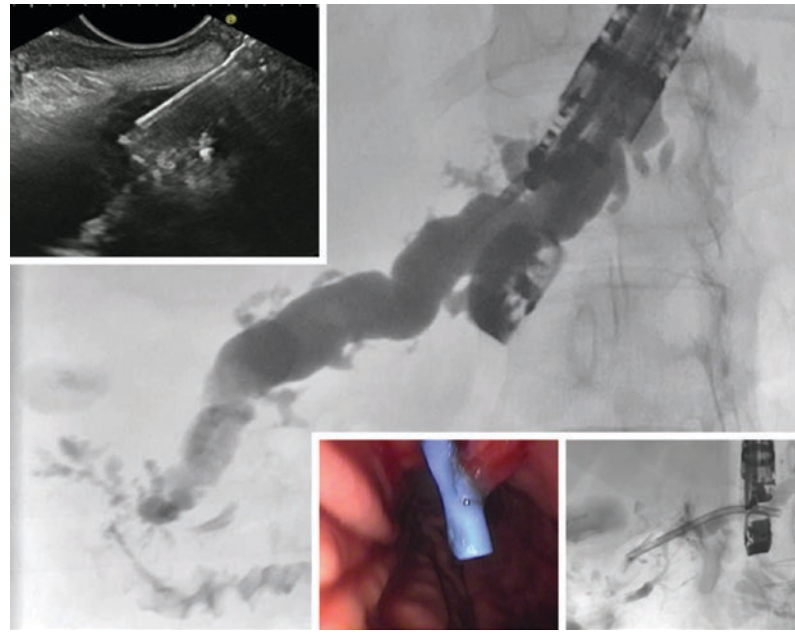

Fig. 16.15 Patient with chronic pain and enlarged pancreatic duct; transgastric EUS-guided drainage

16.2.5 Postinterventional Care and Aftercare

Patients after EUS-PD should be followed up postinterventionally in a manner comparable to patients with ERCP. Mandatory peri-interventional antibiotic therapy has already been mentioned. This therapy should usually be continued for 2–3 days.

During the entire day of intervention, patients remain fasting and receive infusion therapy and, if necessary, pain medication. The first mandatory check of stent function and stent position is performed the following day with a percutaneous sonography. Sonographic signs of air in the decongested pancreatic duct should be placed as signs of a functioning drainage system. The stent is displayed in its entire length, and in particular the section extending into the intestinal lumen and the portion located in the pancreas are to be measured exactly in order to obtain signs of dislocation in the further course of the disease if symptoms are present.

Exudations into the bursa omentalis, sometimes with air inclusions, can be seen after intervention and are considered harmless in symptom-free patients, if the drainage function is regular and the patient does not develop any further complaints or an ascending laboratory chemical inflammatory constellation. If complaints such as fever, abdominal pain, accompanied by an increase in CRP, and leukocytes or lipase occur in the further course of the disease, acute exudative pancreatitis with possible infection must be assumed. In these cases, a sonographic progress of the inflammatory exudation is followed by a percutaneous diagnostic puncture with microbiological examination. In the case of infection, EUS-guided transgastric drainage of the exudation is attempted. The transgastric stents are removed or changed in certain time intervals. The basic conditions that must be fulfilled before removal are the patient's symptoms with a normal laboratory and regular US findings (decongested pancreatic duct with air). If internal antegrade drains are used after balloon dilatation of anastomoses with ring drains, they are removed after 8–12 weeks. Retrograde drains with a straight plastic prosthesis will be changed after ½ year at the latest. If the neo-ostium has a wide opening to the duct, a stent change is not necessary. Metal prostheses (SEM), which per se generate a larger ostium, are removed after ½ year at the latest. The LAMS (Axios) should be removed

after 3 months, as it tends to grow into the stomach wall due to the short distance (buried stent syndrome). No elective controls are required after stent removal. In the event of renewed symptoms due to obstruction of the neo-ostium or anastomosis with retention of the pancreatic duct, EUS-PD can be performed again with the same intention.

Note: Postinterventional ultrasound monitoring is obligatory and can already provide initial signs of possible complications. Elective stent removal or replacement depends on the type of intervention and the type of stent.

16.2.6 Long-Term Experience and Outlook

Endosonographically assisted drainage of the pancreatic duct (EUS-PD) is a new method of treating obstructive pancreatitis in frustrated ERP. To date, approximately 400 patients worldwide have been treated with this new technique, with drainage success rates between 60% and 90% reported. The complication rates are estimated at 15% and 35% (on average 20%) [25–27]. Complications such as peripancreatic exudation, pancreatitis, perforation, infection, and pain are to be expected. Secondary operation rates due to complications or the underlying disease (chronic pancreatitis) are nevertheless remarkable at 5–20% [28]. In any case, the procedure should be discussed in advance with the surgeon, and in the case of chronic pancreatitis without previous surgery, primary surgical treatment should be given priority. Patients with condition after pancreas surgery and recurrent complaints due to anastomosis stenosis with retention of pancreatic duct should benefit most from this new method, as they can be spared a reoperation. In the clinical course, after stent removal with inadequate drainage via the neo-ostium or recurrence of anastomosis stenosis in 15–20% of cases, renewed symptoms may occur. In these cases EUS-PD can be performed again with a different drainage and stent technique including a planned change of the drains. Stent dislocations occur less frequently in retroperitoneal position. Stent obstructions are accompanied by renewed complaints. The examination is challenging and complex with a flat learning curve and should be reserved for specialized centers with extensive experience in interventional EUS and availability of competent visceral surgery and interventional radiology.

16.3 EUS-Guided Enteroanastomoses (EUS-GE, EUS-JJ)

16.3.1 Introduction, Indications, Prerequisites for EUS Enteroanastomosis

For patients with malignant duodenal or gastric outlet stenosis, endoscopic (luminal enteral stents) and surgical (gastroenteroanastomosis) procedures are currently used in palliative therapeutic procedures. The insertion of enteral stents is associated in 10–30% with the risk of dislocation and obturation, while surgical procedures may be associated with higher morbidity due to the greater trauma and, in addition, postoperative atony may limit the functionality of the gastroenterostomy over a longer period of time [29–31].

With the endosonographic-guided gastrojejunostomy, a safe bypass of the malignant stenosis with a functionally sufficient passage can be achieved. Especially in patients with metastatic diseases, due to the lower interventional trauma, this can be preferred to surgical procedures when conventional endoscopic interventions fail.

Comparative studies between surgical and EUS-guided gastroenteroanastomosis have not been conducted so far. The first multicenter studies dealing with EUS-guided surgery are promising [31].

16.3.2 Technical Implementation

In principle, two procedures are described (balloon-assisted puncture and puncture after

water filling), whereby drainage after water filling is becoming increasingly popular, which is to be described briefly. The patients are positioned on the left side (filled water remains on the left side). The tumor stenosis, which cannot be overcome endoscopically, is passed through the gastroscope with a wire, which is placed aborally as far as possible. A 7Fr. nasojejunal drainage is inserted through the wire to the flexura duodenojejunalis, and the position can be checked by application of contrast medium. The probe remains and the EUS device is inserted into the stomach and positioned at the posterior wall of the corpus. To induce intestinal paralysis, butylscopolamine is administered i.v., and subsequently about 300–500 ml of drinking water is introduced via the jejunal probe. Endosonographically the flooding in the jejunum is observed, and we look for a region which is as close and stable as possible to the stomach and which expands optimally due to the water filling. The problem in the system of an EUS-guided GE is the lack of fixation of the small intestinal loop during further intervention, a problem which has to be solved in the future to exclude potential misplacements. Ideally, the localized loop of small intestine should be convex-arched to the stomach, so that the long leg of the small intestine is in the same axis as the LAMS carrier system to be inserted. If this position shows a stable position of the small intestinal loop to the stomach with slight left and right turns, a 20 mm Hot Axios system can be inserted and burned with HF current directly through the stomach and the anterior small intestine into the lumen.

If an instability with dislocation of the small intestinal loop is detected during the positioning maneuvers, a certain fixation can be achieved by inserting a stable wire according to EUS-FNP of the jejunal loop. Contrast medium can be applied via the wire, which increases the safety of the LAMS system, since one is not only dependent on the ultrasound image but also achieves radiographic control. The carrier system of a lumen-apposing metal stent (Hot Axios, 20 mm) is inserted with HF current through the wall of the stomach and the jejunum via the wire. The tip of the delivery system should be clearly visible in the jejunum and should be easily advanced. When advancing far into the lumen, the inner tulip of the stent is released. This is checked radiographically and in the ultrasound image. The secure position of the stent can be well documented by prior introduction of the contrast medium into the small intestine (Fig. 16.16).

The carrier system is then retracted with the opened inner tulip until it deforms in a champagne-like manner against the wall of the jejunum, the proximal tulip of the stent is then released in the canal of the endoscope, and the prosthesis is finally placed in the stomach from the canal of the endoscope under ultrasound view of the inner tulip (Cave: danger of dislocation) under device retraction with slight advance of the carrier system.

The interventional maneuver requires extreme concentration and attention to ensure that the prosthesis does not dislocate from the jejunum or stomach. If such dislocations occur during stent release, emergency surgery is required because the stent has done iatrogenic luminal perforation and at least the jejunal perforation cannot be closed securely. After stent release, the position of the stent should be checked with a gastroscope, and no passage or ballon dilatation should be attempted as this increases the risk of dislocation. After about 3–4 days the stent has spontaneously reached its width of 20 mm and the passage of the food should work.

16.3.3 Long-Term Success and Outlook

The EUS-GE is a new innovative procedure, which offers an advantage over surgical GE, especially due to the low trauma. To what extent this can be established outside of interventional EUS expert centers remains to be seen. Due to the unstable unfixed position of the jejunum, this technique is always a thrill and a technical challenge.

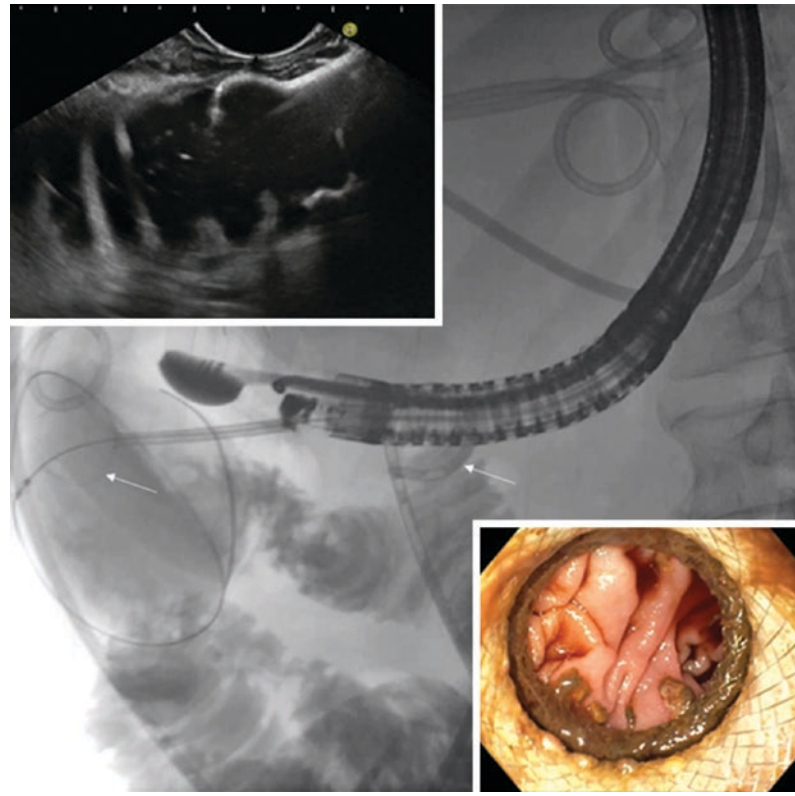

Fig. 16.16 Patient with tumorous stenosis of the stomach and peritoneal carcinosis. Placement of a jejunal tube (*arrow*), and application of contrast medium. Puncture of the jejunum, puncture jejunum with 19G needle, guidewire advancement, Hot Axios stent 20 mm (*arrow*), view through the stomach into the jejunum

16.4 Experimental EUS Interventions

16.4.1 EUS: Tumor Ablation with Alcohol or RFTA

In the literature there are few data on endosonographic ablation of tumors by instillation of alcohol or RFTA in curative intention [32–35]. Primarily only tumors that are encapsulated are considered. So far, these procedures have been reported with success rates of 84% and 60% for the therapy of NET and IPMN, respectively. While in the case of hormone-active tumors (especially insulinoma) with EUS detection of the tumor, an EUS intervention is possible without cytological confirmation, especially in comorbid elderly patients, the entity or dignity of hormone-inactive pancreatic tumors should be confirmed cytologically or histologically before EUS therapy, since this is an experimental therapy. It is mandatory to exclude distant metastases and the patients should be presented in the tumor board and the surgical consult.

At present, only symptomatic or hormone-active patients for whom surgery is contraindicated or associated with an increased risk for other reasons (comorbidity or multimorbidity) are eligible for EUS-EI (ethanol injection). The tumor is conventionally punctured centrally with a 19 G needle, followed by a slow fractionation of 2–4 ml of a 95% alcohol solution, depending on the size of the tumor. Alcohol flooding is shown in the ultrasound image with echogenic artifacts, so that peritumorous flooding is easily detected, which should be avoided if possible. In these cases the needle position should be slightly corrected and the injection slowed down (Fig. 16.17).

In EUS-RFTA, a special 19 G needle is positioned centrally through the tumor with the tip placed approximately 2–4 mm behind the tumor. An electric field is generated between the needle tip and the base after power application, which leads to thermal ablation of the tumor. The

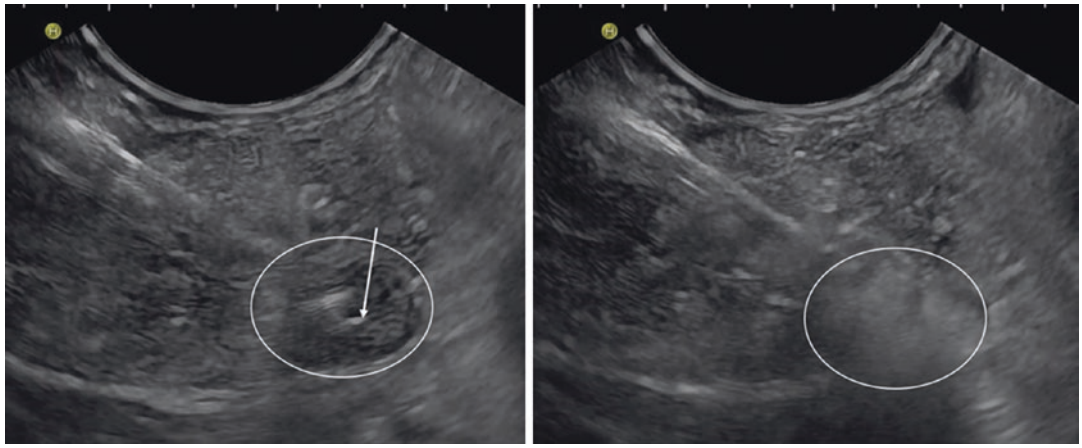

Fig. 16.17 A 87-year-old patient with hypoglycemia, in EUS an hypoechoic tumor 6 mm in pancreatic tail, puncture with 19G needle (tip of needle – *arrow*), application of 1.5 ml 96% alcohol with *white* coloring only of the tumor, normalization of glucose level at the next day

ablation areas are still very limited with the currently available needles and are specified as 6 × 8 mm in one session [36]. This should already be taken into account in the ablation planning, so that for a tumor of 15 × 15 mm at least four overlapping interventions at different locations are necessary to achieve a curative necrosis zone. Since during the intervention water vapor is produced by the heating, which makes it difficult to see through artifacts, the control of the needle in the following interventions can be difficult.

EUS-EI and EUS-RFTA are experimental therapy approaches that should currently only be used in patients with increased surgical risk.

16.4.2 EUS Intervention on Vessels

Gastrointestinal bleeding that cannot be stopped with conventional endoscopic techniques or patients with unclear gastrointestinal bleeding and inconspicuous endoscopy are ideal candidates for endosonography with curative intention [37, 38]. In the EUS, the duodenal and gastric wall can be systematically examined so that intramural varices or atypical arterial vessels (Dieulafoy, pseudoaneurysms) can be detected and treated. For tumors of the upper GIT, which bleed recurrently despite endoscopic and interventional angiographic techniques, the EUS is a procedure which offers the possibility to detect larger tumor vessels by selective perfusion analysis of the tumor and to puncture them. These interventions are considered experimental and should only be used as ultima ratio in the sense of a rescue therapy. It goes without saying that in this transmural EUS intervention multiple punctures of vessels should be avoided. In case of pseudoaneurysms and perigastric or intramural varices, special coils can be inserted after puncture. Immediate endosonographic color Doppler sonographic control of the target lesion provides information about the efficiency. Vessels without Doppler signals after intervention are a sign for the therapy efficiency (Fig. 16.18).

After failed angiographic intervention, vascular recurrent bleeding tumors can be selectively embolized by EUS puncture with a 19 G needle and injection of a histoacryl-lipiodol mixture (Fig. 16.19).

The color Doppler spectra of the tumor with reduction of the color signal or a more sensitive contrast-enhanced endosonography with hypocontrasted behavior after intervention are objective criteria of a successful intervention. In any case, the procedure in these patients should be discussed in an interdisciplinary tumor conference and subjected to a benefit-risk analysis.

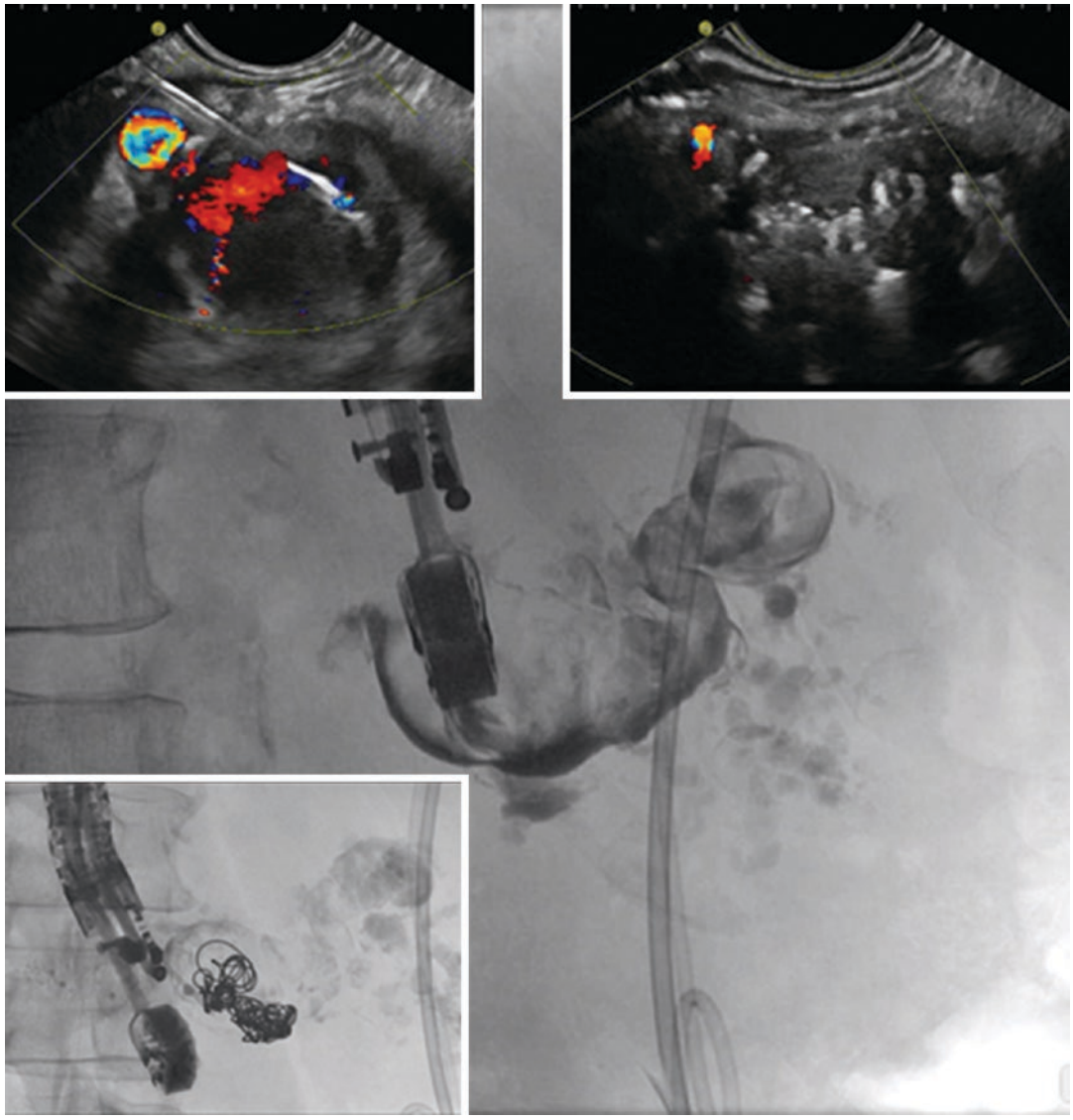

Fig. 16.18 A 83-year-old patient with chronic pancreatitis and hematemesis. In endoscopy – hemosuccus pancreatis. Emergency EUS look for causa found a pseudoaneurysma feeding from the splenic artery with communication to pancreatic duct. EUS-FNP with 19 G needle and application of eight coils stopped the bleeding

16.5 Interventional EUS: Conclusion and Outlook

Endosonography, as a sensible combination of endoscopy and sonography, literally allows cross-border interventions. In the palliative treatment of cholestasis in tumor patients, the EUS-BD drainage procedures are a serious competitor to the primary use of ERCP, as they offer higher success rates with fewer complications. In the treatment of symptomatic obstructive pancreatitis after pancreatic resection procedures, EUS-PD has conquered a field that has so far only been covered by complex surgical reoperation procedures with inherent complication rates. Patients with tumorous gastric, duodenal or jejunal stenosis have been treated with endoscopic luminal prostheses and operative enteroanastomoses. With the EUS-GE, a procedure is now

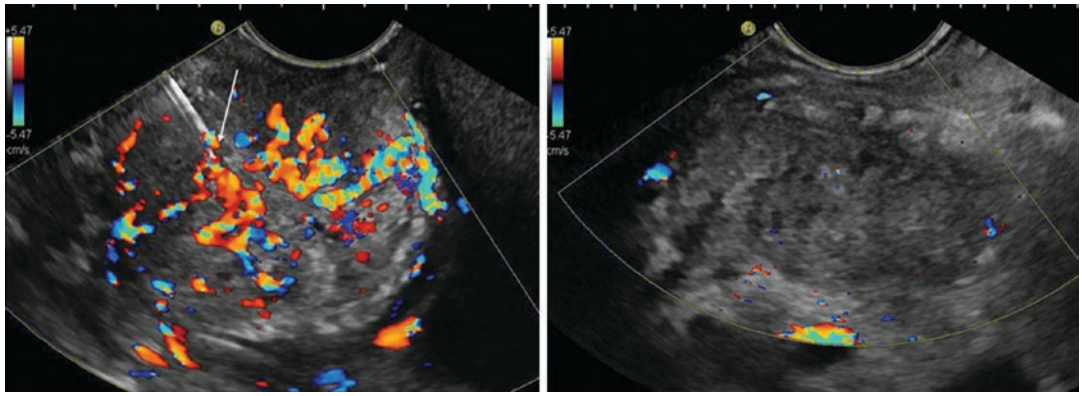

Fig. 16.19 Patient with metastases in the stomach of endometrium cancer with bleeding and ineffective endoscopic and angiographic therapy, rescue therapy – EUS-guided puncture (needle tip in vessel, *arrow*) of feeding artery with application of Histoacryl stopped bleeding (lost of color Doppler signal)

available which restores the passage minimally invasive, with significantly fewer complications. Due to the high resolution of the EUS, the detection of even small hormone-active tumors as well as of vessels in tumors or in the wall of the GIT is possible. Detection is followed by intervention in high-risk or emergency patients (acute therapy refractory bleeding) with instillation of coils, histoacryl, or high-proof alcohol. A targeted curative ablation of smaller hormone-active tumors is also possible with radiofrequency technology (RFTA) via the FNA needle. The spectrum and the possibilities of interventional EUS are increasingly expanding. In centers of maximum care, it has a high value in the interdisciplinary treatment concept. The basis for a successful application of this technique is a basic anatomical understanding, excellent sonographic and endoscopic skills, especially in interventional ERCP, as both procedures complement each other. The courage to tread new paths with interventional EUS, coupled with a responsible view of the well-being of the patients entrusting themselves to us, opens up individually adapted new therapeutic horizons that were previously considered unattainable.

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17 EFTR: Endoscopic Full-Thickness Resection

Andreas Wannhoff and Karel Caca

17.1 Introduction

Endoscopic full-thickness resection (EFTR) is a relatively new endoscopic resection technique. It has rapidly evolved and emerged over the last years and several different techniques and devices are now available. EFTR greatly expands the possibilities of endoscopy and allows endoscopic treatment of conditions or lesions that would otherwise need surgery. Mainstays of EFTR are resection of the target lesion and secure closure of the resulting wall defect. It can be performed in the upper and lower gastrointestinal tract and endothelial as well as subendothelial lesions are amendable to EFTR treatment.

17.2 Indications for EFTR

EFTR might be used for resection of epithelial lesions such as adenomas or early gastrointestinal cancers as well as for treatment of subepithelial tumors (SET), e.g., neuroendocrine tumors (NET) or gastrointestinal stroma tumors (GIST). In selected cases EFTR might also be done for diagnostic purposes.

Colorectal EFTR is the most often performed variant of EFTR. It is usually performed for so-called difficult adenomas. These consist of adenomas with a negative lifting sign or those located at difficult anatomic sites. A negative lifting sign can either be due to scarring in case of residual or recurrent adenoma or due to submucosal invasion in malignant polyps. Difficult anatomic sites are the appendiceal orifice or adenomas located in or at the orifice of a diverticulum. There also is increasing evidence for EFTR in case of early colorectal cancer. In the rectum, EFTR is further performed for treatment of SET. Diagnostic EFTR can be performed in case of suspected motility disorders or a rectal EFTR for evaluation of amyloidosis.

EFTR in the upper gastrointestinal tract is predominantly performed for SET, while epithelial lesions are a much less frequent indication for EFTR. As an exception, EFTR for duodenal adenomas has been described and is currently under further investigation, A technique called STER (submucosal tunneling endoscopic resection), which is often referred to in the context of EFTR despite not being a full-thickness resection technique, enables treatment of esophageal SET and can be used in the stomach as well. Table 17.1 summarizes indications and techniques for EFTR.

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Table 17.1 Indications and techniques for EFTR in the gastrointestinal tract

Site	Indication	Technique
Esophagus	SET	STER
Stomach	SET (≤15 mm)	FTRD (or clip-assisted EFTR)
	SET (>15 mm)	Pure endoscopic EFTR, combined endoscopic and laparoscopic EFTR, STER
	Early gastric cancer	Combined endoscopic and laparoscopic EFTR (very few data), FTRD probably possible as well, but no data available
	Diagnostic	FTRD (or clip-assisted EFTR)
Duodenum	Adenoma	FTRD (or clip-assisted EFTR)
	SET	FTRD (or clip-assisted EFTR)
Colorectum	Difficult adenoma	FTRD (or clip-assisted EFTR)
	Early colorectal cancer	FTRD (or clip-assisted EFTR)
	SET (mostly in the rectum)	FTRD (or clip-assisted EFTR)
	Diagnostic	FTRD (or clip-assisted EFTR)

Summary of indications for EFTR in the gastrointestinal tract and the preferred technique for each indication

17.3 General Aspects of EFTR

Successful EFTR depends on the following two steps: full-thickness resection of the target lesion and secure closure of the resulting wall defect. The order of these two steps defines the difference between exposed and non-exposed EFTR. In exposed EFTR the lesion is resected first and the wall defect is closed thereafter. This causes a short period of time in which the peritoneal cavity is exposed to luminal content. In contrast, in non-exposed EFTR, measures to close resection site are performed first and resection is performed in second step. This avoids exposure of peritoneal cavity to luminal content and reduces the potential risk of tumor cell dissemination.

For full-thickness resection of the target lesion, knives developed for endoscopic submucosal dissection (ESD) or conventional resection snares are used. The development of natural orifice transluminal endoscopic surgery (NOTES) and increasing experience with wall defect closure now allows secure closure of wall defect after full-thickness resection. Closure can be performed using endoscopic clips or dedicated endoscopic suturing devices. Clips can either be applied as through-the-scope clips or using larger and stronger clips mounted on top of the endoscope (OTSC [Over-The-Scope Clip], Ovesco Endoscopy, Tuebingen, Germany, or Padlock Clip, Aponos Medical, Kingston, NH, USA). Dedicated endoscopic suturing devices are GERDX (G-Surg GmbH, Seeon, Germany), OverStitch (Apollo Endosurgery Inc., Austin, Texas, USA), and Double-arm-bar Suturing System. The GERDX suturing device was initially developed for endoscopic antireflux therapy but is now approved for gastrointestinal full-thickness suturing in general, while the OverStitch device was developed for preforming endoscopic sleeve gastroplasty to treat obesity.

It is generally advisable to mark the dissection border prior to resection, e.g., using argon plasma coagulation (APC), and insufflation of carbon dioxide (CO_2) instead of air is mandatory.

While colorectal EFTR, which is done using clip-assisted techniques or the full-thickness resection device (FTRD, Ovesco Endoscopy, Tuebingen, Germany), can usually be done in mild sedation, especially in case of resection of esophageal tumors or larger gastric lesions, general anesthesia and intubation are strongly recommended. In case of larger resections in the upper gastrointestinal tract, we place a nasogastric tube for decompression purpose at the end of the examination, and a routine control endoscopy is performed next day. The patient is left on small amounts of clear fluid for the first day and proton pump inhibitors are given. A single-shot antibiotic is given during all EFTR procedures regardless of anatomic site of the target lesion or technique used.

17.4 Techniques and Devices for EFTR

17.4.1 Full-Thickness Resection Device (FTRD)

The FTRD system combines resection and defect closure in a single device. This has the great advantage of easier use and increased safety. The device consists of a transparent cap with a preloaded modified OTSC and a preloaded resection snare. It is mounted on tip of a standard endoscope. The trigger for deployment of the clip runs through the endoscope's working channel, while the snare handle runs on the endoscope's outside underneath a flexible cover.

A limitation of the device is that lesions are limited to approximately 25 mm due to cap size and amount of tissue that can be incorporated into the cap.

A resection with the FTRD system is performed as follows (Fig. 17.1):

1. Prior to starting resection, the target lesion's border is marked with a special marking probe. This is done without the FTRD being mounted, because visibility with mounted FTRD is impaired and identification of the lesion might be challenging.
2. After the lesion has been reached, it then has to be incorporated into the cap. This can be achieved by use of grasping forceps or a tissue anchor as well as by suctioning the lesion into the cap.
3. When lesion is fully incorporated into the cap, the clip is deployed.
4. The snare is closed immediately thereafter, and resection is started.

17.4.2 Clip-Assisted Full-Thickness Resection

A technique similar to FTRD is clip-assisted full-thickness resection. Therefore, a clip mounted on top of the endoscope (OTSC or Padlock Clip) is applied first to secure the resection base, followed by snare resection. In contrast to the FTRD system, which combines both steps in a single device, in our experience, the risk of thermal injury is increased, and resected specimens are smaller.

17.4.3 Pure Endoscopic Full-Thickness Resection: Special Techniques for the Upper Gastrointestinal Tract

In the upper gastrointestinal tract, several different techniques have been described to perform pure endoscopic EFTR. While the resection is usually done either with a snare or ESD knife, the device for occlusion of the resulting wall defect differed

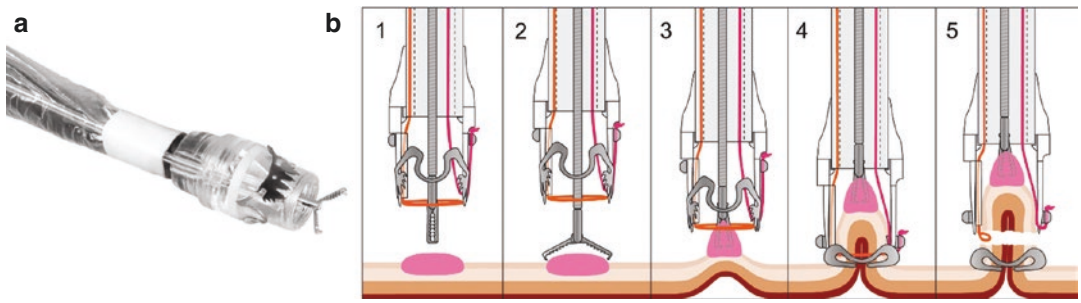

Fig. 17.1 Full-thickness resection device. (**a**) The FTRD system is mounted on the tip of an endoscope. The grasper is advanced through the endoscope's working channel and the snare handle runs under a transparent cover on the outside of the endoscope. (**b**) Utilization of the FTRD system consists of the following steps: (1, 2) identification and grasping of the lesion, (3) pulling the lesion into the transparent cap, (4) releasing the over-the-scope clip, and (5) snare resection of the lesion above the clip. (Figure provide by Ovesco Endoscopy)

between studies. Traditional through-the-scope clips as well as the OTSC have been used. The following dedicated endoscopic suturing devices can also be used to close the resection site: GERDX, OverStitch, or Double-arm-bar Suturing System. They can usually be used to secure the resection site prior to resection and thus to perform non-exposed EFTR. A resection using the GERDX device is depicted in Fig. 17.2.

17.4.4 Combined Endoscopic and Laparoscopic Full-Thickness Resection

Laparoscopic endoscopic cooperative surgery (LECS) combines endoscopy with laparoscopy to achieve full-thickness resection and close the resection defect. Classic LECS consists of the following steps: (i) endoscopic circumferential submucosal incision, (ii) laparoscopic seromuscular incision over three-quarters of the circumference, (iii) turning over the tumor into the abdominal cavity, and (iv) closing the incision with a stapling device and retrieving the tumor laparoscopically. Several modifications of this technique have been developed. Inverted LECS was developed to reduce the risk of tumor cell dissemination into the peritoneal cavity. In contrast to the classic LECS procedure, the tumor is not turned into the abdominal cavity and it is retrieved endoscopically. However, the gastric wall is opened and thus contamination of the abdominal cavity cannot be ruled out. In contrast, the CLEAN-NET procedure and non-exposed endoscopic wall-inversion surgery (NEWS) are forms of non-exposed full-thickness resection. For the CLEAN-NET procedure, seromuscular incision is done laparoscopically and the mucosa is preserved as barrier (a "clean net"). The tumor is then pulled into the abdominal cavity, sutures are applied, and the tumor is resected. NEWS consists of the following steps: (i) marking around the tumor on the mucosal and serosal side, (ii) submucosal injection, (iii) laparoscopic seromuscular incision and suture, (iv) endoscopic submucosal dissection, and (v) oral retrieval of the specimen (Fig. 17.3).

The major disadvantage of these combined procedures compared to pure endoscopic techniques is need for more resources (e.g., endoscopist, surgeon, anesthesiologist, operating room).

17.4.5 STER (Submucosal Tunneling Endoscopic Resection)

STER is a technique based upon the principles of peroral endoscopic myotomy (POEM), which has become an important treatment for achalasia and other motility disorders of the esophagus. STER is performed for resection of esophageal or gastric SET. A submucosal tunnel is prepared as in POEM using an endoscope with a distal attachment cap and an ESD knife. The tunnel is usually started few centimeters (approximately 5 cm) orally of the target lesion. Submucosal injection (e.g., with 0.9% sodium chloride and blue) is made and the mucosa is incised over 10–15 mm. Then the submucosal layer is dissected, and the tunnel is prepared toward the target lesion. Circumferential dissection of the lesion is performed, and the tumor is retrieved endoscopically. It is important to preserve the mucosal layer during preparation and dissection. The entry into the submucosal tunnel is finally closed with endoscopic clips (Fig. 17.4).

17.5 Complications, Complication Management, and Troubleshooting

EFTR should only be performed in endoscopy units experienced in endoscopic resection techniques, treatment of gastrointestinal bleeding, and perforation management, even though development of the FTRD system has significantly increased ease of use and safety. Bleeding therapy consists of use of clips, a coagulation forcep, or injectable agents. Particular peri-interventional bleeding during resection of larger upper gastrointestinal SET is in many cases amenable to treatment with coagulation forceps (e.g., Coagrasper Hemostatic Forceps, Olympus, Shinjuku, Japan). For treatment of perforations OTSC or suturing

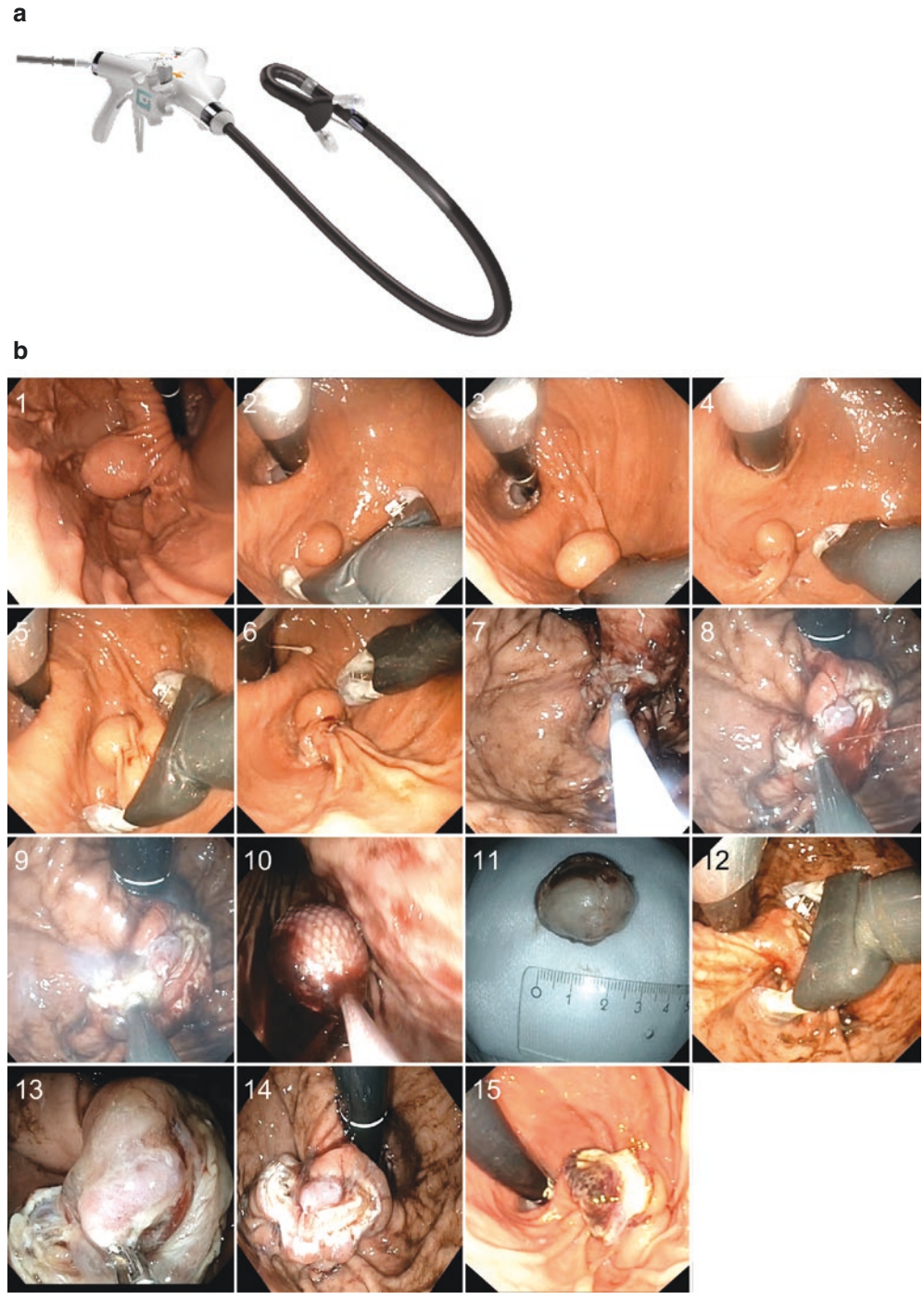

Fig. 17.2 Use of the GERDX device for gastric EFTR. (**a**) The GERDX device can be facilitated for closing of the resection site in full-thickness resection. (**b**) The procedure is performed as follows: (1) subepithelial tumor at the gastric cardia, (2–4) application of the first full-thickness suture underneath the tumor with the GERDX device, (5, 6) application of the second suture, (7) snare resection of the tumor, (8, 9) spurting bleeding from a vessel on the resection site that was successfully treated with a hemostatic forceps, (10) retrieval of the tumor using a net, (11) resected specimen (histology: gastrointestinal stroma tumor), (12) application of a further suture after the resection, (13) prophylactic coagulation of visible vessels on the resection site, and (14, 15) resection site at the end of the procedure and on the following day

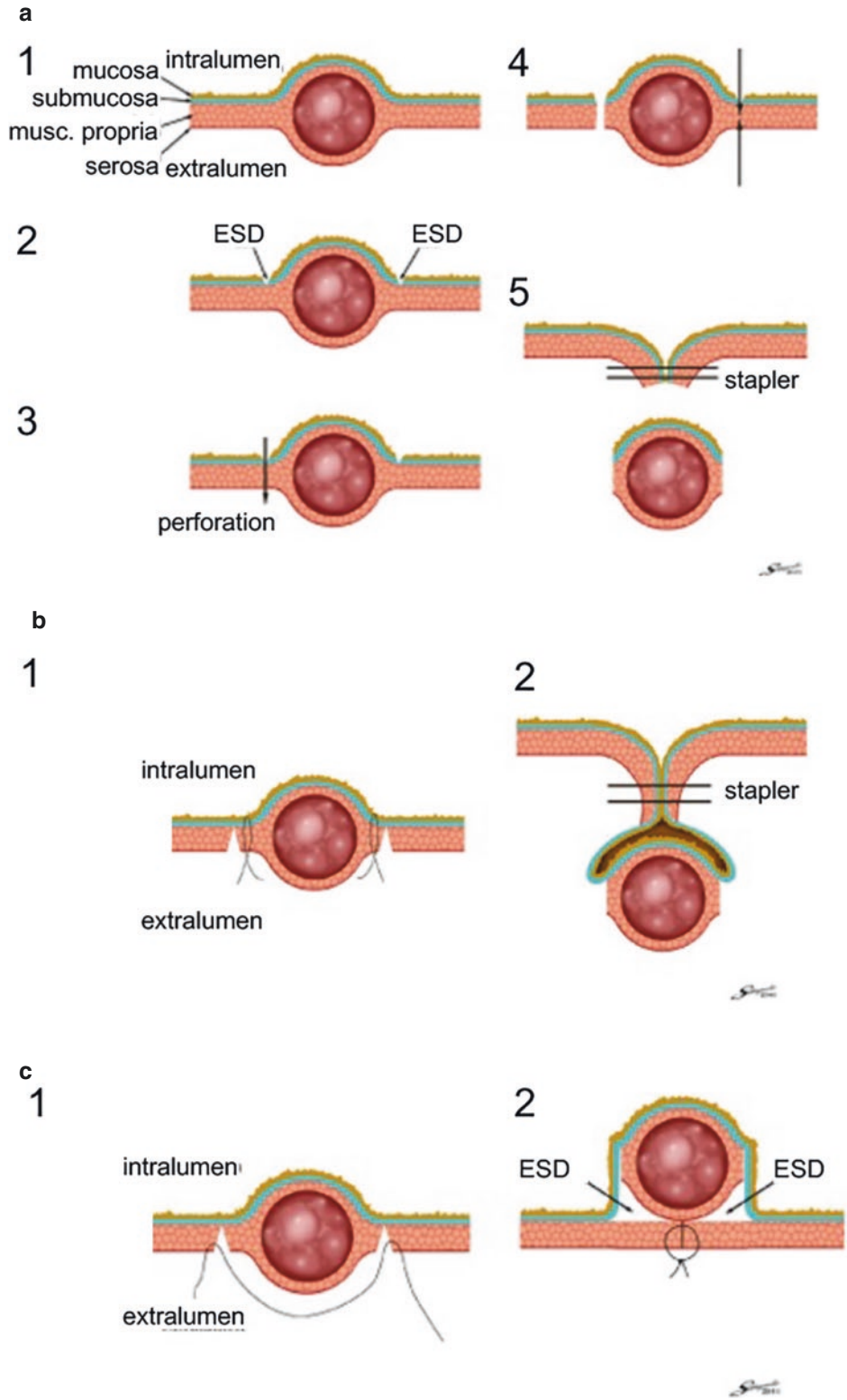

Fig. 17.3 Variants of combined endoscopic and laparoscopic full-thickness resection techniques. Schematic overview of (**a**) classic LECS procedure, (**b**) CLEAN-NET procedure, and (**c**) NEWS procedure. (All figures from Hiki et al. [4]). For details on the procedures see text

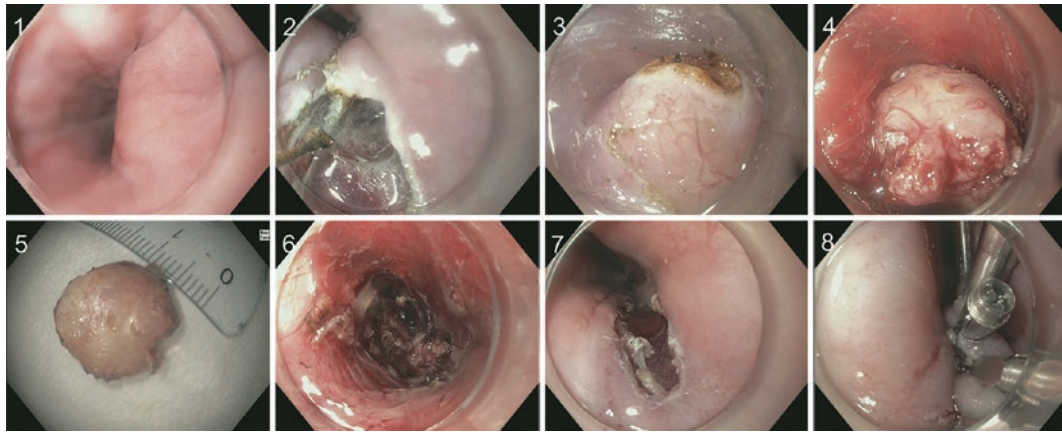

Fig. 17.4 Submucosal tunneling endoscopic resection. STER includes the following steps to resect a subepithelial tumor in the esophagus: (1) SET in the distal esophagus, (2) mucosal incision after prior submucosal injection, (3) preparing of the submucosal tunnel until the tumor is reached, (4) dissection of the tumor and retrieval, (5) resection specimen (histology: gastrointestinal stroma tumor), (6) view of the tunnel and resection site after removal of the tumor, and (7, 8) occlusion of the mucosal incision with through-the-scope clips at the end of the procedure

devices can be used. Successful closure of the perforation should be accompanied by antibiotic therapy. In case of upper gastrointestinal perforation, a gastric decompression tube should be placed and parenteral nutrition or use of a jejunal feeding tube must be performed. Surgery is mandatory in cases with acute peritonitis.

Exposed EFTR or insufficient closure of the resection site in non-exposed EFTR might cause a pneumoperitoneum with subsequent ventilatory failure. CO_2 insufflation instead of air must be used during all EFTR procedures and endoscopists should be experienced with emergency paracentesis for decompression of pneumoperitoneum, e.g., using a venous cannula.

Most difficulties with the FTRD system in the colon occur while advancing the endoscope with mounted FTRD to the target lesion or during incorporation of the target lesion into the cap. Especially passage of the sigmoid colon with FTRD mounted on the endoscope can be challenging in case of severe diverticulosis due to reduced maneuverability and vision. In these cases, prior placement of a guide wire might aid. Incorporation of the target lesion into the FTRD cap can be difficult, particularly when severe scarring is present. Use of the tissue anchor is preferable over grasping forceps in these situations, and the FTRD should be mounted tightly on the endoscope and sealed with tape to enable maximum suction. In some cases snare resection fails after clip deployment. Resection then can be completed with a conventional resection snare; however care should be taken not to include the deployed clip in the resection snare.

17.6 Clinical Experience

17.6.1 Gastric EFTR

Several studies have investigated variants of pure endoscopic full-thickness resection. In studies that utilized exposed EFTR, the subsequent closure of the resection site was done with through-the-scope clips, either alone or in combination with an Endoloop, or with the OTSC. which was shown to be superior for closure after NOTES gastrostomy. The studies are summarized in Table 17.2.

Non-exposed EFTR of gastric SET with the GERDX device (and its predecessor the Plicator, NDO Surgical Inc., Mansfield, MA, USA) and a resection snare was reported on 31 patients with

Table 17.2 Overview of selected studies on pure endoscopic full-thickness resection in the upper gastrointestinal tract

Study	Patients, n	Mean size (Range), cm	R0 resection rate, %	Device for closure	Complications
Exposed EFTR					
Zhou 2011 [19]	26	2,8 (1,2 – 4,5)	100	TTS clips	None
Feng 2014 [20]	48	1,6 (0,5 – 4,8)	100	TTS clips	Five patients developed abdominal discomfort
Huang 2014 [21]	35	2,8 (2,0 – 4,9)	100	TTS clips	None
Shi 2013 [22]	20	1,5 (0,4 – 3,0)	100	TTS clips + Endoloop	Five patients with mild abdominal pain and increased body temperature and received antibiotics
Ye 2014 [23]	51	2,4 (1,3 – 3,5)	98	TTS clips + Endoloop	None
Schlag 2013 [24]	20	1,7 (0,7 – 3,0)	85	OTSC	In six patients pure endoscopic resection was not possible and needed laparoscopic wedge resection; in one further patient the defect was closed with TTS clips
Guo 2015 [25]	23	1,2 (0,6 – 2,6)	100	OTSC	Localized peritonitis in two cases, no surgery needed
Non-exposed EFTR					
Schmidt 2015 [1]	31	20.5 (8–48)	90.3	Plicator/ GERDX	Bleeding and perforation, all treated endoscopically

Summarized are the size, complete resection rate, the devices used for closure of the resection defect, and the complications that occurred in the different studies

a median tumor size of 20.5 mm. A R0 resection rate of 90% was achieved. Perforations occurred in three patients, all of which were successfully treated by application of further sutures. The method was used for tumors of up to 48 mm in size [1]. Full-thickness suturing with the Double-arm Bar Suturing System was compared to the OTSC and hand-sewn sutures in a porcine study and revealed similar strength to the hand-sewn sutures [2]. The OverStitch device has so far only been evaluated in a porcine model too. It was successfully used for defect closure after EFTR with an endoscopic robot device [3].

Recently, first results of EFTR of gastric SET measuring up to 15 mm with the FTRD system in 29 patients were published (Fig. 17.5e). Resection was safe and feasible and allowed definite histological diagnosis in all cases. Complete resection was achieved in approximately two thirds of the patients. FTRD resection of small gastric SET might thus obviate the need for endoscopic surveillance in selected patients. From our own experience, EFTR with the FTRD might as well aid in the diagnosis of scirrhous gastric cancer.

Classic LECS and its variants have been evaluated for resection of SETs and early gastric cancer. With regard to treatment of early gastric cancer, there is only few data available and these techniques cannot yet be recommended [4]. Classic LECS is mostly considered for resection of SET only, because of the potential risk of tumor cell dissemination during exposed full-thickness resection. In contrast, NEWS was combined with sentinel node dissection in a single patient with early gastric cancer [5]. In a further study, an approach that combined laparoscopic-assisted, endoscopic full-thickness resection and laparoscopic lymphadenectomy was reported in 14 patients. However, five of them had to be converted to surgical gastrectomy because of difficulties with wall closure, leakage, or ischemia [6].

17.6.2 Duodenal EFTR

EFTR has been described for resection of duodenal adenomas (Fig. 17.5f) or subepithelial tumors

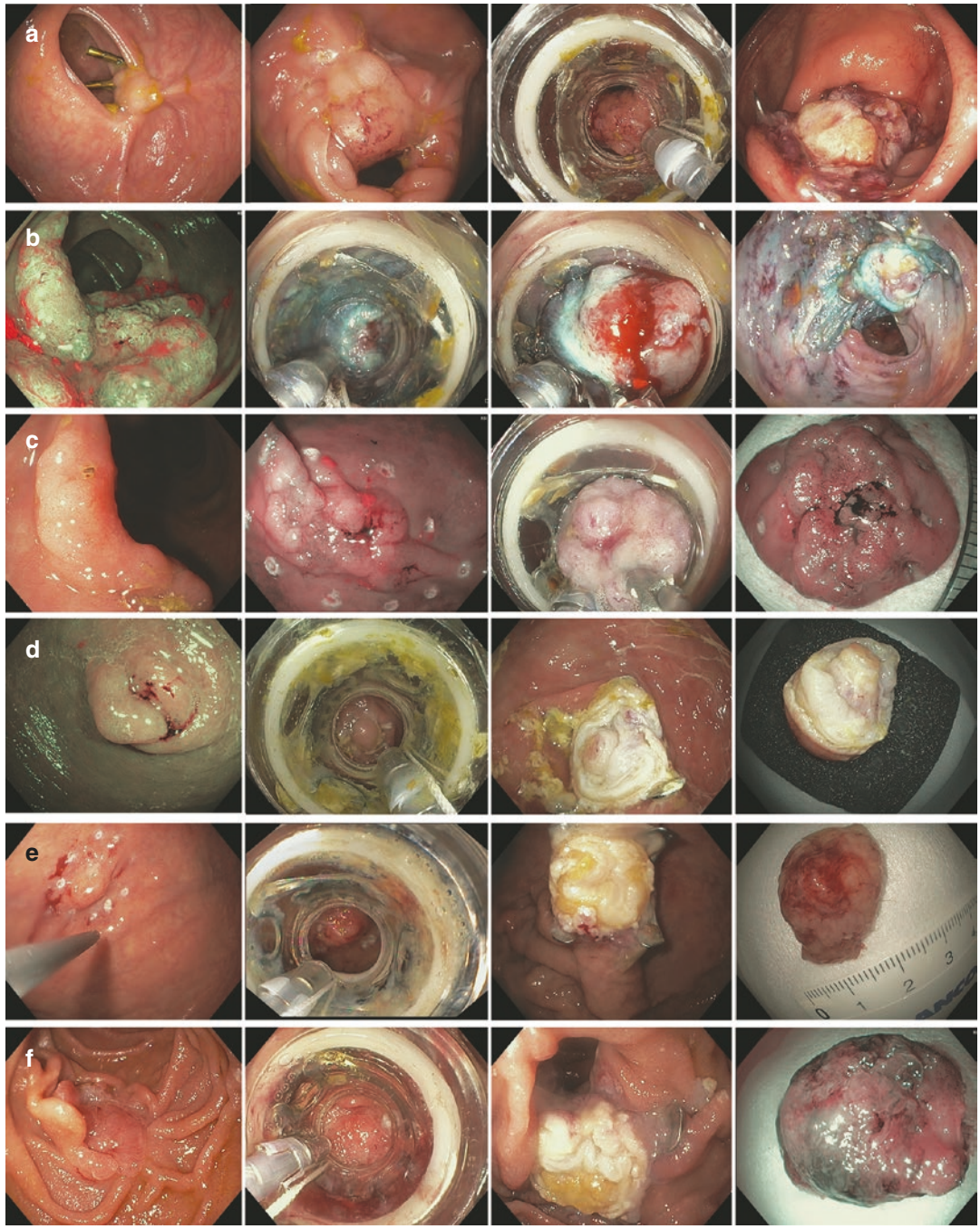

Fig. 17.5 Use of the FTRD for different indications in the upper and lower gastrointestinal tract. FTRD resection of different lesions is shown: (**a**) Recurrent polyp with non-lifting due to scaring. (**b**) Hybrid-EMR-EFTR for a large polyp with partial non-lifting, which is resected with FTRD after the remaining adenoma was removed using EMR. (**c**) Resection of a polyp that was highly suspicious of malignancy and shows a negative lifting sign. It was finally diagnosed as colorectal cancer that was completely resected. (**d**) Removal of a serrated adenoma at the orifice of the appendix. (**e**) Subepithelial tumor (histology: neuroendocrine tumor) in the stomach in a patient with atrophic gastritis. (**f**) Duodenal adenoma

in small and retrospective studies that either used the FTRD system or a clip-assisted technique. Use of the FTRD in a retrospective study including 20 patients showed a successful resection in all cases and a R0 resection in 63.2%. Three events of minor bleeding were noted 1 day after the EFTR procedure, which all could be treated endoscopically [7]. The use of the Padlock Clip in combination with snare resection was described for treatment of duodenal SETs in six patients [8].

17.6.3 Colorectal EFTR

EFTR in the colorectum is mostly done with the FTRD system. A prospective multicenter study from Germany (WALL RESECT) is one of the few prospective studies and the largest study that investigated the FTRD system so far [9]. One hundred and eighty-one patients were included, and major indication for FTRD was difficult adenoma in 173 (79.0%) patients. This was followed by early cancer (stage T1) in 15 (8.3%) and SET in 23 (12.7%) of patients. Target lesions were distributed throughout the colon and were reached with FTRD in 100% of cases. Resection was technically successful in 89.5%, and R0 resection was achieved in 76.9%. In the subgroup of patients who underwent resection for difficult adenoma, R0 resection rate was 77.7%. This data could recently be confirmed in a large retrospective study from the "German colonic FTRD registry" [10] which included 1178 colorectal FTRD procedures and by an unpublished meta-analysis by our group. Registry data revealed a technical success rate of 88.2% and R0 resection rate of 80.0%, and rates in the meta-analysis of 1538 procedures were 90.0% and 77.8%, respectively. The meta-analysis revealed an adverse event rate of 8.0% and need for emergency surgery in 1.0%.

Complete resection of colorectal lesions with the FTRD can be achieved for lesion up to 25 mm in size (Fig. 17.5a). For larger lesions it is possible to combine EMR with FTRD. This hybrid EMR-EFTR technique allows endoscopic resection of large adenomas with non-lifting parts (Fig. 17.5b). First, piecemeal EMR of the lifting area is performed followed by FTRD resection of the non-lifting part. A small retrospective study investigated this approach in ten patients and no complications were reported [11].

Early colorectal cancer seems an interesting target for EFTR (Fig. 17.5c). Results for FTRD resection of early colorectal cancer were reported in a subgroup analysis of the WALL RESECT study. This included 29 patients with early carcinoma as defined by histological examination. In 21 of these patients R0 resection was achieved. In addition to the eight patients with histologically incomplete resection, there were eight patients with a high-risk situation (depth of submucosal invasion >1000 μm) despite R0 resection. Thus, a total of 16 patients were evaluated for surgery. For 11 out of 13 patients with R0 resection and a low-risk situation, 3-month follow-up was available, which remained without signs of recurrent or residual disease in all cases [9]. Recently, a retrospective subgroup analysis from the "German colonic FTRD registry" was published, which included 156 patients. Complete resection (R0) was reported for 71.8%, and 43.9% of the patients were classified as low risk based upon histological examination and underwent endoscopic follow-up. Discrimination between low-risk and high-risk status was possible after FTRD resection in almost all patients. Notably, patients that underwent FTRD resection after incomplete resection of a malign polyp showed low-risk situation in more than 80% and surgery could be avoided in these cases [12].

EFTR of lesions involving the orifice of the appendix was shown to be possible in different studies (Fig. 17.5d). However, a low rate of postinterventional appendicitis was noted in the studies. In a retrospective analysis of 50 patients that underwent EFTR of polyps involving the appendiceal orifice, seven patients developed appendicitis during follow-up, of which four underwent surgery [13].

Rectal neuroendocrine tumors can as well securely and effectively be resected with the FTRD system [14]. Diagnostic full-thickness resection in the colorectum is possible in selected cases as well. This includes diagnosis of motility disorders or amyloidosis.

A two-step method using an over-the-scope clip and a resection snare has been evaluated in the colon as well. There are two studies that either used the OTSC or the Padlock Clip prior to resection [15, 16]. The studies reported the outcome in 17 and 26 patients and the success rates in the two studies were 94% and 100%, respectively.

17.6.4 STER

Several studies have assessed STER for resection of esophageal and gastric SET. In a meta-analysis including 728 lesions in the upper gastrointestinal tract, a pooled rate of complete resection of 97.7% was found [17]. STER is feasible for resection of larger SET as well. This was shown in a study of 101 patients with tumors ≥4 cm. Complete resection was achieved in 86.1%. Complications occurred in 12.9%, but all could be managed conservatively. Tumor size was an independent predictor of incomplete resection and complications [18].

17.7 Summary

Endoscopic full-thickness resection has emerged over last years and expanded the spectrum of therapeutic endoscopy. While some procedures are available in specialized endoscopy units only, the FTRD system has gained widespread use due to ease of use and low complication rate.

The main indication for EFTR is treatment of difficult colorectal adenomas. In these cases, treatment with the FTRD system is well evaluated and should be considered as standard of care. Endoscopic treatment of gastric SET can be performed in specialized centers, either as pure endoscopic full-thickness resection or as combined endoscopic laparoscopic therapy. The role of EFTR for duodenal adenomas is currently under investigation; the diagnostic capabilities of EFTR should not be forgotten.

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18 New Endoscopic Tools for Special Indications

Alexander Meining and Karl-Hermann Fuchs

18.1 Introduction

The basic design of flexible endoscopes was developed decades ago mainly for diagnostic purposes. It is amazing that today interventional endoscopy still uses this scope design together with flexible endoscopic tools, usually advancing them through a narrow working channel. Despite these conditions, endoscopists have demonstrated a tremendous success story in enabling high-end therapeutic endoscopic procedures such as endoscopic submucosal dissection, stent placement, hemostasis, and many others [1].

More recent endoscopic developments have created highly innovative techniques and new technology for replacing surgical procedures such as tumor resections, myotomies, and bypassing malignant stenoses [2, 3]. A number of new ideas and technologies around endoscopic tools are emerging to improve diagnostic accuracy and therapeutic efficacy of procedures. This chapter will focus on a few of these new endoscopic tools for special indications.

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18.2 New Endoscopic Tools in Diagnostic Procedures

Biopsies of intraluminal tumors in the gastrointestinal tract and from masses adjacent to the gut wall are important endoscopic tasks to establish accurate diagnoses. With the help of endoscopic ultrasound fine needle aspiration and fine needle biopsy (EUS-FNA and EUS-FNB resp), diagnostic work-up can be improved and provides valuable information for therapeutic planning in tumor boards [3]. The accuracy of these methods depends on the tissue material and accessible location of the lesions as well as on the biopsy needle size and number of required passes through the lesion [4–8]. In addition, for example, modern classification of a pancreatic tumor may require a histologic diagnosis rather than a cytologic assessment [7–9].

Technical limitations may lead to necessary repetitive investigations [9]. An optimal approach has been considered the repeat biopsies until the on-site pathologist has enough tissue for the diagnosis [10]. Also, an unfavorable angled position of the endoscope in regard to the mass may limit the biopsy results. An alternative has been the approach in modifying the needle tip in order to harvest more material [11, 12].

We performed an experimental study using models for pressure measurements and prototypes enabling the conversion of axial force to axial movement combined with rotation of the

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biopsy needle tip [13]. This combination may lead to lowering the necessary pressure, which may be needed to penetrate hard and rigid tissue of a mass, if the movement of the needle has an advancing *and* twisting component [13]. The results of our study showed that the pressure can be significantly lowered with this twisting feature, thus enabling a better approach [13]. The amount of tissue harvested in the experimental study (using a hard foam plate simulating tissue) was similar to the regular 19-gauge FNB. We could conclude that our rotating fine needle needed less pressure to penetrate artificial tissue without decreasing the amount of tissue acquisition [13].

Another diagnostic, clinical problem is the detection of polyps and mucosal abnormalities during colonoscopy, which is essential for patients. Clinical experience shows that the diagnostic accuracy can be limited by the nature of the colon with folds and bends in between the haustrae of the colon, since the mostly antegrade visual spectrum of the classic colonoscope can miss lesions in the corner of folds. Solutions have been developed by creating full-spectrum colonoscopes [14].

We have used an adjustable cap, which can be mounted on a regular colonoscope [15]. The cap can be produced by a 3D printer and can carry two micro-cameras fixed on the cap, which allows for two additional views backward and sideward of the regular colonoscopic view (Fig. 18.1). We performed a study involving 14 endoscopists. The withdrawal time did not differ between standard colonoscope and side-optic colonoscope; however, the number of detected flat lesions had a significant difference [15].

Fig. 18.1 3D-printed cap to be mounted on a colonoscope and attached with two micro-cameras for simultaneous antegrade and retrograde endoscopic view during diagnostic colonoscopy

18.3 New Endoscopic Tools for Bouginage and Dilation

Especially esophageal stenoses can impair the patient's quality of life substantially. Stenotic tumors or benign strictures, downsizing the esophageal lumen by 50%, lead to dysphagia [16]. Endoscopic-assisted bouginage and dilatations are well-established techniques [16–19]. All these techniques usually require endoscopic assistance in the placement of a guidewire for the bougies and/or the dilation balloon. A direct endoscopic visual control during the bouginage or dilation is not possible, which may be important in preventing lacerations and even perforations [16–19]. An early attempt to use an endoscopic visual control during bouginage was established by a transparent multi-diameter bougie device, which could be mounted on a flexible endoscope [20]. The material was quite rigid and the transparency was limited. More recent studies of a flexible transparent dilator mounted over a standard endoscope (Optical Dilator; Ethicon, Cincinnati, Ohio, USA) were performed [21].

Based on these experiences, we developed a "BougieCap" (Ovesco Endoscopy AG, Tübingen, Germany) (Fig. 18.2) [22]. This device is a disposable, clear, and conical shaped over-the-scope cap. It allows for advancement of the endoscope under visual control through the stenosis and a bouginage of the stenosis. It is secured on the scope by a circular tape. There are several sizes available as shown in Fig. 18.2. In our study, 50 patients were treated [22]. The underlying diseases for the stenoses were peptic strictures in 46%, radiation strictures in 26%, and anastomotic stenoses in 12% [22]. A successful dilatation was possible in 48 out the 50 patients. Dysphagia scores improved significantly after the treatment. No cases of perforations occurred.

18.4 New Technology for Endoscopic Resections

Endoscopic resections such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and endoscopic full-thickness resections (EFTR) are modern interventional endoscopic techniques, which are increasingly used in patient care [23–25]. Although, experienced interventional endoscopists can manage endoscopic mucosal resections with the commercially available instruments quite safely, the wish for independent traction and countertraction on the tissue in the target area rises, whenever these maneuvers are difficult. Several attempts to develop technical features to allow for these instrument manipulations were made in the past, for example, with a double-channel endoscope [26]. More sophisticated platforms were created, but never reached the market [27, 28] (see chapter: Endosurgical platforms).

We reported on our experience with a 3D-printed overtube system for ESD in a porcine model (Fig. 18.3) [29]. The overtube device is fixed on the procedure table, and the endoscope docking station is fixed on the endoscopists allowing the investigator to use both hands for necessary manipulations. Dissection and manipulations with the two instruments can be performed following a more surgical paradigm. The device was successfully applied in an experimental model [29].

Fig. 18.2 BougieCaps in several sizes mounted on an endoscope to treat stenoses in the GI tract by endoscopic means

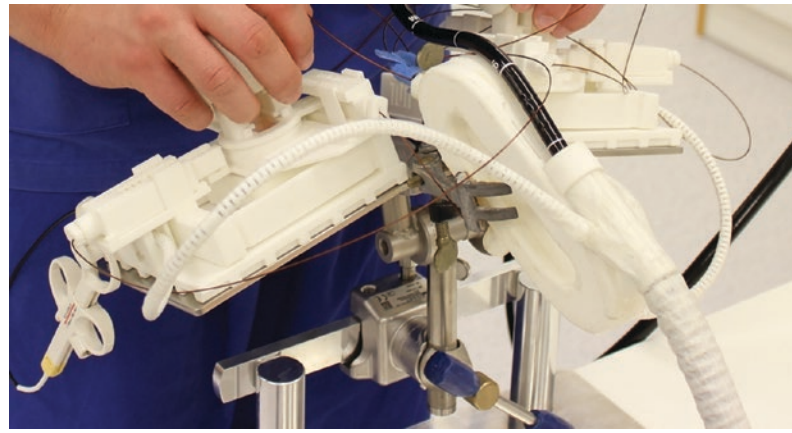

Fig. 18.3 3D-printed endoscopic manipulator system with overtube and steering mechanism of endoscopic instruments

Another easy to use technique can be the application of an external additional working channel (AWC), attached to a regular commercially available endoscope to perform an endoscopic resection of a flat lesion, as published earlier [30]. After appropriate preparations and regulatory work, we have used the AWC (Ovesco, Tübingen, Germany) in patients for lesions in the lower and upper gastrointestinal tract (Fig. 18.4) [31]. The results were very promising in that the system could be successfully applied in eight patients for EMR and ESD.

18.5 The Perspective of Using 3D-Printing Technology for Endoscopic Instruments

Since several years the perspective of using 3D-printing technology in medicine especially in surgical models and instruments has been investigated [32–35]. The advantage of this technology is the creation of an individualized model or instrument in reasonable time at a reasonable price. As a consequence, 3D models are used in preoperative planning, for example, based on preoperative imaging data [32–34]. Another option is the production of a special instrument prototype, which may be necessary or of a certain advantage in a given procedure [35]. Recently authors have planned a special endoscopic and surgical approach in the esophagus, where they needed an individualized spaceholder for the exposure of the esophageal lumen [36].

This technology opens a new perspective in instrument development both for endoscopic and surgical instruments. The step from an idea concerning an innovative procedure with special instruments to a usable prototype is shortened and has become an affordable reality [37]. This allows for the creation of prototypes of instruments, which lowers the threshold of testing new innovative ideas within a reasonable time frame [37].

18.5.1 The Perspective of "Endoneering"

The term "Endoneering" stands for a combination of endoscopy and engineering, which was coined to characterize the new cooperation between engineers and endoscopists [38]. A similar fruitful combination has been established with engineers and surgeons creating "Surgineering" [39]. The diagnostic and therapeutic innovations have advanced to new levels in endoscopic surgery or surgical endoscopy, some turning out to be unrealistic, others have stood the test of time. One of the main offspins of the "NOTES-Hype" has been the creation of a synergistic network between engineers and clinicians. As a consequence, this group of experts will bring clinical demands and technical concepts together [40].

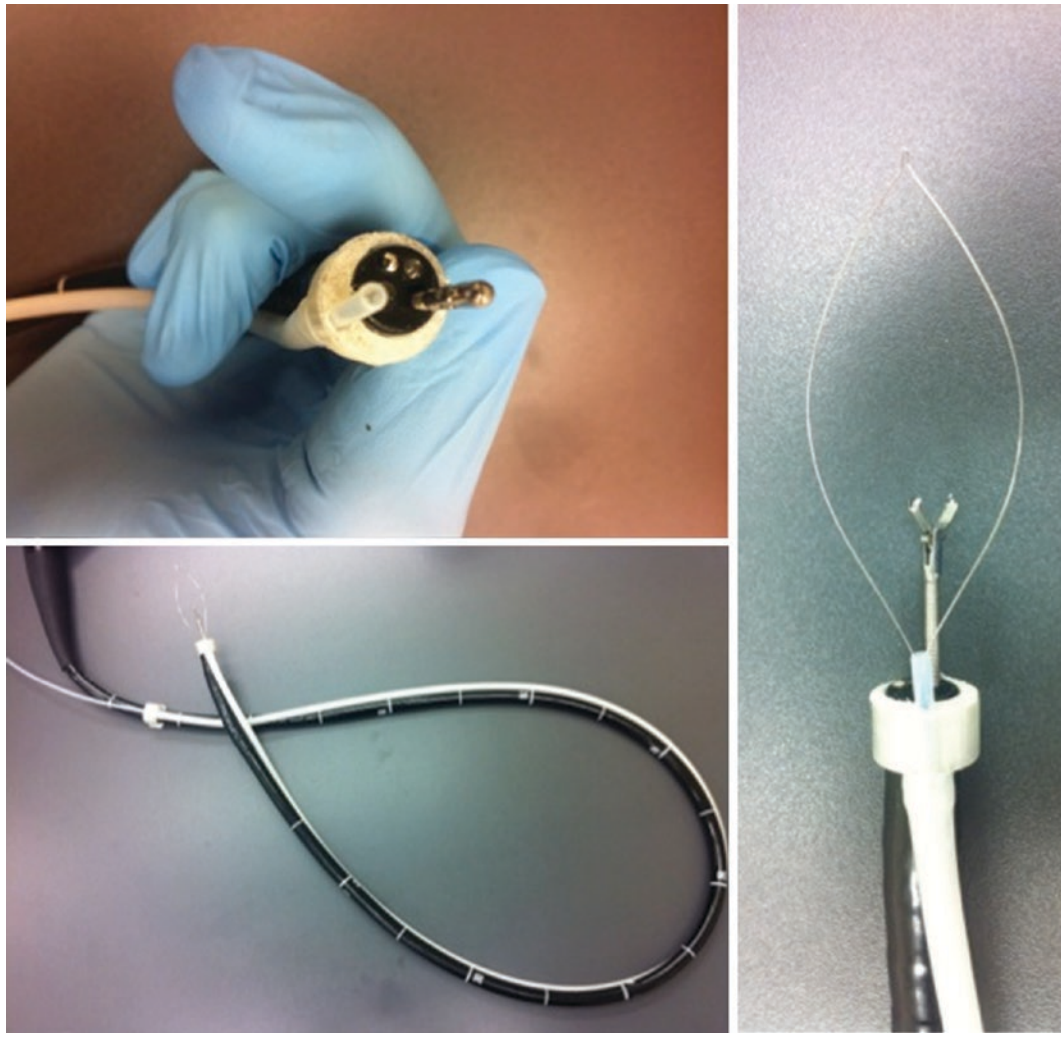

Fig. 18.4 An external "Additional Working Channel" (AWC) is attached to the endoscope to allow for additional instruments to be used in interventional endoscopy. The channel is fixed on the tip of the scope by a 3D-printed cap

Endoscopists and surgeons will get a deeper insight in the technical background of instruments and will get an important exposure in technical ideas, when communicating with engineers; and vice versa: engineers will learn to understand clinical needs and technical shortcomings of procedures and instruments, when experiencing a common exposure and discussion with clinicians. This interaction may be very fruitful in the future for the development of innovative endo-surgical procedures [38–40].

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ESD: Indications, Techniques, and Results

19

Motohiko Kato and Naohisa Yahagi

19.1 Introduction

Before ESD was developed, EMR with a snare was the only available method for local resection of superficial neoplasia. However, this method was limited to relatively small lesions and lesions without fibrosis in the submucosa. In addition, EMR for large mucosal lesions often turned to be piecemeal resection, which makes histological assessment difficult and sometimes inaccurate. The development of ESD has allowed us to treat patients despite these limitations of indications. On the other hand, it is technically challenging and has a higher risk of adverse events. This chapter describes the indications, details of ESD procedure including management of complications, and its clinical outcomes.

19.2 Indications of ESD for Gastrointestinal Tract Neoplasms

Unlike EMR, indications of ESD are not limited by size or location. On the other hand, ESD is just a local treatment, and it is indicated for only lesions without lymph node metastasis. Previous reports with that reviewed numerous cases revealed that certain pathological criteria predict a low risk of metastasis in each organ. Among these criteria, invasion depth is one of the most important predictors of lymph node metastasis. Generally, tumors restricted to the mucosal layer or slight invasion into the submucosal layer are candidates for ESD. It should be noted that the concrete depth of "slight invasion" differs according to the organ. Invasion depth should be estimated prior to treatment. In addition to morphological findings by conventional white-light imaging, endoscopic ultrasonography is used to diagnose invasion depth. In addition, image-enhanced endoscopy (IEE)-magnified endoscopy (ME) has been shown to be useful in the esophagus and colon.

19.2.1 Indications of ESD for Esophageal Neoplasms

Japanese, European, and American societies have published practice guidelines on indications for ESD in the esophagus. The Japan Gastroenterological Endoscopy Society (JGES) guidelines do not specify whether to choose EMR or ESD for squamous cell carcinoma (SCC), but for adenocarcinoma, ESD is strongly recommended due to the high en bloc resection rate. On the other hand, ESD is limited to cases

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larger than 15 mm with poor lifting in European Society of Gastrointestinal Endoscopy (ESGE) and American Gastroenterological Association (AGA) guidelines because the superiority of ESD over EMR has not been shown. Moreover, the occupied circumference is also an important factor among the indications, since post-ESD stricture can become a serious issue after wide-field resection. The JGES guidelines do not indicate ESD in cases with whole-circumferential lesions more than 50 mm in size or lesions with suspected invasion of muscularis mucosae. Similarly, the AGA guidelines limit absolute indications for ESD to lesions that are less than 2/3 circumferential (Table 19.1).

19.2.2 Indications of ESD for Gastric Neoplasms

Indications of ESD for early-stage gastric cancer are based on the criteria proposed by Gotoda and Hirasawa [4, 5] (Table 19.2). These criteria were constructed by narrowing the population at very low risk of lymph node metastasis through the analysis of thousands of surgically resected cases and have also been accepted in the United States and Europe. These criteria are based on disease-specific 5-year survival rates of 99% and 97% for T1a(M)N0M0 and T1b(SM)N0M0 patients who underwent radical gastrectomy, respectively, and are quite strict, as the upper limit of the statistical confidence interval of estimated lymph node metastasis is 1–3%. Therefore, there may be room for stratification of the risk of death from other diseases, such as in the elderly, to determine a treatment plan based on the individual risk of lymph node metastasis [6].

19.2.3 Indications of ESD for Colorectal Neoplasms

According to the JGES guidelines for colorectal ESD/EMR, early colorectal cancers (carcinoma in situ (Tis)/T1) except lesions with clinically suspected T1b cancer (submucosal invasion depth ≥1000 μm) are good candidates for endoscopic treatment. Whether EMR or ESD is recommended is based on the necessity and

Table 19.1 Descriptions of indications of ESD for esophageal neoplasms according to guidelines [1–3]

Guideline	Squamous cell carcinoma	Adenocarcinoma
JGES (2020) [1]	*Clinical T1a-EP/LPM* Noncircumferential Circumferential ≤5 cm *Clinical T1a-MM/T1b-SM1 (<200 μm)* Noncircumferential	T1a (m1–m3)
AGA (2019) [2]	HGD to moderately (G1 or G2) Paris 0–II lesions *Absolute indication:* m1–2 less than 2/3 *Expanded indication:* m3 or sm <200 μm	HGD to moderately (G1 or G2) T1a (m1–m3) Larger than 15 mm
ESGE (2015) [3]	ESD is the first option except for tumors smaller than 10 mm, expected to be resected by EMR	Larger than 15 mm Poorly lifting At risk of SM invasion

Table 19.2 Indications of ESD for gastric neoplasms [4, 5]

	Intramucosal cancer				Submucosal cancer	
	Ulceration (−)		Ulceration (+)		SM1 (<500 μm)	SM2 (≥500 μm)
Histology	≤20 mm	>20 mm	≤30 mm	>30 mm	≤30 mm	>30 mm
Differentiated	Absolute	Absolute	Absolute	Not indicated	Absolute	Not indicated
Undifferentiated	Expanded	Not indicated	Not indicated	Not indicated	Not indicated	Not indicated

Table 19.3 Indications of colorectal ESD [7]

1. Lesions for which en bloc resection with snare EMR is difficult to perform LST-nongranular (NG), particularly LST-NG (pseudodepressed type) Lesions showing a VI-type pit pattern Carcinoma with shallow T1 (SM) invasion Large depressed-type tumors Large protruded-type lesions suspected to be carcinoma
2. Mucosal tumors with submucosal fibrosis
3. Sporadic localized tumors in conditions of chronic inflammation such as ulcerative colitis
4. Local residual or recurrent early carcinomas after endoscopic resection

possibility of en bloc resection based on lesion size and macroscopic findings (including the subtype of laterally spreading tumors; LSTs) (Table 19.3) [7]. Both ESGE and AGA guidelines make similar recommendations [2, 3]. There is no restriction on size in these current guidelines. However, practical indication should be made according to operator's skill level.

19.2.4 Indications of ESD for Duodenal Neoplasms

ESD of the duodenum has been reported to have many more serious complications, than ESD of other organs; therefore, it has not been widely indicated. In fact, there are no descriptions of duodenal ESD in the Japanese guidelines, and the ESGE and AGA guidelines do not recommend the routine use of duodenal ESD due to its high incidence of complications [8].

19.3 Techniques

The ESD technique consists of submucosal injection, mucosal incision, and submucosal dissection. Moreover, there are troubleshooting techniques, including to deal with intraoperative bleeding; perforation; difficult situations, such as dissection of scarred lesions; and the prevention of adverse events. These topics are discussed below.

19.3.1 Submucosal Injection

Submucosal injection is an essential step when performing a safe and secure mucosal incision and submucosal dissection. It is technically important to inject a sufficient amount of injection fluid, especially in mucosal incisions, and to create a shaped fluid cushion that facilitates the incision. Due to the abundance of blood vessels around the mucosal fascia plate, shallow mucosal incisions can cause bleeding. On the other hand, inadequate injection can cause perforation, especially in the thin-walled esophagus and colon. The solution should be carefully injected into the submucosal layer to avoid injection into deeper layers of the gastrointestinal wall. If the injection needle punctures too deeply, it may result in injection into the subserosal layer, and if the injection pressure is too high, it may result in injection into the muscle layer. It is important to feel the resistance of the needle during injection without inserting it too deeply. In addition, it is important to control the direction of the injection needle tip to form a uniform bulge with few indentations to control the shape of the bulge.

Regarding the type of injection solution, it is known that a high osmotic liquid such as 10% glycerin produces a better submucosal cushion than saline solution, whereas a high osmotic dextrose solution damages tissues [9]. Sodium hyaluronate has the ability to produce a good submucosal cushion; therefore, it is used for lesions with severe fibrosis. Recently, sodium alginate and thermosensitive agents have also been reported as novel injection solutions that can create long-lasting submucosal fluid cushion [10, 11].

19.3.2 Mucosal Incision

The direction of the mucosal incision depends on the type of energy device. When making an incision with a needle-type energy device, the incision should be made from the proximal side to the distal side. This is because if a mucosal incision is made from the distal side to the proximal

side, the tip of the device is gradually directed toward the muscle layer, and there is a risk of perforation. Conversely, if the incision is made with an energy device with an insulated tip, such as an insulated tip-type knife, the incision should be made from the distal side to the proximal side (Fig. 19.1).

19.3.3 Submucosal Dissection

Principally, the submucosal layer should be dissected under direct visualization. A good visual field is important to avoid intraoperative perforation or major bleeding due to inadvertent vessel damage. The hood attached on the tip of the endoscope is useful for going below the mucosal flap and stabilizing the operating field. However, it should be noted that attempting to visualize the submucosal layer with the hood very early stage in the dissection process directs the tip of endoscope toward the muscle layer and may increase the risk of perforation. For this reason, initial submucosal dissection should be performed while maintaining a tangential approach to the muscular layer until the mucosal flap becomes large enough to go below (Fig. 19.2).

After getting below the mucosal flap, it becomes possible to stabilize the operating field. by putting the hood on the target tissue. The pocket creation method is a modified submucosal dissection technique that was proposed by Miura et al. [12] in which the submucosa is dissected like a pocket without extending the mucosal incision around the lesion. Moreover, a novel technique utilizing water pressure from the water jet function of an endoscope has been recently reported. In this technique, water pressure improves the visibility of the submucosa at a very early stage of submucosal dissection [13, 14]. Traction devices are also helpful to obtain good visualization and improve the outcomes [15–17].

Another important point during submucosal dissection is to try to recognize blood vessels. The presence of a whitish or reddish cord-like structure or adipose tissue in the submucosa can indicate where blood vessels may be located. After finding the blood vessel, it is important to dissect the surrounding submucosal layer as much as possible so that the blood vessel can be isolated. If vessels in the submucosal layer are thin (smaller than those in the energy device), hemostasis is possible with the energy device using a high-frequency electric current with a usual coagulant effect (e.g., swift coagulation or forced coagulation). If the vessel is relatively large, hemostasis can be achieved using a high-

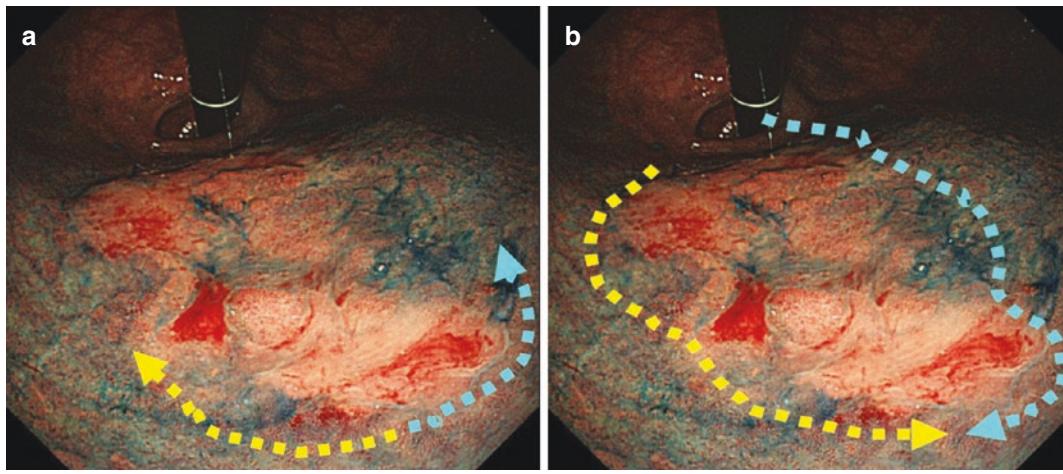

Fig. 19.1 The direction of the mucosal incision according to the type of energy device. (**a**) A mucosal incision should be made from the proximal to the distal side when using a needle-type device. (**b**) A mucosal incision should be made from the distal to the proximal side when using an insulated tip-type knife

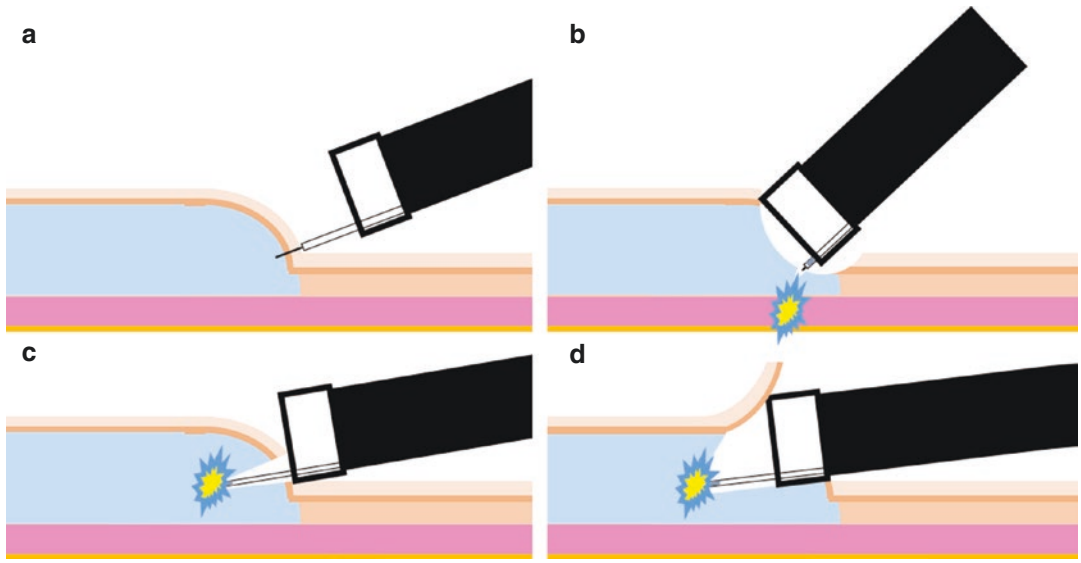

Fig. 19.2 Initial submucosal dissection using a needle-type energy device. (**a**) Submucosal dissection. (**b**) Attempting to utilize the hood very early in the dissection process can direct the tip of endoscope toward the muscle layer. (**c**) Keeping distance from the lesion to maintain a tangential approach. (**d**) Direct visualization is easier after making a large mucosal flap

frequency current with a hemostatic effect (e.g., forced coagulation with a very low setting). For larger vessels, hemostatic forceps should be used for pre-coagulate (mainly soft coagulation).

19.3.4 Troubleshooting

The most common complication during ESD procedure is bleeding. Intraoperative minor bleeding can be stopped with an energy device. For massive, spurting bleeding, hemostatic forceps are required. After the bleeding point is identified, hemostasis is achieved by applying a high-frequency current (mainly soft coagulation). A technical tip is to securely grasp the bleeding point and to pull the forceps slightly away before applying the current to avoid damage to the muscle layer. Recently, a novel IEE using long wavelengths was reported to be useful for the identification of bleeding points. This new method is expected to improve the outcomes of ESD [18].

The other common complication during the procedure is perforation. The most important thing when dealing with intraoperative perforation is to stay calm. Small perforations can be closed by clipping, but if the clip is applied too early, it will interfere with further dissection. Therefore, it is important to continue submucosal dissection to have enough space to apply endoclips. Carbon dioxide insufflation can prevent excessive pneumoperitoneum, but if it takes a long time to close the perforation, decompression of the abdominal cavity with a venous catheter may be required to prevent progression to abdominal compartment syndrome.

19.3.5 Prophylaxis for Postprocedural Adverse Events

Post-ESD adverse events include delayed bleeding, delayed perforation, and stricture. As a preventive measure for delayed bleeding after treatment, especially after gastric ESD, bleeding can be prevented by cauterizing exposed vessels in the post-ESD mucosal defect after resection with coagulation waves. On the other hand, excessive electrical current should be avoided in the colon and duodenum, which may induce delayed perforation due to the thin wall.

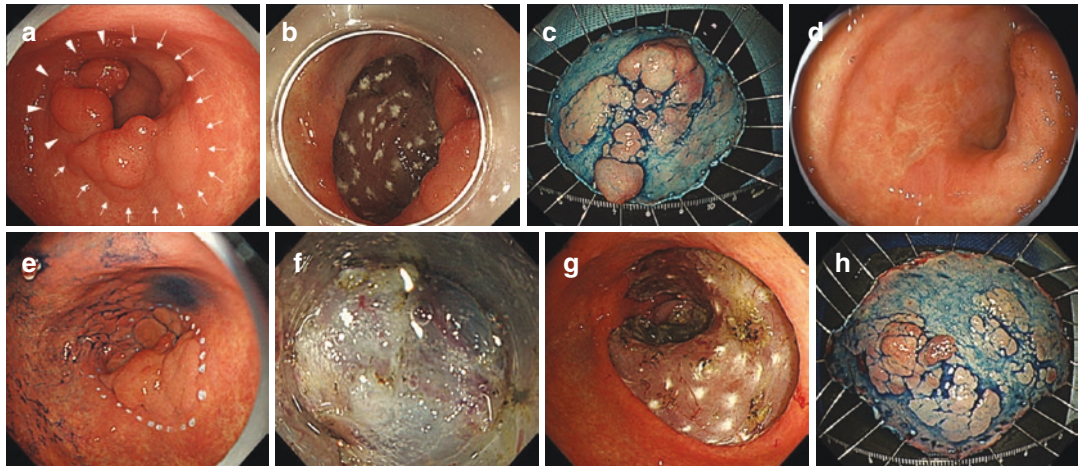

Fig. 19.3 Two-step ESD to prevent stricture for a semi-circumferential gastric lesion. (**a**) A 20 mm elevated lesion (arrowheads) and a 40 mm flat elevated lesion (arrows) were detected in the gastric antrum. (**b**) Initial ESD was performed for the lesion on the anterior wall and triamcinolone was injected to the remaining submucosa of the resection bed. (**c**) Resected specimen revealed "Tubular adenocarcinoma, Type 0-I, 20X14mm, pM, ly0, v0, pHM0, pVM0." It was judged as curative. (**d**) Scarred ulcer 4 months after initial ESD without stricture. (**e**) Second ESD was performed for the lesion on the posterior wall. (**f**) Careful dissection for severe fibrosis of initial ESD. (**g**) Lesion was completely resected without complication and triamcinolone was injected to the remaining submucosa of the resection bed. (**h**) Resected specimen revealed "Tubular adenocarcinoma, Type 0-IIa, 42×28 mm, pM, ly0, v0, pHM0, pVM0." It was judged as curative

Another means of preventing adverse events is suturing the mucosal defect after resection. Complete closure of the post-ESD mucosal defect has been shown to significantly reduce the incidence of delayed adverse events after duodenal ESD, for which the risk of adverse events is known to be extremely high [19, 20]. Similarly, it has been reported that suturing the mucosal defect significantly reduces the incidence of post-polypectomy electrocoagulation syndrome after colorectal endoscopic resection [21]. There are several methods of suturing, including simple clip-only suturing, an indwelling snare, and a clip with string [19, 22], and more recently, novel suturing devices have been reported [23, 24].

Postoperative stricture is also an issue, especially after extensive esophageal ESD. Direct injection of triamcinolone, a kind of steroid suspension, into the submucosal layer remaining at the bottom of the post-ESD mucosal defect or peroral administration of prednisone has been reported to prevent post-ESD stricture [25]. Local injection of triamcinolone is sometimes used also in the stomach when semi-circumferential or circumferential resection is performed at pylorus or cardia to prevent stricture formation (Fig. 19.3). Although the above methods are effective, there are concerns that locoregional injection may increase the risk of tissue fragility [26, 27], and systemic treatment may increase risk of infectious disease [28].

19.4 Outcomes

Previous studies reported an en bloc resection rate of more than 80% for ESD regardless of the organ. These good results have been reported in both Japan and Western countries, though the results are limited in high-volume centers in Europe and the United States [29–33]. Currently, ESD is getting popular as an organ preserving minimally invasive treatment even for large and difficult lesions (Figs. 19.3, 19.4, and 19.5). The incidence of adverse events has been decreasing annually, and recent studies showed that the incidence of adverse events in the stomach, esophagus, and colon is less than 5% [3, 31, 34].

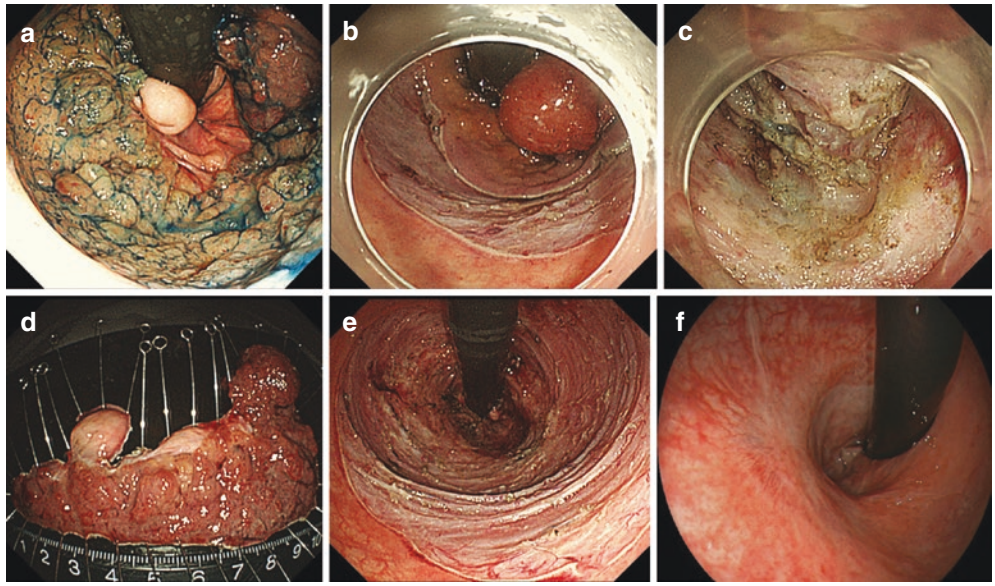

Fig. 19.4 ESD for a semicircumferential recurrent rectal lesion after trans-anal polyp resection. (**a**) A huge semicircumferential rectal recurrent lesion was detected with a few years interval after trans-anal polyp resection. (**b**) ESD was carefully conducted since this patient refused colostomy. (**c**) Extremely severe fibrosis was observed under the lesion. (**d**) The tumor was completely resected and it revealed "Well-differentiated tubular adenocarcinoma in tubulovillous adenoma, Type 0-Is+IIa, 11×6 cm, pM, ly0, v0, pHM0, pVM0." It was judged as curative. (**e**) Since resection bed was huge, betamethasone suppository was used for 2 months to avoid stricture. (**f**) Very smooth scar was observed at 6 months after ESD without stricture formation

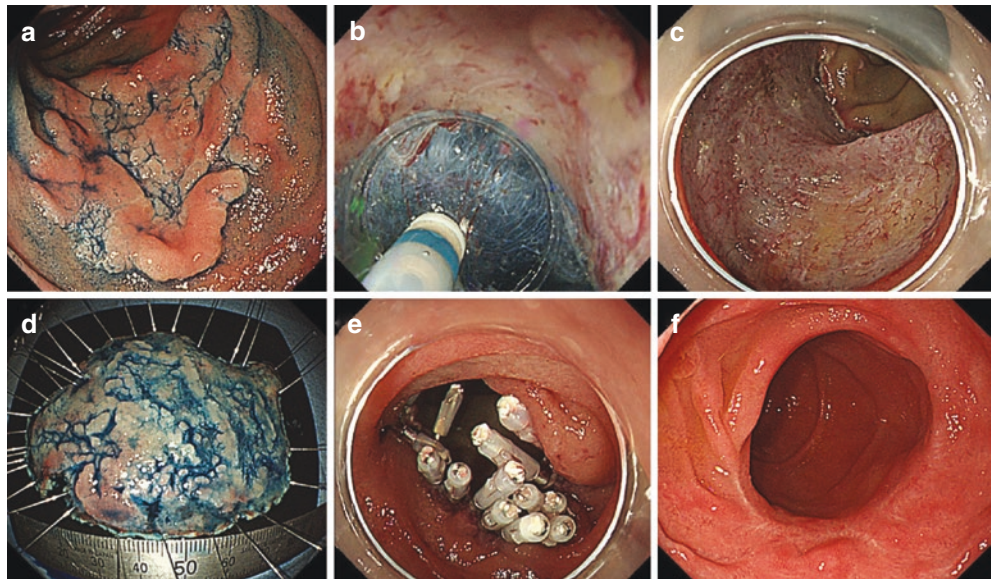

Fig. 19.5 ESD for a half circumferential duodenal lesion. (**a**) A half circumferential lesion was located at posterior wall of the second part of duodenum. (**b**) ESD was carefully conducted using "Water pressure method". (**c**) The lesion was completely resected without complication. (**d**) Curative resection was achieved since resected specimen revealed "Tubular adenocarcinoma in adenoma, 0-IIa, 57 × 42 mm, tub1>>tub2, pTis, ly0, v0, pHM0, pVM0". (**e**) Resection wound was completely closed by "String clip suturing method". (**f**) Clinical course was very smooth and there was no deformity at 6 months after ESD

Unfortunately, duodenal ESD has been reported to have a high risk of adverse events, including an intraoperative perforation rate of more than 10%, even in Japanese high-volume centers [8, 35]. However, pancreaticoduodenectomy can be avoided by ESD with complete closure of resection wound (Fig. 19.5). Therefore, duodenal ESD should be performed by highly selected expert in advanced institution. Excellent long-term results have also been reported, with few instances of local recurrence when R0 resection is obtained in a population with low lymph node involvement throughout the GI tract [3, 29, 36].

19.5 Summary

ESD achieves secure respectability and accurate pathological diagnosis due to its high rate of en bloc resection regardless of localization, size, and presence of fibrosis in the submucosal layer. As a result, ESD contributes to organ preservation and improves postoperative quality of life. Although it has a higher risk of adverse events than EMR, recent advances in endoscopic devices, ESD techniques, and methods to prevent adverse events have improved outcomes and generalized its indications.

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The "Rendezvous": Principle in Endoscopic and Surgical Procedures

20

Arielle M. Lee, Catherine Tsai, Ryan C. Broderick, and Karl-Hermann Fuchs

20.1 Introduction

One of the early publications around the "Rendezvous" principle in endoscopy and surgery was in 1987, when gastroenterologists described an internal biliary drainage with a combined transhepatic and endoscopic retrograde method [1]. An internal biliary drainage was already the treatment of choice in inoperable malignant stenosis of the hepatic ducts and common bile duct [1, 2]. If an endoscopic, internal drainage was impossible because of the high grade of obstruction in the common bile duct, the possible solution was a rendezvous maneuver. This was a combined approach from intraluminal via the papilla and by a transcutaneous and transhepatic way of assisting the intraluminal operations. In this procedure an endoscopic papillotomy (EPT) is performed by conventional endoscopic technique. In addition, a percutaneous puncture and transhepatic connection to the common bile duct is performed. A catheter is advanced through the transhepatic channel via the common bile duct (CBD) through the obstruction (e.g., a tumor) into the duodenum. Thus, a connection between the intrahepatic bile ducts above the obstruction and the distal CBD is generated, which will enable or at least facilitate via this procedure the placement of a drainage across the obstruction. The conversion of the percutaneous drainage into an internal biliary drainage was followed in many cases. Later this method was established together with radiologic assistance as PTCD (percutaneous transhepatic cholangioscopic drainage) [3].

Another form of early "Rendezvous" maneuver was developed by using laparoscopic and endoscopic techniques [4, 5]. This technique was applied in patients with gastric tumors and gastric lesions, which needed to be resected for histologic clearance [4, 5]. The experience goes back to the early days of laparoscopic partial gastric resections and the treatment of early gastric cancer. In 1997 the authors published their first experience in patients with early gastric cancer treated by a combination of laparoscopic gastric wedge resection using a "lesion lifting method" with the help of flexible endoscopy [4, 5]. For this procedure the patient is brought in general anesthesia, and a laparoscopy of the upper abdominal quadrants was started. Simultaneously a gastroscopy was performed to identify and locate the lesion in correspondence and coordination with the laparoscopic surgeon. Once the lesion was intraluminally localized by the endoscopist, the laparoscopic surgeon used either a grasper or some holding sutures to lift up the area of the tumor. Once this lesion was lifted toward the abdominal wall, a wedge resection with the linear stapler was performed, which was nicely

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facilitated by the combination of endoscopy and laparoscopic technology [5].

These two examples of endoscopic "Rendezvous" techniques stimulated further work in this field.

20.2 Technique of Combined Laparoscopic: Endoscopic Local Resections of Gastric Tumors

20.2.1 Developments of Combined Techniques

The advent of minimally invasive surgery stimulated investigations and early applications of laparoscopic techniques to perform limited gastric resection and excisions [4]. At the same time it became obvious that with these laparoscopic techniques a major feature of surgical manipulations in open surgery, i.e., the digital exploration and haptic feedback of the surgeon's "manual experience," was lost. This loss could only be compensated by an intensified observation and more visual information. This was provided at least partially by flexible intraluminal endoscopy, identifying and localizing the lesions.

An early experience with the "Rendezvous" principle, applied in local gastric resections, was performed by Ohgami et al. [4, 5]. They had collected between 1992 and 1997 more than 50 patients and published their experience with the "lesion lifting method" (Fig. 20.1) [5]. The latter combined laparoscopic-endoscopic rendezvous procedure for early gastric cancer has been quite popular during these days, which was before the widespread use of endoscopic submucosa dissection [4–6].

Several modifications of this basic combined laparoscopic and endoscopic rendezvous technique were introduced in the following years in clinical practice [5–10]. The advantage of this full-thickness resection of the gastric wall in early gastric cancers and gastrointestinal stroma tumors (GIST) was the possibility of a full histologic evaluation of a radical resected tumor.

This combined laparoscopic technique is performed under general anesthesia. The patient is placed in a beach chair position with spread legs, so the surgeon can stand between the legs. Several trocars are used to explore the upper two quadrants of the abdomen. One option of the procedure is the laparoscopic wedge resection, which is based on the early "lesion lifting method" (Fig. 20.1) [6, 7]. Endoscopy explores the intraluminal environment of the stomach and identifies the tumor and its location. Then in close correspondence and coordination with the laparoscopic surgeon, the lesion is lifted either by a laparoscopic grasper or by several holding stitches (Fig. 20.1). It is important to perform these holding stitches with sufficient margins around the lesion for radical excision. Then the lesion may be resected with a full-thickness resection or wedge resection using a linear stapling device.

If the lesion is in an unfavorable position, where an easy approach for resection with a linear stapler is not possible, another option is a tumor resection via a gastrotomy and intragastric removal of the tumor (laparoscopic intragastric resection) (Fig. 20.2) [7]. Afterward closure of the gastrotomy must be done by laparoscopic means.

Laparoscopic intragastric resection may be favored based on the similar rendezvous principle [7, 8]. This is especially helpful in lesions of the posterior wall of the stomach. Again, the lesions are identified and localized endoscopically. The lesion can be lifted by flexible endoscopic assistance or by laparoscopic assistance via a gastrostomy. Then a linear stapler can be inserted via a trocar and advanced via the minigastrostomy for a tangential application of stapler to resect the lesion. The endoscopist together with the laparoscopic surgeons has to coordinate and direct the movements of the stapling device in the correct position around the lesion in order to perform a radical resection. These different dissection procedures may be facilitated by submucosal fluid injection similar to the endoscopic way of submucosal dissection to lift the lesion and facilitate the resection.

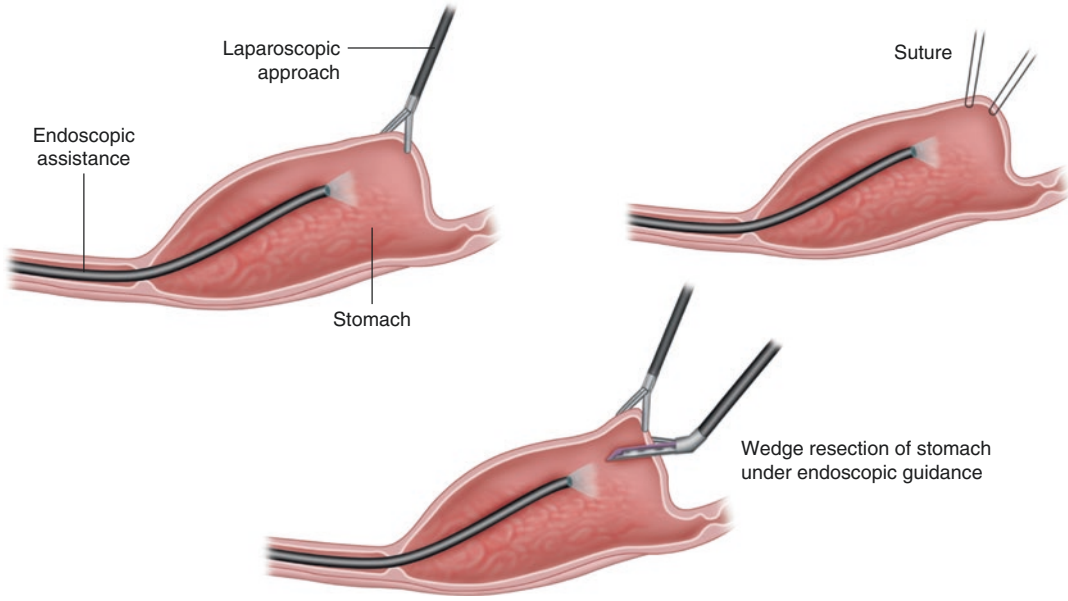

Fig. 20.1 Concept of "Rendezvous" between laparoscopic and endoscopic access to the stomach to resect a lesion by endoscopic assistance. Endoscopic assistance facilitates technically the laparoscopic application of a wedge resection by endoscopically identifying the lesion and maneuvering the laparoscopic instruments precisely under flexible endoscopic guidance

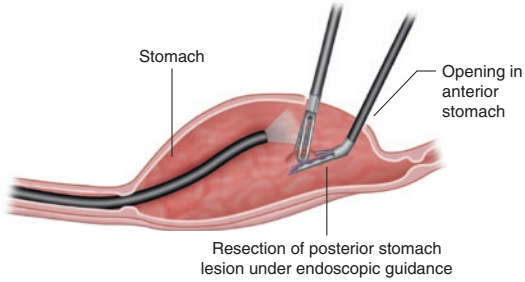

Fig. 20.2 Concept of "Rendezvous" between laparoscopic and endoscopic access to the gut to resect a lesion by endoscopic assistance. A lesion at the posterior wall of the stomach is identified and localized by endoscopy. The posterior location may require an opening of the stomach at the anterior wall to move the laparoscopic instruments toward the lesion. The endoscopic assistance facilitates the laparoscopic application of a wedge resection by a more focused maneuvering of the resection tools

20.2.2 Bands Lifting Laparoscopic Resection

These combined laparoscopic and endoscopic techniques were further modified in the upcoming years. In this specific technique a 9-French rubber band was used to loop around the basis of a tumor, which had been previously identified and localized by flexible endoscopy [9]. This technique is usually used for GIST resections. There are no comparative studies to the lesion lifting techniques available.

20.2.3 Non-touch Lesion Lifting Method

For GIST a wedge resection of the stomach is the ideal method from the oncologic standpoint. However, this is not always possible, because the lesions may be located at the posterior wall and a wedge resection in this area may be sometimes not possible. In this special technique of the non-touch lesion lifting method, the patient is placed again in a Trendelenburg position, and a laparoscopic setup for the upper abdominal quadrants is established [10]. The gastric lesion is identified and localized by flexible endoscopy. After coordination with the laparoscopic surgeon, traction sutures are placed at the stomach wall near the

tumor to pull this part of the stomach out of the abdominal wall. Then the perigastric vessels and tissue can be dissected. The traction sutures are also used by these authors for lesions at the posterior wall of the stomach. Care must be taken to preserve the basic shape of the stomach in these procedures to prevent for later either mechanical or functional obstruction of the pathway of food.

20.2.4 Double Endoscopic Intraluminal Resection

In some cases, endoscopic mucosal resection may be limited in its indications by the size of the gastric lesion [11]. The double endoscopic intraluminal operation (DEILO) to remove a gastric tumor was performed in deep sedation [11]. Two endoscopes are used; one endoscope has a 9 mm outer diameter, and the second endoscope has a 6.6 mm outer diameter. The authors have used an overtube to pass the pharynx [11]. First, the larger endoscope is advanced into the stomach to identify and localize the lesion. Endoscopic ultrasound may be used prior to the actual resection to gain more information about the tumor characteristics. Initially a needle forceps is inserted into the submucosa under the lesion to inject epinephrine and saline solution for hemostasis and lifting.

Now the second endoscope is advanced into the upper GI tract and is used for elevation of the lesion with a forceps. Then the mucosal resection is started by dissecting the mucosal margin with a newly developed monopolar shares, brought in via the first endoscope (Fig. 20.3). This scissor is able to cut any mucosa and simultaneously coagulate bleeding vessels. The important points of this double endoscopic intraluminal operation are the grasping and pulling up of the tissue by the forceps of the smaller endoscope and the excising of the mucosa using electrocautery and scissors by the active operating scope. The advantage of using two endoscopes compared to a two-channel endoscope is the possibility of independent maneuvers and manipulations of the two endoscopes, when performing the resection.

Other authors have used laparoscopic intragastric resections with either intragastric trocars

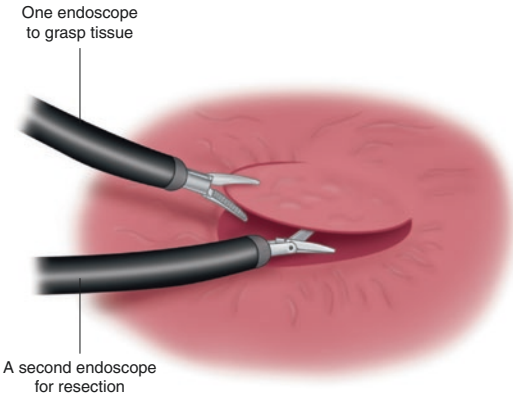

Fig. 20.3 A "Rendezvous" technique with two endoscopes in the gut. One endoscope is used to grasp the lesion and expose it with traction to enable a second endoscopist (with independent maneuverability) to cut around the lesion and perform the actual resection

using a purse-string suture at the trocar penetration site or after intra-abdominal gastrotomy to proceed with a more "open" approach [6–10]. The lesion is excised and resected by a linear stapler. The specimen should be moved into a retrieval bag and removed from the stomach either by endoscopy or by laparoscopic means, depending on the size of the tumor.

In these cases, endoscopy has to be performed not only as part of the preoperative evaluation but also as important intraoperative assistance. Since tactile feedback is limited in laparoscopy, endoscopic demonstration of the lesion and localization, simultaneously projected to the laparoscopic surgeon, together with the laparoscopic vision, is an important condition to perform such procedures. Currently, many of these limited gastric resections can be performed by endoscopic full-thickness resections (EFTR) [12, 13].

20.3 Combined Laparoscopic and Endoscopic Procedures for Lesions in the Gastrointestinal Tract

Similar to the abovementioned techniques, which were initially used in the stomach, all these procedures could be applied also in other regions of the gastrointestinal tract and colon for lesions,

which may be difficult to remove by gastroscopy or colonoscopy alone, if they are in an unfavorable position behind a fold or at a flexure [5–13]. As a consequence combined endoscopic and laparoscopic approaches have been performed and several options have been tested [12, 13]. In fact, the same principles can be applied as in the stomach with laparoscopic-assisted endoscopic resections, an endoscopic-assisted laparoscopic resection, and an endoscopic-assisted laparoscopic transluminal resection [7, 8, 12–16]. Also an endoscopic- assisted laparoscopic segmental colon resection can be combined.

In a *laparoscopic-assisted endoscopic resection*, the major operator is the endoscopist, who performs the resection by endoscopic polypectomy or any other flexible endoscopic technique. The role of the laparoscopist is the assistance in these circumstances to manipulate the colon wall in such a way that the endoscopic intraluminal maneuvers can be facilitated (Fig. 20.4). This may be especially of advantage in lesions, which are positioned behind folds or in colonic flexures, where a local stretching or a local lifting of the colon wall by an external laparoscopic grasper at the lesion may help. The push of the lesion by an extraluminal grasper into the endoscopic snare may be the only missing part in an otherwise routine endoscopic resection.

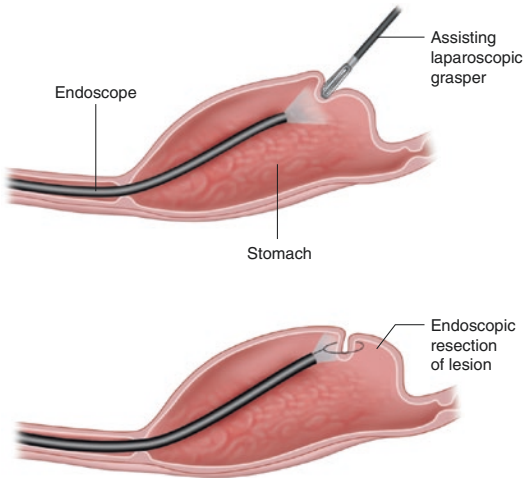

Fig. 20.4 A laparoscopy-assisting endoscopic resection of a lesion in the gut, which may be difficult to reach by endoscopic means alone. An assisting, laparoscopic grasper will enable an easy application of an endoscopic radical resection of the lesion

In *endoscopy-assisted laparoscopic resections*, the exact endoscopic localization of the lesion is the important role for the endoscopist, while the laparoscopic surgeon is performing the actual resection of the lesion, which is similar to the description the removal a gastric lesion (see also Fig. 20.1). In addition, the endoscope may be advanced beyond the segment of the lesion to ensure a free lumen, while the lesion is resected by laparoscopic tangential application of a linear stapler. In addition the endoscopic role may also be a push of the endoscope or an instrument through the working channel of the endoscope, which may facilitate the tangential resection of a colon lesion with a laparoscopic linear stapler.

The *endoscopy-assisted transluminal resection* is a helpful technique for lesions, which are located in unfavorable positions and often near the mesentery of the gut. Initially the lesion is precisely located and identified by endoscopy during colonoscopy. If the lesion cannot be removed endoscopically, because the mesentery is in the surrounding area and the lesion cannot be caught in an endoscopic snare, the resection must be performed by a linear stapler from outside the lumen by laparoscopic means. The latter requires a colostomy and intraluminal approach with a linear stapler as well as a laparoscopic closure of the colon later (concept, see Fig. 20.2).

Today these different procedures are not used very often, because endoscopic full-thickness resection (EFTR) and endoscopic submucosal dissection (ESD) can be applied in most of these cases as endoscopic alternative [12, 13, 16].

The *endoscopic-assisted segmental resection of the colon* is basically a regular laparoscopic resection of a colon segment under endoscopic guidance regarding the identification and localization of the tumor. Since haptic exploration of the colon by laparoscopy is very difficult, this technical concept is used very frequently in clinical routine in small tumors that cannot be removed by ESD or EFTR. Nevertheless, currently many of these limited tumors that do not need a complete oncologic lymphadenectomy are

treated today by therapeutic endoscopy such as EMR, ESD, and EFTR [12–16].

20.4 The "Rendezvous" Principle in Biliary Surgery

An early version of a rendezvous maneuver in biliary obstruction was the combination of an external, transhepatic drainage and an endoscopic assistance [1–3]. If an internal passage of a high grade of obstruction in the common bile duct was impossible, the possible solution was a rendezvous between an intraluminal, endoscopic transpapillary approach via the papilla and a percutaneous and transhepatic way of assisting the intraluminal operations such as a PTCD (Fig. 20.5).

In the late 1990s another endoscopic and surgical "Rendezvous" procedure was developed and published regarding biliary surgery [2, 3, 17]. In many centers the routine clinical practice in patients with CBD stones consisted of a preoperative endoscopy, ERCP, and papillotomy (EPT) to remove the stones and subsequently a laparoscopic cholecystectomy [3, 17, 18]. This concept of "therapeutic splitting" was favored in many hospitals. If endoscopic sphincterotomy and stone retrieval failed in patients with CBD stones and this happened after laparoscopic cholecystectomy, these cases had to be reoperated to clear the common bile duct. This could be a quite serious procedure with risk for complications.

Based on the combination of laparoscopic and endoscopic technology, the "Rendezvous" principle can be applied in using flexible endoscopy during a standard laparoscopic cholecystectomy [17, 18]. Once the gallbladder and the anatomy is dissected, an endoscopic sphincterotomy is performed by the endoscopist. Then a Dormia basket is passed through the cystic duct into the duodenum to clear the stones in the common bile duct (Fig. 20.6). This combined laparoscopic-endoscopic procedure was established in those units, where preoperative therapeutic splitting was not commonly used or had not been successful.

Based on the clinical experience in many countries, the management of cholelithiasis and especially CBD stones has been focused in most countries on therapeutic splitting, i.e., first endoscopic management of the CBD stones, followed by laparoscopic cholecystectomy [18]. Surgery for CBD stones remains a medical problem for the patient with a certain risk of increased morbidity and even mortality. Many solutions have been applied in different institutions in the past 30 years depending on the local expertise. One of

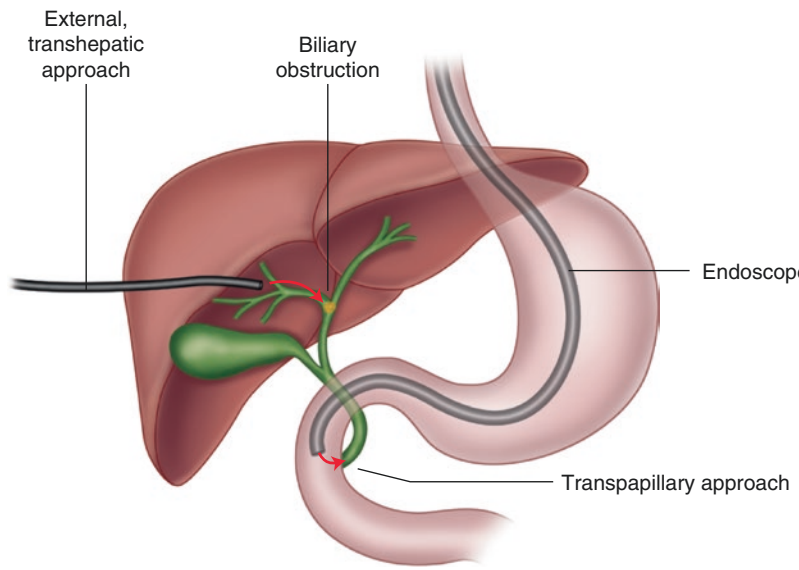

Fig. 20.5 Early concept of "Rendezvous" in the biliary tree between the external, transhepatic, and the transpapillary approach to biliary obstruction

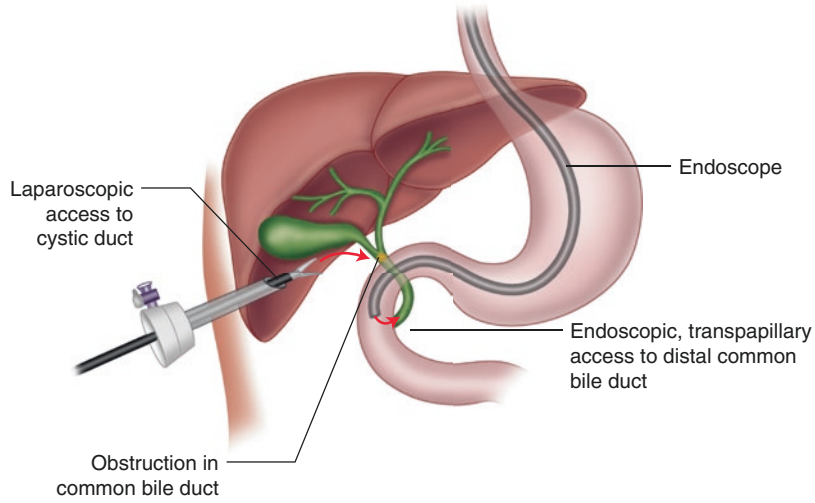

Fig. 20.6 Concept of "Rendezvous" for an obstruction in the common bile duct (CBD), using a laparoscopic access to the cystic duct and an endoscopic, transpapillary access to the distal CBD. From both sides maneuvers can be performed to pass the obstruction and solve the problem. This can be an incarcerated stone in the CBD, which needs removal either toward the duodenum by combined force from above and below

the most popular concepts in Europe is the "therapeutic splitting" as mentioned above.

One option is the laparoscopic cholecystectomy and added laparoscopic common bile duct exploration and clearance of the stones in one procedure. The latter requires a surgical opening of the common bile duct to remove the stones and subsequent T-drain placement with possible elevation of risks for postoperative complications.

Another option is a simultaneous laparoscopic and endoscopic "Rendezvous" technique by performing the cholecystectomy and stone retrieval in one combined procedure [18]. The latter would have the advantage of only one hospital stay for the patient, only one episode of general anesthesia, and one episode of post-therapeutic pain management. The intraoperative combination of laparoscopic and endoscopic rendezvous concept requires certain logistics of an endoscopic and surgical cooperation, which is not possible in every institution. In an early randomized trial regarding this question, these options were compared [18]. In addition, preoperative diagnosis of CBD stones may be improved in the last years by magnetic resonance imaging (MRI). The technical and logistic problems of the rendezvous concept must be discussed, since on one hand this requires specialists in both fields and the supine position of the patient during surgery as well as the intraluminal gas insufflation as needed for endoscopy may interfere with the quality of laparoscopy. A solution for the latter is the early laparoscopic dissection of the gallbladder and the common bile duct under good vision, before the endoscopy requires insufflation of gas into the upper GI tract. Intraoperatively the surgeon can assist the endoscopist by facilitating the cannulation of the papilla. The surgeon uses the cystic duct to advance a guidewire through the duct into the duodenum, which can be used nicely by the endoscopist to enter the CBD with their instruments to remove the stones. This early study showed that the laparoscopic and endoscopic rendezvous concept was associated with a higher success rate, a shorter hospital stay, and less costs compared to the stepwise "therapeutic splitting" technique with preoperative ERCP and sphincterotomy and followed by separate laparoscopic cholecystectomy [18].

In a recent meta-analysis for the Cochrane database, all available studies were evaluated [19]. Five randomized trials could be identified for further assessment. As expected, the laparoscopic and endoscopic combined procedure

required a longer operative time, but may reduce the length of hospital stay, when compared to therapeutic splitting. However, the quality of the evidence was rather low. Subsequently the conclusion was that the pros and cons for one or the other option depend very much on the local circumstances in the hospitals and the individual quality of the available team to apply one or the other therapy to the patients.

20.5 The Rendezvous Principal for the Treatment of Obstruction and Endoscopic Recanalization

In the 1980s esophageal obstruction by malignomas has been treated by combined endoscopic rendezvous procedures, using endoscopic approaches from above and from below the obstruction [20, 21]. In these individual malignoma cases, endoscopic recanalization could not be achieved by the usual assistance of radiographic support to follow guidewires or by laser tumor vaporization. Often endoscopic maneuvers from above the tumor were too frustrating to continue or the fear for perforations was too big to continue. In these cases, a small mini-laparotomy was performed and the stomach was pulled up to the abdominal wall and outside. Then via a small gastrotomy, a second endoscope was advanced from distally to the cardia and further up into the esophagus toward the obstruction. Now, from the proximal endoscope, a guidewire or any passing instrument could be more easily identified in the obstruction by the distal endoscope and a guidewire could be passed through the stenosis (Fig. 20.7). By combining these two techniques and advancing catheters through the obstruction and being able to withdraw these two performances, then a dilation of the obstruction made a recanalization quite successful. This rendezvous concept was also performed for benign strictures [21, 22].

Recently, these techniques have been reactivated [23]. The combined peroral and retrograde endoscopic rendezvous for recanalization of esophageal obstructions should be an individual approach in patients, in whom this situation cannot be solved differently. The main aim among these patients is to regain the possibility for swallowing liquids and especially avoiding a situation, in which patients are no longer able to swallow their saliva, since this is some of the worst impacts in their quality of life. The endoscopic tools to open up the stenosis can be any

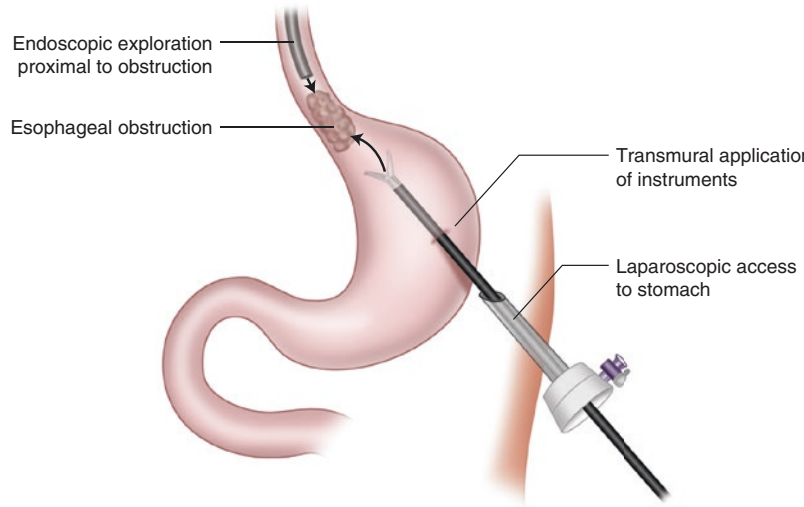

Fig. 20.7 Concept of "Rendezvous" applied to an esophageal obstruction by using an endoscopic exploration in the proximal esophagus and a laparoscopic access to the stomach with transmural application of instruments to enable manipulation and visualization from the distal part of the obstruction

coagulation devices, TT-knife, snares, bougies, and/or large grasping forceps to remove the tumor tissue. Any LASER device that vaporizes the tissue can be helpful in performing these procedures. It can be helpful for the patient's safety to follow these maneuvers under fluoroscopic control. These are individual indications in these patients and therefore this method is performed in limited numbers. The advantage of a combined laparoscopic approach is that it can be applied via trocars.

Therefore, this principle can be used for any other obstruction in the upper gastrointestinal tract using a small bowel loop to approach the obstruction from distally. Currently the "Rendezvous" principle is also applied in management of malignant and benign biliary obstructions [24].

More distal and also anastomotic obstructions can also be approached by an endoscopic rendezvous technique [25]. A distal segment also in the colon can be reached endoscopic means from above, if an ileostomy or colostomy is present. This would allow for a proximal endoscopic approach of the obstruction, combined with the second endoscopic approach transanally. Thus, the obstruction can be identified and localized. Subsequently the obstructing tissue can be passed with the guidewire from one to the other endoscopic approach quite easily. Once the guidewire is passed, a safe dilation or ablation of the tissue can be performed with less danger for perforation or penetration. More permanent therapies may follow.

Comments

The "Rendezvous" principle as a combination of laparoscopic and endoscopic techniques in the gastrointestinal tract has been used since several decades now. Quite often these approaches are individual procedures reasoned and indicated by special individual situations of a patient. Based on these ideas, one could develop more perspectives for combined concepts to facilitate or enable an individualized technical approach for a special situation. This could be a very time-consuming approach to perform an endoscopic tumor removal or any other endoscopic procedure, which may be lacking just a little support and extraluminal assistance. The latter could be easily provided by laparoscopic technology.

Also vice versa in laparoscopic surgery, for example, a multiple previously operated abdominal situation with massive adhesions, where bowel loops, gastric wall and colon can hardly be separated from each other or even recognized. In these situations, intraluminal endoscopic support by localizing and identifying loops or lesions or by supporting the definition of anatomy using local endoscopic diaphanoscopy may save time and may prevent complications such as perforations and may therefore be of advantage for the patients.

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21 Percutaneous Endoscopic Intragastric Surgery in the Treatment of Stromal Tumors at Esophagogastric Junction

Eiji Kanehira

21.1 History and Rationale

The way human race observed inside the stomach for the first time was the percutaneous route through a gastrostoma caused by a trauma, which dates back almost 200 years [1, 2] (Fig. 21.1).

In the 1990s, the percutaneous approach into the gastric lumen became actively used for surgical treatment. Atabeck et al. performed drainage operation for a pancreatic pseudocyst with surgical instruments inserted into the stomach percutaneously, which were controlled under peroral gastroscopy [3].

Kitano et al. successfully treated intractable bleeding inside the stomach, performed with a rigid endoscope and instruments inserted into the stomach via the percutaneous route [4].

Ohashi et al. performed the first tumor resection utilizing the percutaneous route and gave a name "intragastric surgery" to this procedure [5, 6]. In the same year, the author and Ogami started intragastric surgery in a similar manner [7, 8].

In the 1990s, the main indication of intragastric surgery was a wide en bloc mucosectomy in the treatment of gastric cancer in situ. But later these indications were treated by endoscopic submucosal dissection (ESD), as enthusiastic endoscopists made a rapid progress in this technique with a flexible endoscope. However, intragastric surgery is not extinct, but still performed for tumors originating from the stroma cells, which are basically resected with full thickness of the gastric wall. Although intragastric surgery is not a frequently performed operation, an important rationale is that this surgical technique can preserve the entire stomach both in the figure and function in the patient, who, otherwise, is supposed to undergo total gastrectomy or proximal gastrectomy, which significantly deteriorates the postoperative quality of life.

The author has been performing intragastric surgery for 27 years, since 1993, and reported favorable short- and long-term outcomes [9]. Moreover, we have amended the operative technique so that it would become further less invasive [10]. Herein the details of four different operative techniques of intragastric surgery are described, and its clinical results are reviewed.

21.2 Terminology

Terminology of the current surgical procedure is rather confusing. Ohashi, one of the first surgeons developing this operation, gave a name of "intragastric surgery" [5, 6]. However, the same or similar operations are called by a variety of other names. Some call it "transgastric approach" [11]. But this name is also used in another operation, which utilizes a peroral flexible endoscopy,

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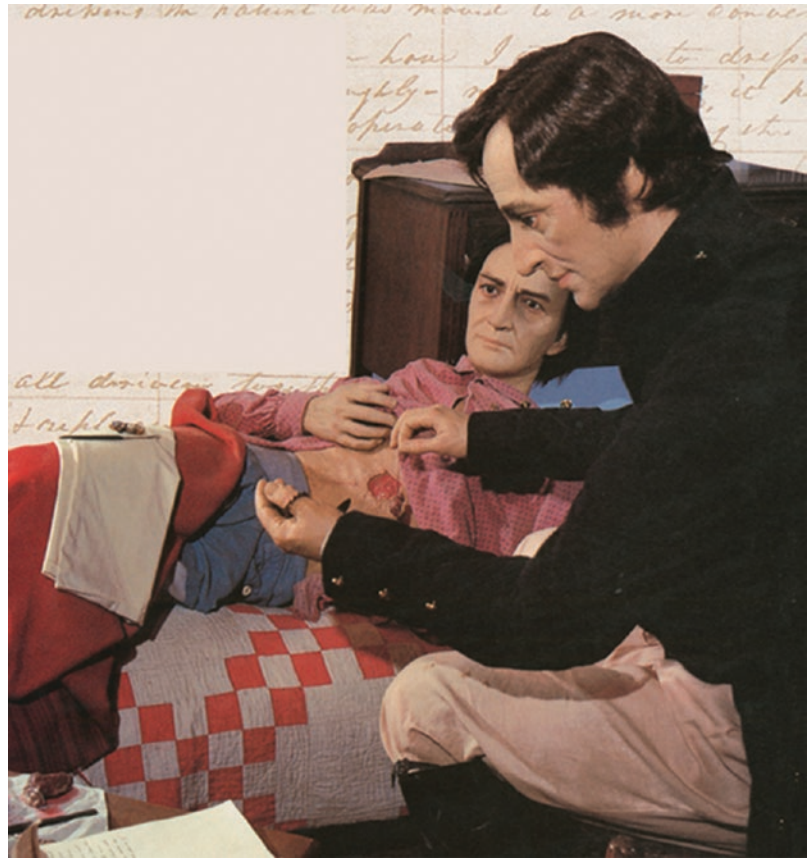

Fig. 21.1 William Beaumont's and his patient, Alexis St. Martine, with a gastrostoma caused by an accident. The first observation inside the human stomach was performed through his gastrostoma by percutaneous route

penetrating the gastric wall from inside to outside to approach to the peritoneal cavity [12, 13]. Besides, some others call the current operation "endoluminal approach" [14, 15] to mean a procedure performed in the gastric lumen with a peroral endoscope, which possibly causes confusion. Cuesta et al. gave a name of "transgastric endoluminal surgery" to avoid this confusion [16]. Laparoscopic intragastric surgery is a frequently used terminology for the current operation [17]. However, because the location, where the rigid endoscope works, is not the peritoneal cavity, but the gastric lumen, this endoscope should not be called laparoscope, but must be called "gastroscope." In this context, the convincing terminology, which accurately expresses the essence of the current operation, should be "percutaneous endoscopic intragastric surgery" [7, 18]. In this textbook the current operation is called so and abbreviated as PEIGS.

21.3 Patient Selection

Patients for PEIGS must be carefully selected. Basically, stromal tumors found in the cardia are most suited candidates. Endosonography and CT scan are mandatory to estimate the precise localization of the tumor, its growth type and nature, the layer of gastric wall it is originating from, and whether there is any metastasis.

The distance between the tumor edge and the esophagogastric junction is a crucial condition for a successful operation. When it is larger than 2 cm, the risk of perforating the gastric wall during the intragastric procedure becomes high, which results in collapse of the gastric cavity and significant deterioration of operative performance. In case the tumor is located 2 cm or more distant from EGJ, the author performs CLEAN-NET (combination of laparoscopic and endoscopic approaches for neoplasia with

non-exposure technique) [19, 20]. When it is 2 cm or closer to the EGJ, even when defect of the gastric wall becomes full thickness, the insufflation of the gastric cavity is usually well maintained and operation is not disturbed. This is probably because there is a thick fat tissue around the EGJ, which wraps up the perforated part.

The growth type of the tumor is crucial, too, in selecting patients. When the tumor is highly exophytic, the approach from inside the stomach may fail, as the gastric wall should be necessarily perforated during the tumor resection, which results in collapse of the stomach. For such highly exophytic tumors, the author performs CLEAN-NET.

The size of the tumor is an important element to decide which type of PEIGS should be chosen or whether PEIGS should not be indicated. For the classical PEIGS or needlescopic PEIGS, in which the resected specimen is retrieved through the esophago-oral route, the diameter of the tumor must be 3.5 cm or smaller. In single incision PEIGS, when the temporary gastrostoma is constructed with a wider opening, larger tumor can be extracted through it.

Each hospital must take into consideration that validation of minimally invasive surgery for large stromal tumors >5 cm is still controversial, although there have been reports with favorable outcomes [21, 22].

21.4 Operative Techniques

Operative technique of three different types of PEIGS is described. In our institute, single incision PEIGS is the standard operation today, while for beginners, "classical PEIGS" is recommended as the initial experience and single incision PEIGS may be challenged once the surgical team is well experienced. "Needlescopic PEIGS" is a very special operation, extremely minimizing the operative scars. This operation should be performed only for limited patients, who insist on almost invisible scars. Surgeons are required to be trained for precise manipulation with thin caliber instruments.

21.4.1 Single Incision PEIGS

With influence from the wave of single incision endoscopic surgery, the authors developed single incision PEIGS in 2011 (Fig. 21.2a,b). The main intention to develop this operation, however, was rather aiming at the treatment of larger tumors, which cannot be retrieved via the esophago-oral route, but can be extracted via the temporary gastrostoma of single incision PEIGS.

Setup Under general anesthesia the patient is placed supine with legs spread apart. The surgeon stands between the patient's legs, and the assistant surgeon stands on the right side of the patient to hold the laparoscope. The scrub nurse stands on the left side of the patient (Fig. 21.3).

Construction of a Temporary Gastrostomy The navel is incised 2.5 cm longitudinally for entry into the abdominal cavity. When the stomach does not reach to the navel, the incision site is amended to cephalad. Through this parietal wound, the greater curve of the gastric angle is caught and pulled to the outside so that a temporary gastrostomy is constructed (Fig. 21.4). When the tumor is large, the size of the skin incision and the gastrostoma is set larger accordingly. Through this gastrostomy, the inner ring of the x-Gate® [23] (a multichannel access port for single incision endoscopic surgery; Sumitomo Bakelite Japan; (Fig.21.5)) is inserted into the stomach and fixed. The stomach is insufflated with CO2 gas at 8 mmHg. In addition to the x-Gate®, a needle port (BJ port®, Nition Company, Chiba, Japan) is punctured to the gastric lumen at the left upper quadrant, through which a 2 mm forcep (BJ needle®, Nition Company, Chiba, Japan (Fig.21.6)) is used [10, 24].

Intragastric Procedure Through the channels of x-Gate® and the BJ port®, instruments are inserted into the gastric cavity to facilitate intragastric procedure. A 5 mm laparoscope with an oblique-view angle of 30 degrees is brought into the stomach through one of the channels in x-Gate®, by which the EGJ (esophagogastric junction) area including the target tumor is clearly visualized. The scheduled resection line is marked

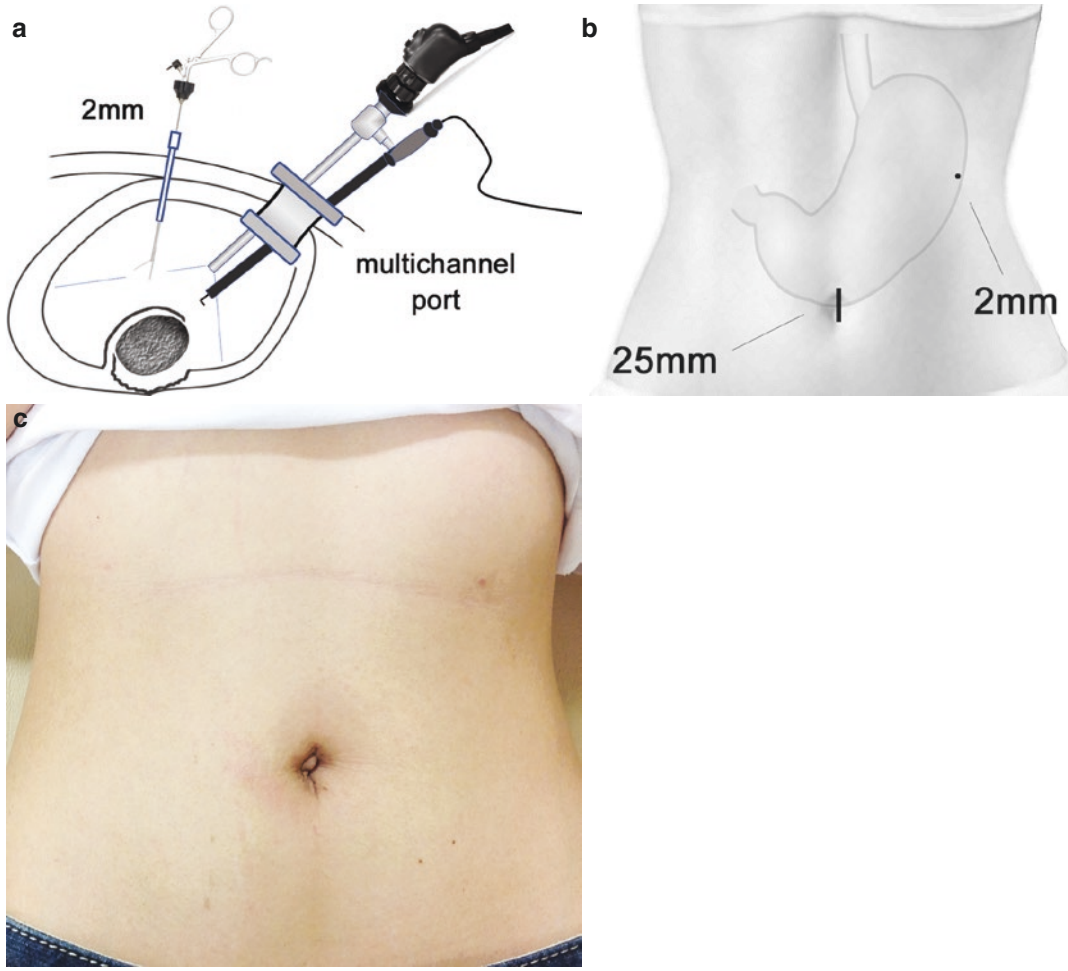

Fig. 21.2 (**a**) Schematic illustration of single incision percutaneous endoscopic intragastric surgery (single incision PEIGS). Through a temporary gastrostoma, a multichannel port is inserted into the stomach, through which a couple of instruments are used. A 2 mm needle puncture is added in the left upper quadrant to allow insertion of a 2 mm instrument. (**b**) The port sites and the location of the stomach. (**c**) The cosmetic result of the patient undergoing single incision PEIGS

by coagulation dots around the tumor (Fig. 21.7a). Saline is then injected into the submucosal layer, using an injection needle catheter (Pettit Needle®, Hakko Company, Nagano, Japan) (Fig. 21.7b). Resection is started with cutting the mucosal layer with a high-frequency hook. A grasping forceps is inserted in the other port to retract the mucosa. When the mucosa is cut enough, and the submucosa is dissected, the tumor surface (pseudocapsule) is clearly identified (Fig. 21.7c). The normal muscle bundles around the tumor are meticulously dissected with a high-frequency hook (Fig.21.7d). When resection is completed, extragastric fat is often visualized at the bottom of the defect (Fig. 21.7e). The defect on the gastric wall is closed by an interrupted suture with 3/0 absorbable monofilament thread (Fig. 21.7g). The resected specimen is entrapped in a plastic retrieval bag and brought out through the x-Gate®. Figure 21.7k,l,m show an example of a large tumor at the EGJ, measuring 55 mm in diameter, which can be treated by single incision PEIGS.

Repair of the Gastrostomy The x-Gate® is removed and the gastrostomy is closed by suturing extracorporeally. The tiny puncture wound in the upper gastric body made by the BJ port® is left untreated (Fig. 21.7n).

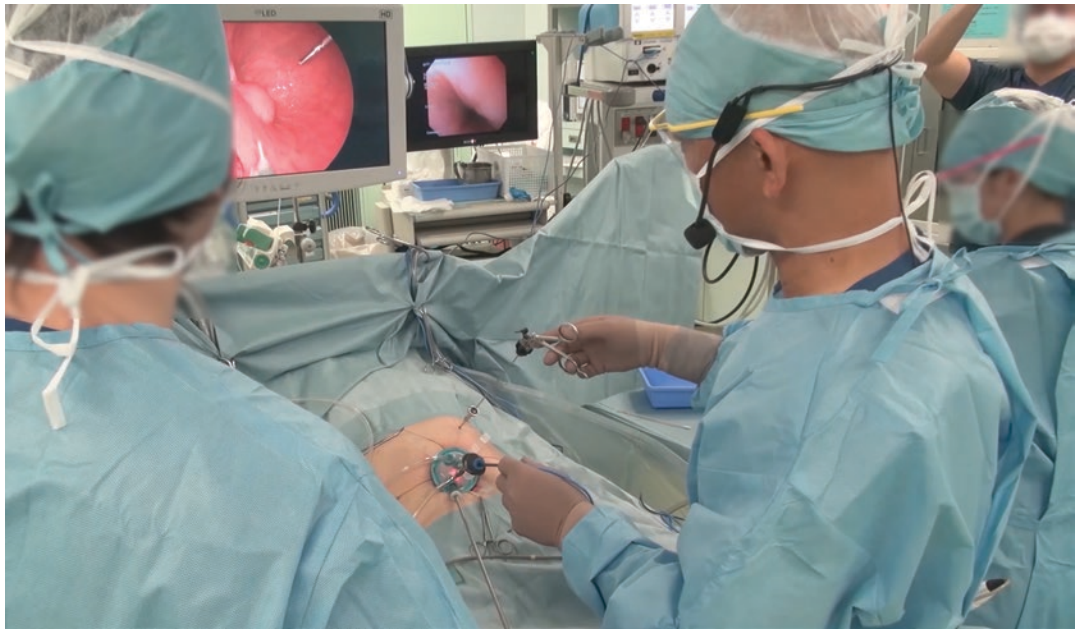

Fig. 21.3 Standing place of each surgeon and the scrub nurse. The operator stands between the patient's legs, and the assistant surgeon stands on the right side of the patient to hold the laparoscope. The scrub nurse stands on the left side of the patient (Fig. 21.3)

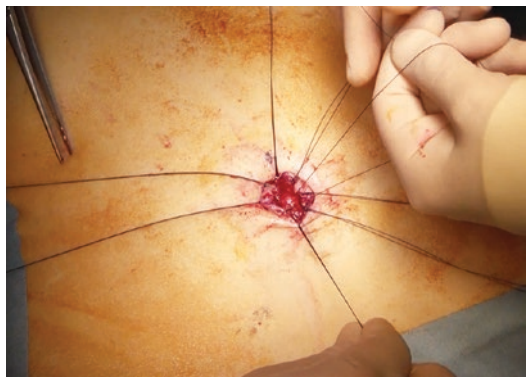

Fig. 21.4 Construction of the temporary gastrostoma. When the stomach reaches down the navel, the navel is incised 2.5 cm longitudinally. When the stomach doesn't reach the navel, the incision site is amended to cephalad

21.4.2 Classical PEIGS

Classical PEIGS is basically the same procedure with the one, which has been performed since 1993 [7] (Fig. 21.8a, b).

Setup The same manner as described in *Operative technique I.*

Access Route Peroral endoscopy is performed and the stomach is insufflated. When the stomach is inflated and it reaches the navel, the navel is incised 2 cm longitudinally and the peritoneal cavity is entered. When the stomach does not reach the navel, the skin incision must be made accordingly in the cephalic direction. A 12 mm port is inserted through the first incision and the peritoneal cavity is insufflated with 10 mmHg CO2 gas. After confirming that there is not any significant adhesion around the stomach, the pneumoperitoneum is suspended, and the first port is removed. Then peroral gastroscopy is performed to inflate the stomach until the greater curvature side of the anterior wall of the lower gastric body is identified and touched via the parietal wound in the first incision. Under the control of gastroscopy, the anterior wall of the lower gastric body is percutaneously sutured to the abdominal wall on each lateral side to the navel area. To facilitate this, we use Funada's gastropexy device (Fig. 21.9) (Create Medic Co., Ltd., Kanagawa, Japan) [25]. A 12 mm expandable port (Step® trocar, Covidien, USA) is inserted via the parietal wound in the first incision and further into the

Fig. 21.5 x-Gate®, a multichannel access port for single incision endoscopic surgery, used in single incision PEIGS

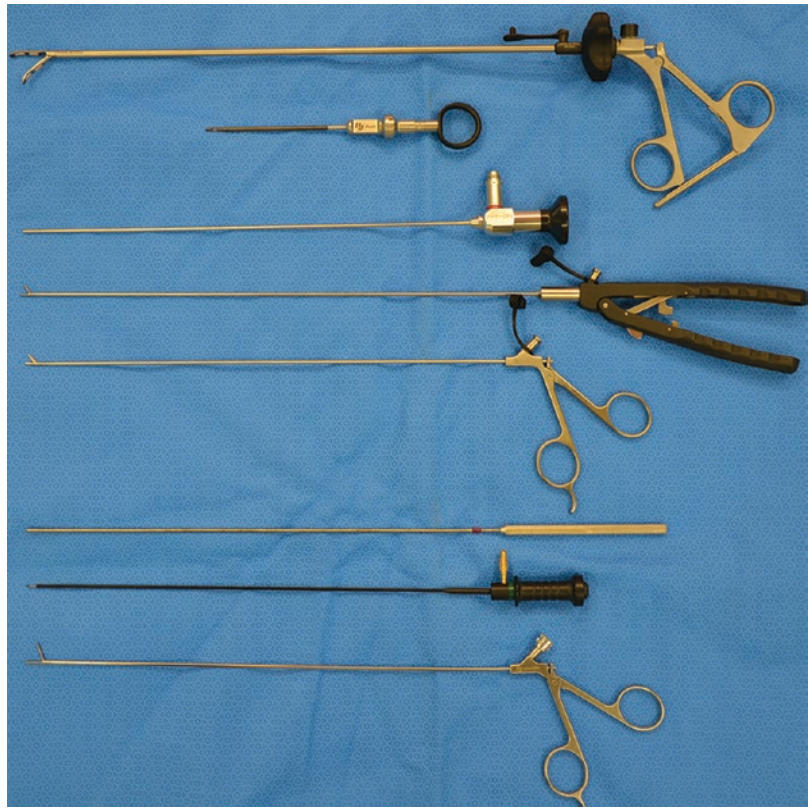

Fig. 21.6 Lineups of BJ needle® for needlescopic surgery. The shaft diameter of all BJ needle series is only 2 mm. The lineup includes port, grasper, hook-shaped electrocautery, scissors, needle driver, and so on

gastric lumen. In addition, two 5 mm expandable ports are inserted percutaneously into the gastric lumen in the same manner. The gastric lumen is inflated with CO2 gas at 8–10 mmHg (Fig.21.10).

Intragastric Procedure Resection of the tumor and the closure of the defect by hand-sewn suturing are performed by the same manner as described in technique of single incision PEIGS.

Extragastric Procedure When the intragastric procedure is completed, all three intragastric ports are withdrawn from the gastric wall but remained in the peritoneal cavity. The three stab wounds on the anterior gastric wall are closed by hand-sewing.

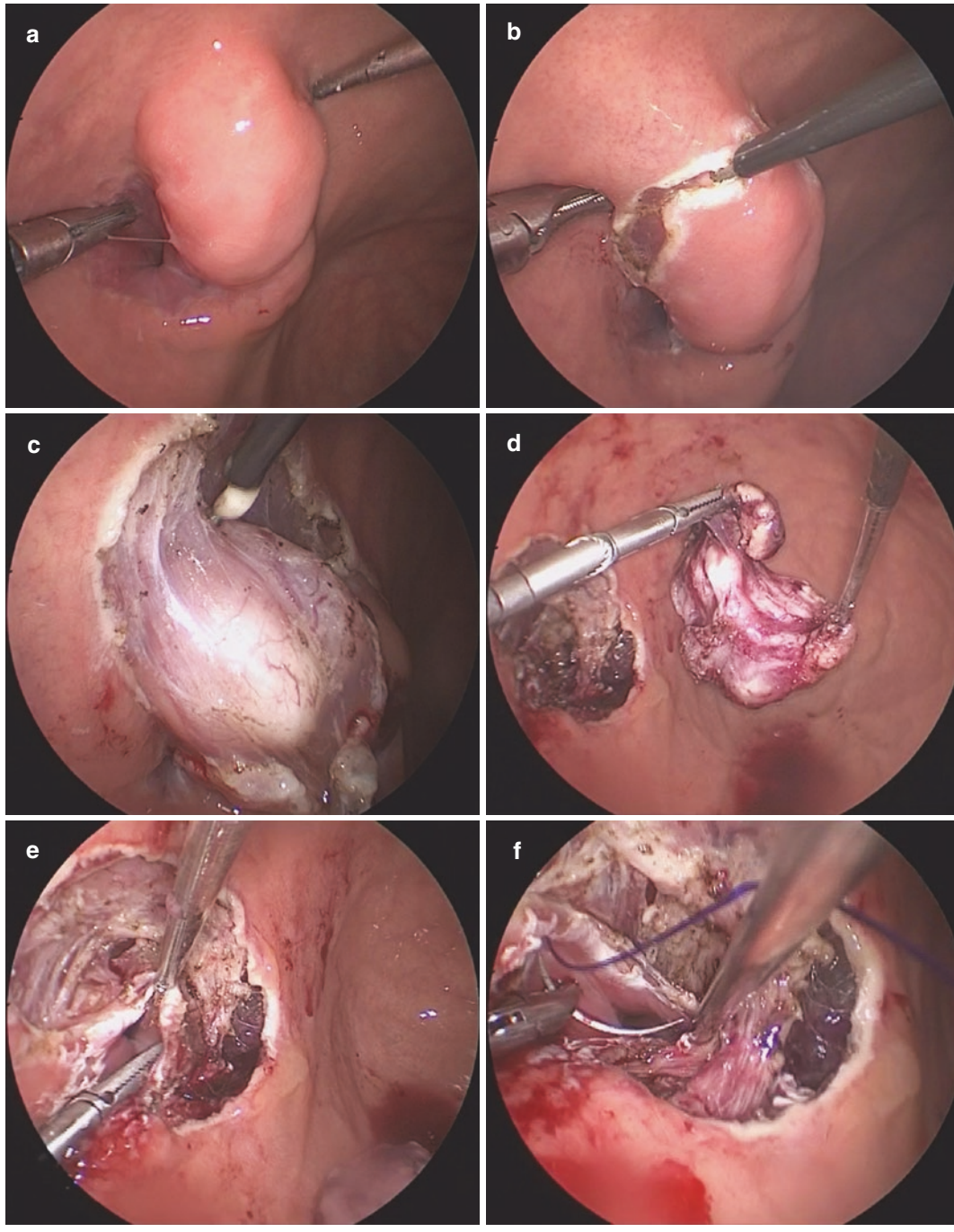

Fig. 21.7 Operative procedures of single incision PEIGS by endoscopic pictures. (**a**) A submucosal tumor located at the esophagogastric junction (EGJ) is clearly visualized by a 5 mm rigid endoscope inserted through x-Gate®. (**b**) Resection is started with cutting the mucosal layer with a high-frequency hook. (**c**) By meticulous dissection of the submucosal layer, the surface of the tumor is identified. (**d**) The tumor excision is completed. (**e**) The defect at EGJ is about 60% circumferential round the exit of the esophagus. (**f**) Hand-sewn suturing to reconstruct the EGJ. It is important to avoid stenosis by performing interrupted suture at the radial direction and approximating both muscle layers of the esophagus and stomach. (**g**) The closure of the defect is completed. EGJ is well reconstructed in shape. (**h**) By inserting the flexible endoscope into the stomach, non-stenotic EGJ is confirmed. (**i**) Another case with a larger tumor at EGJ, measuring 60 mm in diameter. (**j**, **k**) By experienced hands, this type of large tumor can be treated by single incision PEIGS. (**l**) The temporary gastrostoma is closed by suturing extracorporeally to finish the operation

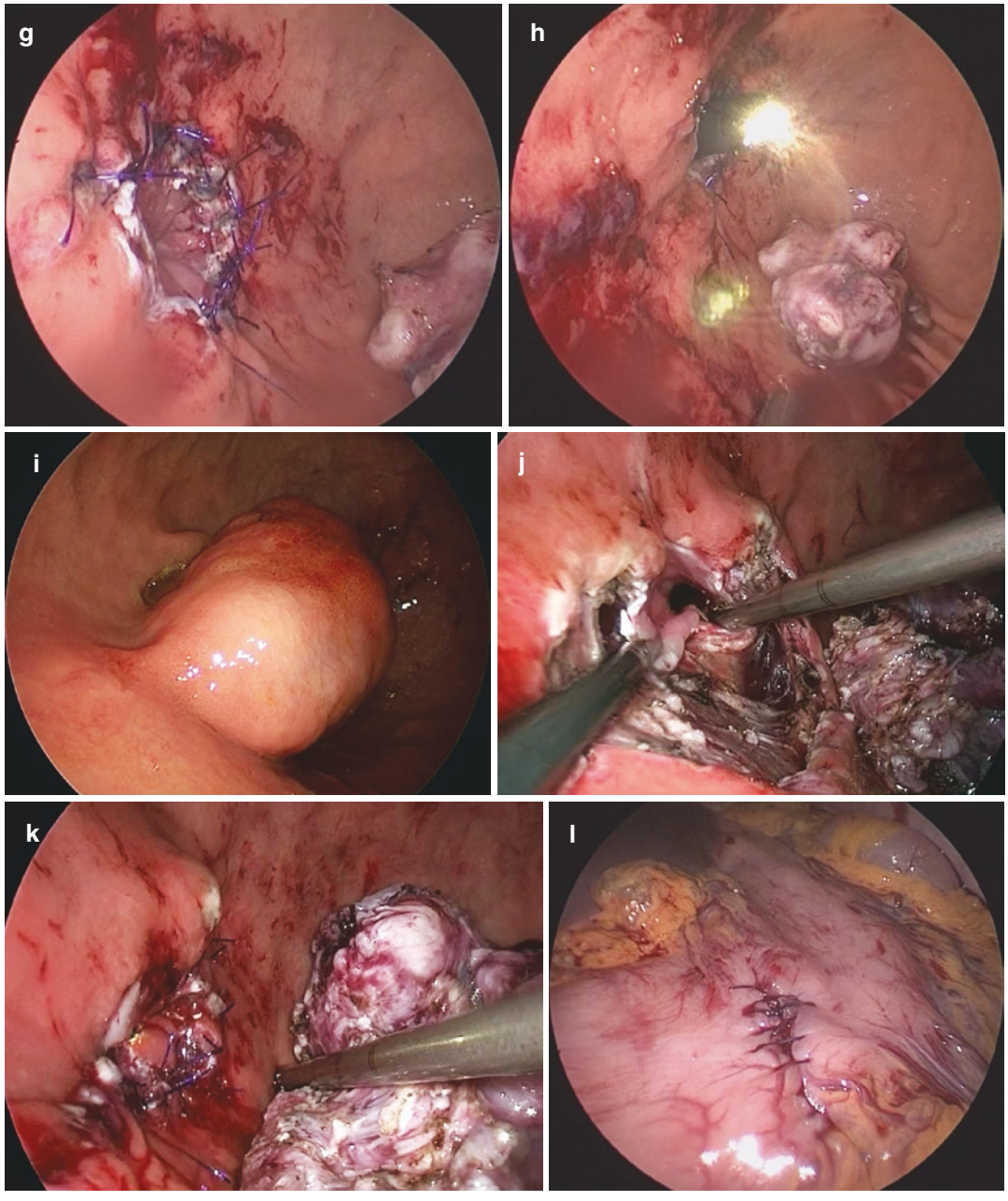

Fig. 21.7 (continued)

21.4.3 Needlescopic PEIGS

As a challenge of further minimizing the operative scars in PEIGS, we started needlescopic PEIGS in 2015, which utilizes only one 5 mm port and two 2 mm ports (Fig. 21.11a, b) [10].

Setup The same manner as described in *Classical PEIGS*.

Access Route Peroral endoscopy is performed and the stomach is insufflated. When the stomach reaches the navel, the navel is used for the puncture of the first trocar. When the stomach does not reach the navel, the lowest point of the midline epigastrium, where the stomach reaches, is used for the first trocar. Prior to the insertion of the first trocar, the abdominal wall and the gastric wall are

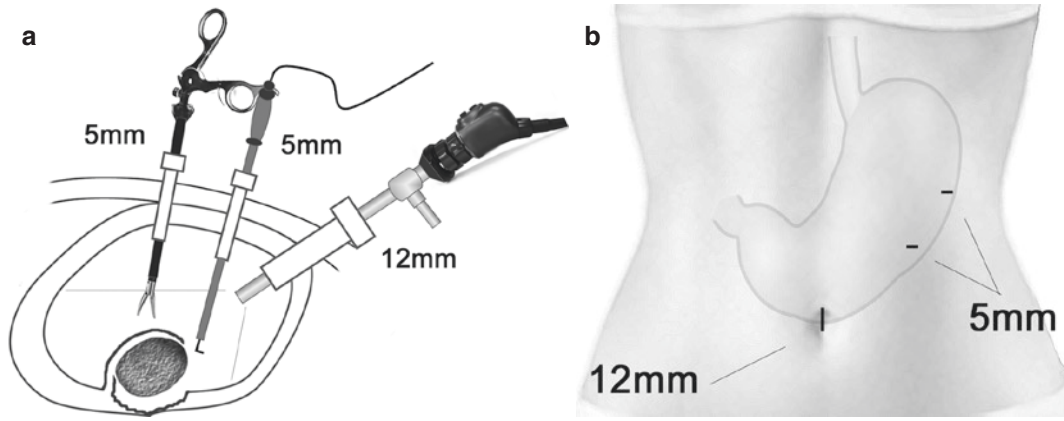

Fig. 21.8 (**a**) Schematic illustration of classical PEIGS. Three intragastric ports are fixed, penetrating both the abdominal wall and the anterior wall of the stomach. (**b**) The port sites and the location of the stomach

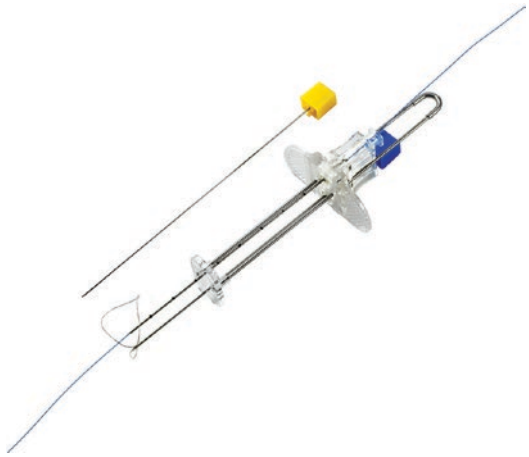

Fig. 21.9 Funada's gastropexy device. The usage of this device is to stabilize fixation of the intragastric ports

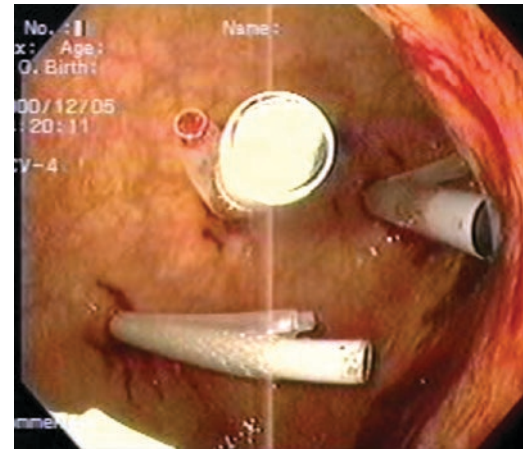

Fig. 21.10 Three intragastric ports seen from the EGJ by peroral flexible endoscopy

sutured with Funada's gastropexy instrument. Then the skin is incised 5 mm longitudinally, through which a 5 mm Step® trocar (Covidien, New Haven, CT, USA) is inserted into the gastric lumen. Insertion of the Step® trocar is observed by peroral gastroscopy. Once the 5 mm port is inserted, gastric lumen is insufflated with CO2 gas to maintain the pressure at 8–10 mmHg. Then two 2 mm ports (BJ port® or Mini-port®, Covidien, USA) are punctured percutaneously into the gastric lumen in the left subcostal area (Fig. 21.12).

Intragastric Procedure Resection of the tumor and closure of the defect at the EGJ are performed by the instruments brought into the stomach through the three ports (2 mm, 2 mm, and 5 mm). A 5 mm laparoscope is brought into the stomach through the 5 mm port to visualize inside the stomach. Resection is started with cutting the mucosal layer with a BJ hook® (Nition Company, Chiba, Japan) inserted through a 2 mm port, while a BJ needle® is inserted in the other port to retract the mucosa. Then the submucosa is dissected to identify the tumor surface (pseudocapsule). With avoiding cut into the tumor surface, the normal muscle bundles around the tumor are meticulously dissected with a high-frequency hook (Fig. 21.13a). The defect in the esophagogastric junction wall is closed by an interrupted suture with a 4/0 absorbable monofilament thread with a 17 mm 3/8 circle needle (Maxon®: Covidien, New Haven, CT, USA).

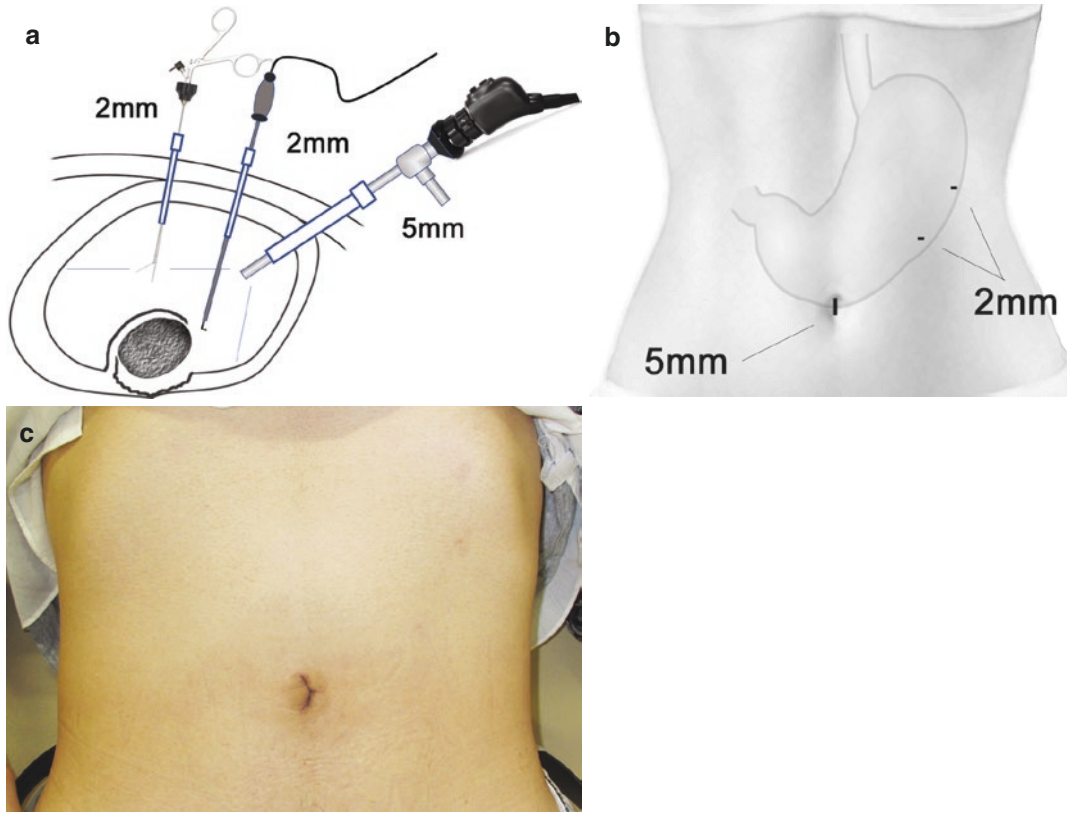

Fig. 21.11 (**a**) Schematic illustration of needlescopic PEIGS (PEIGS 252). (**b**) Port sites and the location of the stomach. Two 2 mm ports and a one 5 mm port are used. (**c**) Cosmetic result of the patient undergoing needlescopic PEIGS

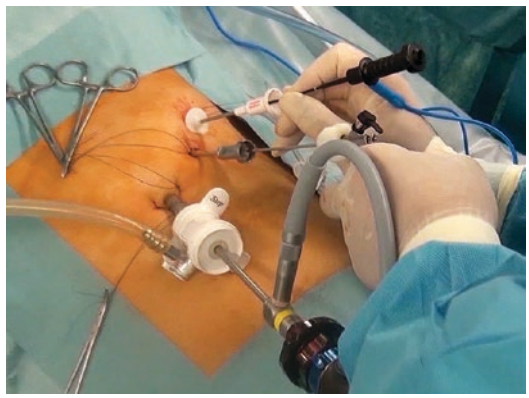

Fig. 21.12 The operation scene of needlescopic PEIGS. It needs some experience to become familiar with the flexibleness of the needlescopic instruments

This needle can pass the 5 mm port. The suturing is facilitated by usage of BJ pico® (Nition Company, Chiba, Japan), a 2 mm needle driver (Fig. 21.13b). To cut the thread in each suture, another 2 mm instrument, BJ scissors® (Nition Company, Chiba, Japan), is utilized. Interrupted suture is performed in radial direction around the esophagus and the layout of approximation is meticulously adjusted. After completing the closure of the defect, the peroral endoscope is brought into the stomach again passing the EGJ to confirm it is not stenotic. The excised specimen is entrapped in a retrieval bag and extracted via the esophageal-oral route with an aid of peroral endoscope. The retrieval bag we use is homemade by cutting the thumb part of a surgical glove. The rim of this bag is purse-string sutured so that the bag can be closed when the tumor is brought in. This bag can be inserted into the stomach via the 5 mm port.

Extragastric Procedure When the intragastric procedure is finished, all three intragastric ports are withdrawn from the gastric wall but remained

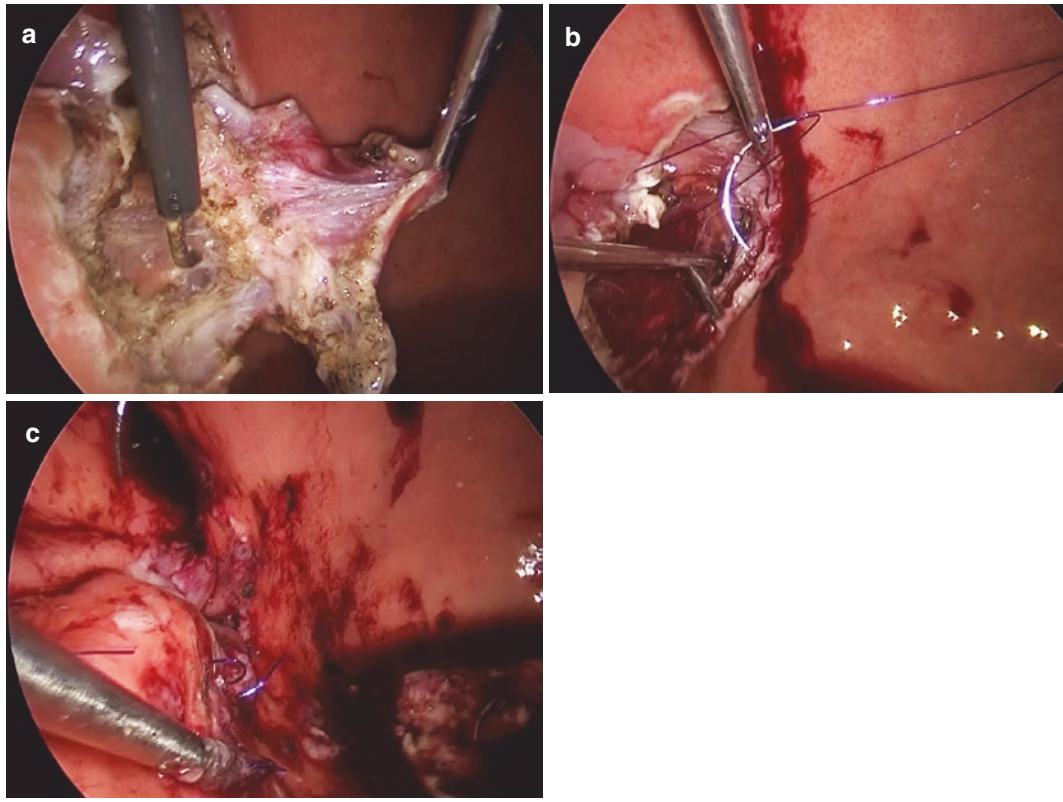

Fig. 21.13 Operative procedures of needlescopic PEIGS by endoscopic pictures. (**a**) A submucosal tumor measuring 25 mm in diameter is being resected with thin-caliber instruments (a 2 mm grasper and a 2 mm electrode). (**b**) BJ pico® is a 2 mm needle driver, which facilitates hand-sewn suturing in needlescopic PEIGS. (**c**) Reconstruction of EGJ is completed

in the peritoneal cavity. The 5 mm stab wound is closed by hand-sewing with the same thread and needle as in the intragastric procedure (4/0 Maxon®). The other two 2 mm puncture wounds are left untreated.

Finally, the navel incision was closed in a cosmetic manner, while the two puncture sites were left untreated.

21.5 Postoperative Management

In our postoperative management, all patients receive intravenous infusion with antibiotic administration for 3 days. Proton-pump inhibitor is injected for 3 days and it is taken per orally for 6 weeks thereafter. The patients start clear fluid diet on POD1, soup and puree on POD3, and soft diet on POD6, when the patient is discharged.

In postoperative week 6, the patients undergo endoscopic control to check how the wounds in the stomach are cured, whether the EGJ is not stenotic and whether the peristalsis of the stomach is normal (Fig. 21.14). The follow-up plan depends on the final pathological diagnosis and risk stratification of the resected specimen.

21.6 Short-Term Outcomes

One of the advantages of PEIGS compared to total gastrectomy or proximal gastrectomy is its low incidence of postoperative complications. Although we need to have clinical reports of large number of patients to prove this, there have been very few, so far. Our team has reported on the outcomes of PEIGS from the largest series of patients (n = 59), which showed stability and

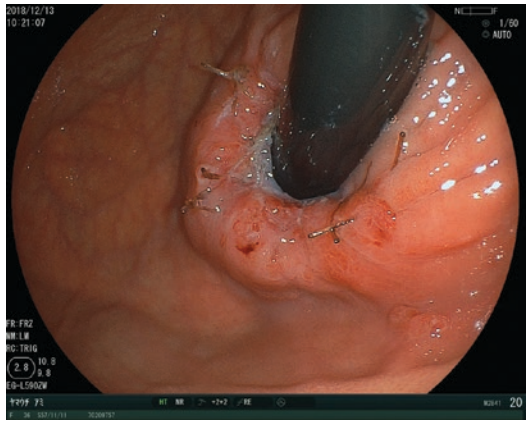

Fig. 21.14 Endoscopic control of EGJ in postoperative week 6. The sutured site is well healed and EGJ is not stenotic

safety of the operation [9]. In that report, there was no conversion to another operation and major postoperative morbidity was not encountered. Boulanger-Gobeil et al. [26] collected eight cases with gastric submucosal tumor treated by PEIGS and reported that no major morbidity occurred postoperatively. Likewise, Wang et al. [27] reported there was no major complication in the perioperative period in 12 patients undergoing PEIGS for gastric submucosal tumor. Virgilio et al. [28] reviewed 19 articles on PEIGS performed for early gastric cancer, in which the operative morbidity was noted in 9 out of 72 patients (three conversions, three bleedings, and three stenoses).

Another important aspect of the short-term outcome is whether the operation achieved R0 resection. In our report with 59 patients with GIST, excellent results of R0 resection in all cases were demonstrated [9]. Other reports by Boulanger-Gobeil et al. [26] and Wang et al. [27] also supported the good resection ability of PEIGS, resulting in R0 resection in all tumors.

Those reports may confirm that PEIGS can be performed safely. However, it should be cautioned that PEIGS must be performed by experienced surgeons especially with an enough skill of hand-sewing in narrow space.

21.7 Long-Term Outcomes

To evaluate the oncological outcomes, long-term follow-up data of the patients undergoing PEIGS for GIST must be collected. However, there have been only few literatures with such data. Our report deals with the largest number of GIST patients with long-term oncological outcomes with max. follow-up for 108 months [9]. This report revealed no local recurrence but two cases of recurrence out of 59 patients. In both cases the recurrence was detected in the form of liver metastasis, which is not supposed to be attributed to the operative technique but should be due to original nature of the tumor. The report by Novitsky et al. [29] included 20 patients undergoing PEIGS, who survived up to 84 months without local recurrence. Mino et al. [30] reported the long-term outcomes of 15 cases, who were followed up for max. 61 months and presented no recurrence. The long-term oncological outcomes of PEIGS may be acceptable, as far as only a few available literatures are reviewed. Together with the fact that PEIGS can perform R0 resection in very high success rate, shown in the previous section, this organ-preserving operation may be oncologically justified. To be more convincing, more studies with larger number of patients with precise clinical data are necessary.

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Endoscopic Surgical Platforms

22

Ryan C. Broderick, Catherine Tsai, Arielle M. Lee, and Karl-Hermann Fuchs

22.1 Introduction

With the development of advanced minimally invasive therapy, the role of endoscopic involvement in therapeutic procedures in the gastrointestinal (GI) tract has substantially increased [1–11]. The trend of minimizing access trauma has stimulated gastroenterologists and surgeons to use interventional endoscopic technology to replace a number of procedures, which were a mainstay in open surgery and even some in laparoscopic surgery [2, 5, 7, 8–11]. The more these procedures require sophisticated steps, the more traditional endoscopes will reach a limitation in their technical abilities. One can be surprised that using the traditional endoscopic technology – designed half a century ago for diagnostic purposes – was able to be utilized for effective endoscopic hemostasis, perform tumor resections in the gut, treat gastroesophageal reflux disease, and get involved in bariatric procedures [7–9]. These procedures are made possible by a number of specially developed endoscopic tools, mainly based on commercially available, flexible endoscopes [5–9].

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During the introduction of natural orifice transluminal endoscopic surgery, a number of endoscopic and surgical platforms emerged from different companies and institutions [3–5]. These platforms seemed to become major "game changers" for intra-abdominal surgery using a transgastric route [12–14]. However, today we know that these ideas were premature to make it into clinical practice. It was too early for the readiness and willingness of the most important industrial players to further invest, develop, and provide sophisticated platforms necessary to put these disruptive ideas into clinical practice together with the medical community [12, 13].

There were a few exceptions [14, 15]. Many involved parties have learned that this interruption in development does not lower the value of some of these highly advanced technologic ideas. These platforms for improved endoscopic surgery in the gastrointestinal tract using a combination of flexible endoscopic and laparoscopic paradigm and technology are still needed [4, 5, 12–18]. One may ask what exactly an "endoscopic surgical platform" should be and what characteristics this system must fulfill to qualify for such a description.

An endoscopic surgical platform (ESP) should be able to maneuver within the gut with its intraluminal restrictions and at the same time carry the potential to be used for basic surgical tasks such as cutting, dissecting, traction, and countertraction, as well as suturing.

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https://doi.org/10.1007/978-3-030-78217-7_22

22.2 Prerequisites and Limitations of Endoscopic Surgical Platforms

There is a *size limitation* in the GI tract for instruments, which accounts especially for procedures in the upper GI tract with an esophageal diameter at a maximum of around 2 cm. The latter requires a platform size of a diameter below this borderline as a prerequisite for clinical use (Fig. 22.1).

Another prerequisite is the *visualization* of the anatomical region of interest (target area) combined with the need for the precise application of instruments under visual control. This level of visualization can be implemented by all modern commercially available endoscopes in a high quality.

Triangulation is important in surgical manipulations and should be possible with these platforms (Fig. 22.1). A rather simple way of providing some degree of triangulation was implemented in the dual-channel endoscopes. Triangulation was possible by modifying the working channels and their distal exit at the tip of the scopes for endoscopic instruments with an Albarran-steering lever, with which one can modify the direction of these instruments. This allowed for steering the endoscopic tools through the working channels. A movement regarding their axis toward the target organ, for example, moving an instrument up-and-down or side-to-side is possible. As a consequence, one could use a grasper in a slightly different axis causing some traction and use the other instrument for dissec-

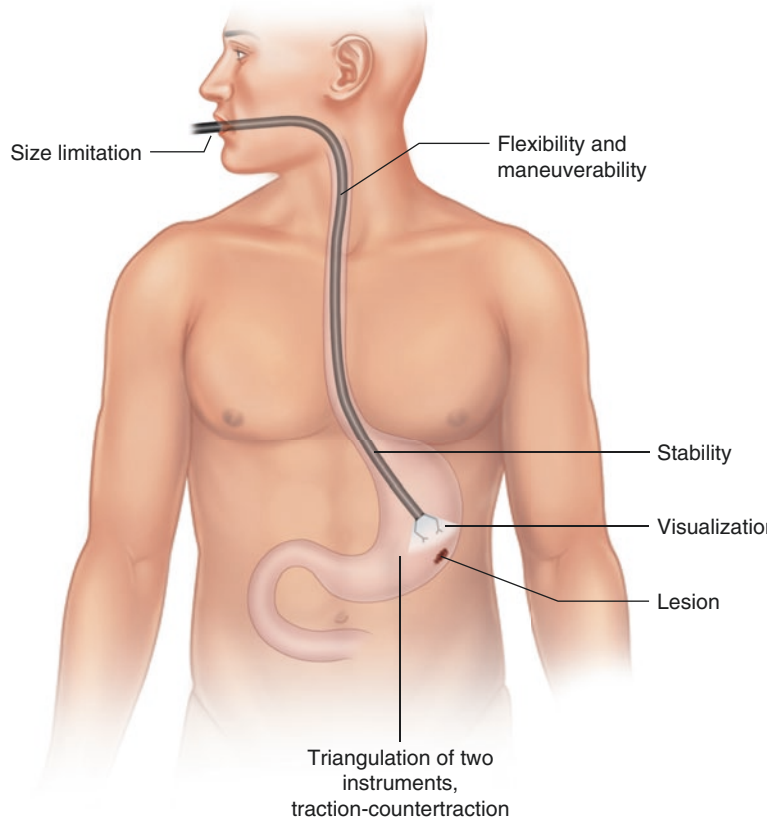

Fig. 22.1 Schematic overview of the important features on an "ideal" endoscopic platform for intraluminal and transluminal endoscopic surgery: the requirements concern size limitations, visualization, triangulation, both stability and mobility, sufficient force to drive the end-effectors, independence of visualization, and precision in end-effector manipulation

tion. However, there would be no complete independency between visualization and action of the end-effectors.

For surgical actions at the tissue level, a triangulation of at least two instruments in the target area is needed to perform normal surgical maneuvers such as cutting, grasping, and suturing. Endoscopists with a gastroenterlogy background may argue that they do not need triangulation to perform interventional endoscopy, which they have proofed many times. However, a performance of more sophisticated surgical procedures, especially those where traction and countertraction as well as surgical dissection in "defined tissue layers" is needed, would require a full set of surgical tools. This is especially true for routine surgical suturing, safe adaptation of anastomoses, and tissue closure.

Sufficient *stability and mobility* of the endoscopic surgical platform is another prerequisite to perform precise maneuvers of the end-effectors at the tissue level (Fig. 22.1). This requires, on one hand, a maneuverability of the complete platform to move in and out of the GI tract and back and forth to advance toward the target area. On the other hand, the platform must have a feature to "freeze" in a stable position to apply a strong retraction and countertraction and/or to enable the "frozen platform" to serve as a basis for "high-precision" movements of its end-effectors to perform surgical manipulations at the tissue level in the "target area."

An important prerequisite is the *force* that should be translated from the handles to the end-effectors by moving steering handles from the outside of patients. The earliest attempt to use a special endoscopic platform for suturing was the Endo- Cinch™ system, using a suturing device mounted on a flexible scope [19]. This technology was initially used for the treatment of gastroesophageal reflux disease in narrowing the cardia [19, 20]. Unfortunately, the sutures could only be placed quite superficially into the mucosa rather than a necessary "deep bite" through the muscle of the lower esophageal sphincter, and therefore, this technique was only partially successful in treating gastroesophageal reflux disease [20, 21]. This highlights a problem of a flexible endoscopic platform in lacking substantial force at the end-effector level because of the otherwise necessary flexible shaft to overcome the distance between the external manipulation site of the platform (at the mouth) and the target area, for example, in the stomach.

Another limitation in using an endoscopic surgical platform efficiently is the lacking *independence* between the visualization and the end-effector maneuvers (Fig. 22.1). Often, these two functions are combined in the hardware, which limits the overview and precise manipulation of the instruments as the experience shows in early prototypes of endoscopic surgical platforms. When performing precise surgical maneuvers with the end-effectors, a good overview on the complete target area as well as the surrounding organs is required to fulfill some tasks safely. If the vision is limited because the visual window is moved in a wrong direction following only one end-effector, since they are mechanically connected, optimal overview is destroyed or at least reduced. Therefore, an independence of these two functions is advisable.

In addition, this also limits the ability of efficient intra-abdominal control for safety during the procedure. The latter will have its influence on the limitation of the necessary *precision* of end-effector movements and maneuverability.

22.3 The Development of Endoscopic Platforms

Endoscopic suturing has been around for almost 20 years. Early suturing was performed by Bard EndoCinch™ (USA) with limited success since the force and depth of the suturing bites in the gastric wall were insufficient [19–21]. Another promising project was the Olympus prototype Eagle Claw, which seemed to provide abilities for deeper bites, but remained a prototype. Eventually this prototype was taken over by Apollo Endosurgery, Austin, TX, USA [22–25]. This company modified it into a commercial product, which is successful on the market and used quite frequently (OverStitch, Apollo Endosurgery) (Fig. 22.2) [13, 23–25]. In addition, the concept

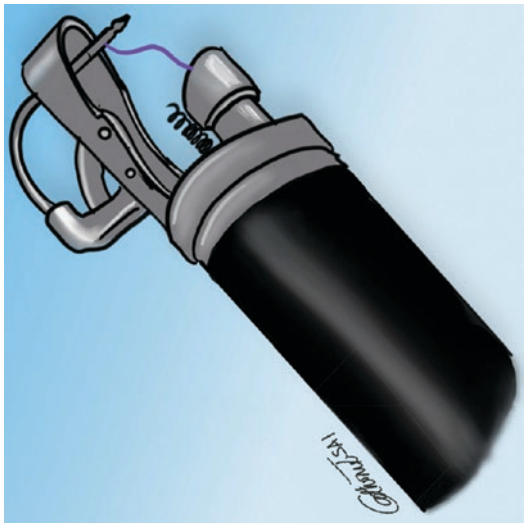

Fig. 22.2 Scheme of the OverStitch endoscopic suturing system, which allows for an application of a needle through both rims of a lesion to adapt and close it by a sufficient suture and knots

Fig. 22.3 Scheme of the "Plicator," which came on the market initially as therapeutic tool for creating a gastroplication, a fundic fold to augment the lower esophageal sphincter. It has two strong branches for establishing a sufficient suture through the gastric wall.

of T-bars was introduced (Wilson-Cook, NC, USA), but did not succeed in the market.

More effective than the first suture device was the "Plicator," which was able to perform deep sutures in the gastric wall, simulating a plication of the fundus (Fig. 22.3) [3]. This concept was later taken over by GERDX™ (G-Surg, Seeon-Seebruck, Germany). GERDX™ is a device with sufficient depth in suturing to plicate the fundic wall from intraluminally to create a sufficient gastroplication [3, 12, 26].

The current GERDX™ system and the Apollo OverStitch™ system are those systems with a reasonable spread in clinical use. The Apollo OverStitch™ system has been used widely for flexible endoscopic suturing and closure of perforations in clinical routine (Fig. 22.2). Several authors report on the success of this method requiring training and a dedicated team [13, 23–25].

Specially designed flexible endoscopic instruments with more surgical character were developed such as a Maryland dissector to manipulate tissue with more force than a regular endoscopic grasper and scissors with larger blades similar to laparoscopic scissors (Ethicon, Cincinnati, USA). These instruments had joints in their shaft for angulation and improved mobility for intraluminal and intra-abdominal applications (Fig. 22.4). The handling of these instruments was adapted to a more surgical use. Laparoscopic surgeons were used to handles with a laparoscopic paradigm. Endoscopists usually use flexible endoscopic instruments with a completely different design of instruments and handles [27]. As a consequence, the optimal handles depend on the function of the instrument and on the educational and training background of the team that is using these instruments.

22.4 Specialized Endoscopic Surgical Platforms

Initially, some intraluminal devices could be used for special indications such as suturing or adaptation, but a stable platform was lacking. An early company to focus on special instruments for natural orifice surgery was USGI Medical (San Capistrano, CA, USA), focusing on the stability of an endoscopic system within the gastric lumen to perform more sophisticated maneuvers [14].

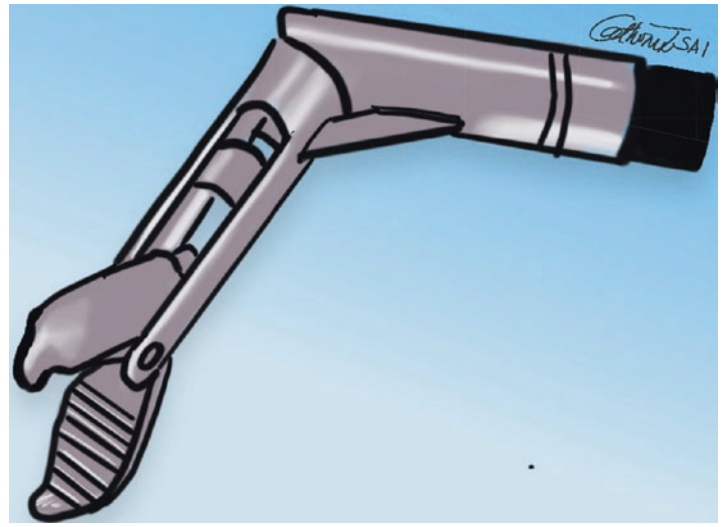

Fig. 22.4 A grasper with integrated joints (Ethicon-toolbox instruments), allowing for angulation of the end-effectors, which enabled very precise manipulations of these instruments at the tissue level in the target area.

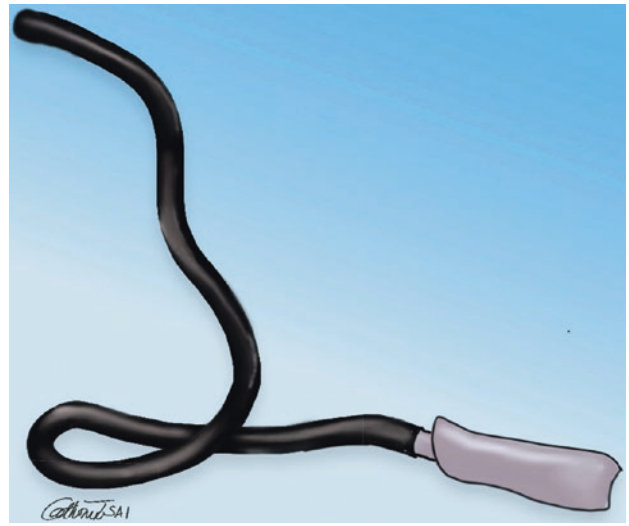

Fig. 22.5 Scheme of the "shapelock" system by USGI, an access system for the use with commercially available endoscopes and special instruments. The system provided more stability of the endoscope and therefore more precision of the end-effectors at the tissue level.

This company developed an access system for the use with commercially available endoscopes and special instruments from this company. One special instrument was the "shapelock" system for flexible scope and endoscopic instruments (Fig. 22.5).

This system can be stiffened, while carrying an interior "daughter scope," which subsequently could be fixed in its position to perform dedicated endoscopic surgical tasks via the endoscopic tools, which are brought in via the working channels. Several ports were connected with the shaft to carry endoscopic and surgical flexible instruments. The system could be inserted like a regular endoscope into the gut. Furthermore, the system could be locked (stiffened) into a position at the target area to perform more delicate surgical maneuvers. One prototype was developed for suturing (9-Prox USGI Medical, USA).

A true multitasking platform for endoscopic surgical procedures was the Cobra system (USGI Medical, USA) (Fig. 22.6). In this prototype device, the request for triangulation of instruments is implemented perfectly since three instrument arms are established for surgical maneuvers [14, 28]. Others have used a similar

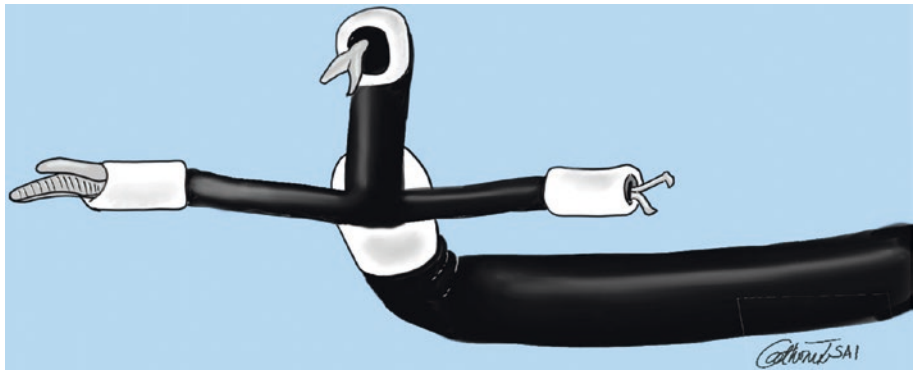

Fig. 22.6 Scheme of the USGI-Cobra system, one of the first multitasking platforms to perform surgical manipulations with triangulation with a flexible endoscopic tool. It contained several features to work intra- and transluminally.

device [15]. Again, a 6mm flexible endoscope can be used through the channels of the system. Under visual control of the endoscope, the system can replicate "laparoscopic-like" maneuvers such as dissection and suturing. Another advantage of the system was the possibility to achieve some traction and countertraction.

The transformation of forces and manipulations for the end-effector movement was realized by mechanical system. While complex movements of manipulation were quite possible, suturing was difficult because of the lacking strength and translated force on the arms. Also, knot tying remained quite troublesome.

This platform was designed for intraluminal and also intra-abdominal applications using either a transgastric or the transrectal route. With a diameter of 15 mm, it was quite easily possible to advance this system through the esophageal lumen into the stomach, where it could be used to penetrate the gastric wall, and after further advancement, one was able to perform intra-abdominal surgery.

Another endoscopic surgical platform was the EndoSAMURAI™ (Olympus Corp., Tokyo, Japan), which was tested and investigated between 2007 and 2011 to assess the feasibility of surgical procedures [16, 29]. The endoscopic surgical system consisted of an endoscopic shaft with a traditional endoscopic steering unit, connected to an interface that can be used as "laparoscopy-like" working station to perform the surgical maneuvers (Fig. 22.7).

At the tip of the flexible endoscope, two working arms were connected, which have working channels for the end-effector instruments, brought out for surgical manipulations. The two articulating working arms could be moved out of the original diameter of the scope and therefore provided more triangulation with an elbow-like function, which could be deployed within the lumen of the gut or within the abdominal cavity. The shaft of the endoscope was connected to a traditional steering unit of the endoscope at its proximal end and a mechanical connection to a separate working station, from which an operator could manipulate the end-effectors. The endoscopic control mechanism was operated by an endoscopist (Fig. 22.7).

A surgeon operated the work station with a laparoscopic paradigm using bimanually manipulations, which could be observed on a video screen. The laparoscopic workstation mechanically transmitted the motion of the handles of the effector instruments to the tips of the end-effectors that were advanced through the flexible working channels into the working arms. The system is similar to a traditional endoscope a light source and insufflation. There are also standard functions for suction and possibility of rinsing the endoscopic lenses. This system consists of a classic endoscopic component, which is launched via a natural orifice in the body and a laparoscopic work station unit, that can be operated with laparoscopic surgical abilities. Therefore, the system is operated best by two

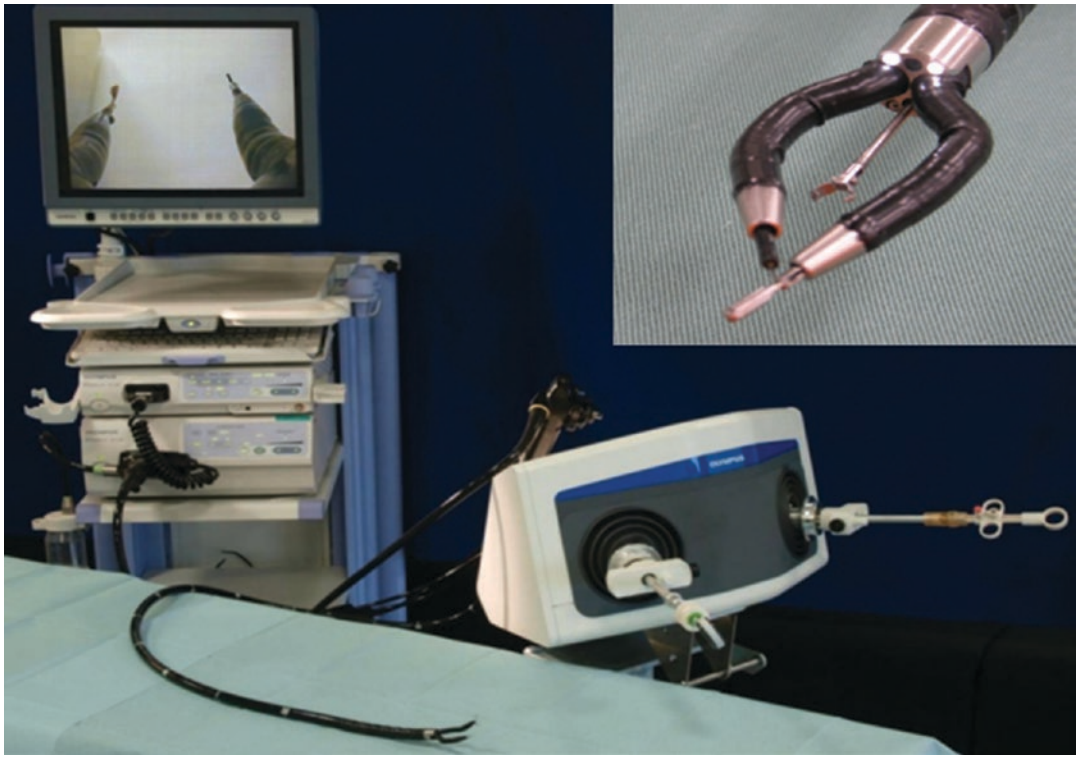

Fig. 22.7 EndoSAMURAI™ (Olympus Corp. Tokyo, Japan), an endoscopic platform with a laparoscopic paradigm. A surgeon can use a workstation to manipulate handles, which will steer end-effectors via a flexible endoscope intraluminally and transluminally. An assisting endoscopist handles the necessary manipulations of the flexible endoscope.

individuals; on one hand, the active surgeon at the work station, and on the other hand, a camera assistant, who is responsible for the general maneuvering of the tip of the endoscope as well as the in–out movements of the endoscope in order to advance or withdraw the endoscope within the gut and/or in the abdominal cavity. Exchangeable instruments via the working channels of the scope allow for a variety of applications of the working arms such as grasping, retracting, tissue cutting, coagulation, hemostasis, as well as suturing with a needle holder. The stability of the platform was ensured by the rigidity of the steerable overtube.

Training experience was established and published [16]. This consisted of Box-training and training in the animal laboratory for small bowel resections. This endoscopic surgical system serves well as a multifunctional endoscopic platform for the use of transgastric small bowel resection and anastomosis (Fig. 22.8).

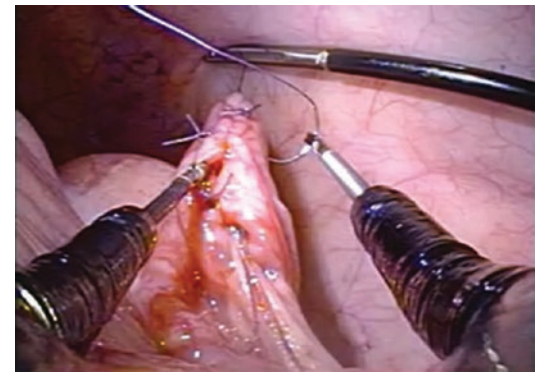

Fig. 22.8 The completion of a bowel anastomosis is possible with the EndoSAMURAI™ platform by suturing the anastomosis in a classical surgical way with needle holder and grasper. The system had sufficient stability and force as well as precision in movements to complete these tasks.

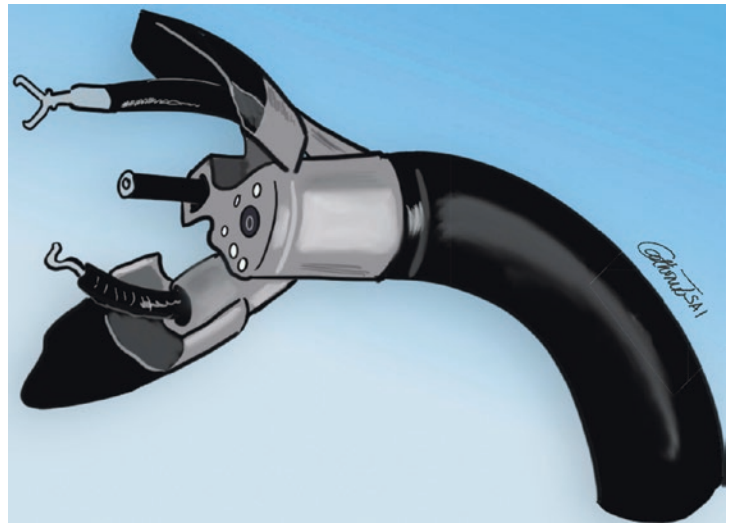

Fig. 22.9 Scheme of the Karl Storz Anubiscope™ system, a platform for intraluminal and extraluminal endoscopic surgical tasks. The system can be used for dissecting, retracting, and suturing.

A similar development is the Anubiscope™ (Karl Storz, Tuttlingen, Germany) (Fig. 22.9) [17]. In this system, a flexible endoscopic carrier with endoscope technology has also several working channels for flexible surgical instruments and steering mechanisms to maneuver these instruments at the target area [17]. The manipulation of the instruments can be done by two mechanisms: (1) by the tip design of the carrier endoscope with two triangulating arms that can be opened, thus manipulating the flexible instrument through the working channels, and (2) by flexible instruments that are advanced through the working channels of the carrier, being steered from the external handle of the instruments.

The system allows for working within the gut and transluminal also in the abdominal cavity once the carrier is penetrated through the gastric wall [17]. The tip of the sophisticated carrier endoscope is quite blunt and needs an incision to penetrate through the gastric or colon wall. Once the carrier endoscope is positioned at the target area, special flexible instruments with a surgical character can be moved with independent motion. A certain drawback is the necessity of two endoscopists cooperating very closely together. One endoscopist operates the necessary maneuvers of the carrier endoscope, and the other endoscopist operates two flexible endoscopic instruments through the working channels of the carrier. The two endoscopists must work together at a high level to coordinate the necessary maneuvers and procedures. This platform has been used in clinical cases [17]. Since the closed tip of this endoscopic carrier is quite blunt, there is no need for an overtube to pass through the pharynx into the esophagus. However, the maneuverability is limited in a narrow and intraluminal channel.

Other similar platforms were developed such as the prototype Direct Drive Endoscopic System (Boston Scientific, DDES™) [15].

22.5 Robotic Endoscopic Surgical Platforms

Meanwhile, robotic technology has been introduced in endoscopic and surgical concepts [30–34]. More advanced systems are based on robotic technology such as the "Master-and-Slave Transluminal Endoscopic Robot (MASTER)" from the University in Singapore [35]. This system is a conventionally cable-driven manipulator with combined robotic technology, providing a six-degree freedom of motion at the end-effectors, which is excellent for precise maneuvers at the target area (Fig. 22.10) [35, 36].

It is associated with a regular endoscope. It requires two operators/endoscopists. In the past 10 years, several publications report on the experience with this system [35, 36]. However, unfor-

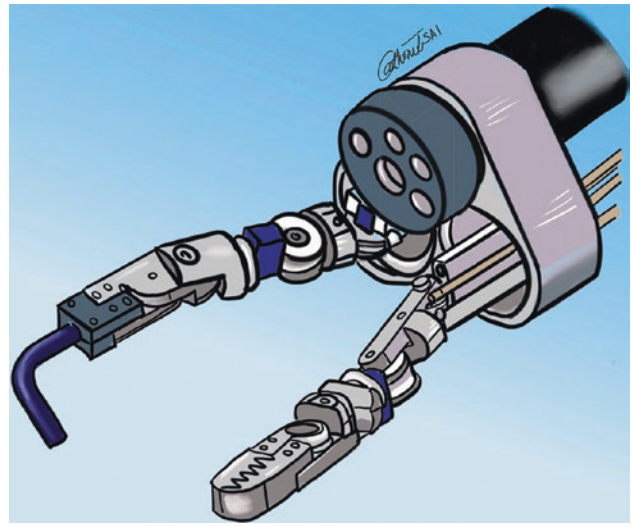

Fig. 22.10 The "Master-and-Slave Transluminal Endoscopic Robot (MASTER)" is a system with a conventionally cable-driven manipulator with combined robotic technology, providing a six-degree freedom of motion at the end-effectors. Complex surgical procedures are possible.

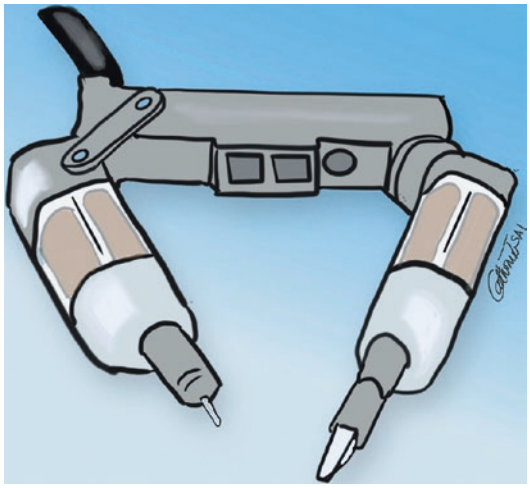

Fig. 22.11 The scheme of the future of robotic technology may be envisioned with this device, a miniature robotic system, which is small enough to be advanced through a trocar into the abdominal cavity. Once inside the abdomen, the miniature robot can angulate its arms to create some triangulation with two mechanically active arms.

tunately the systems have not reached a routine clinical application.

An even more sophisticated and futuristic system is an intraperitoneal miniature robot developed by the University of Nebraska (Fig. 22.11) [37, 38]. The concept of this device is an application of miniature robotic system, which can be advanced through a trocar into the abdominal cavity. Once inside the abdomen, the miniature robot can angulate his arms to create some triangulation with two mechanically active arms for surgical manipulations, steered via remote control from outside the body [37, 38].

22.6 Future of Endoscopic Technology

Facing a meanwhile 15-year-long, rather unsuccessful history of endoscopic platforms, the costs of complicated mechanical and also robotic-based technologies seem to have one drawback, which is hard to overcome: the unrealistic costs. As a consequence, there has been a recent reflection on more simple, mechanical systems, which may be more realistic to develop than complex robotic systems [38–45].

An "easy-to-use" mechanical manipulator platform may be developed in reasonable time with reasonable costs without major investment for a hospital, which may be a more attractive alternative for industry and others [43–45]. As a consequence, if modern tools can be developed, which can be applied through commercially available endoscopes without major additional investments, this concept may be more realistic in times of financial constraints in medicine. Furthermore, flexible endoscopic instruments are following currently still the size limitations of a narrow working channel on endoscopes,

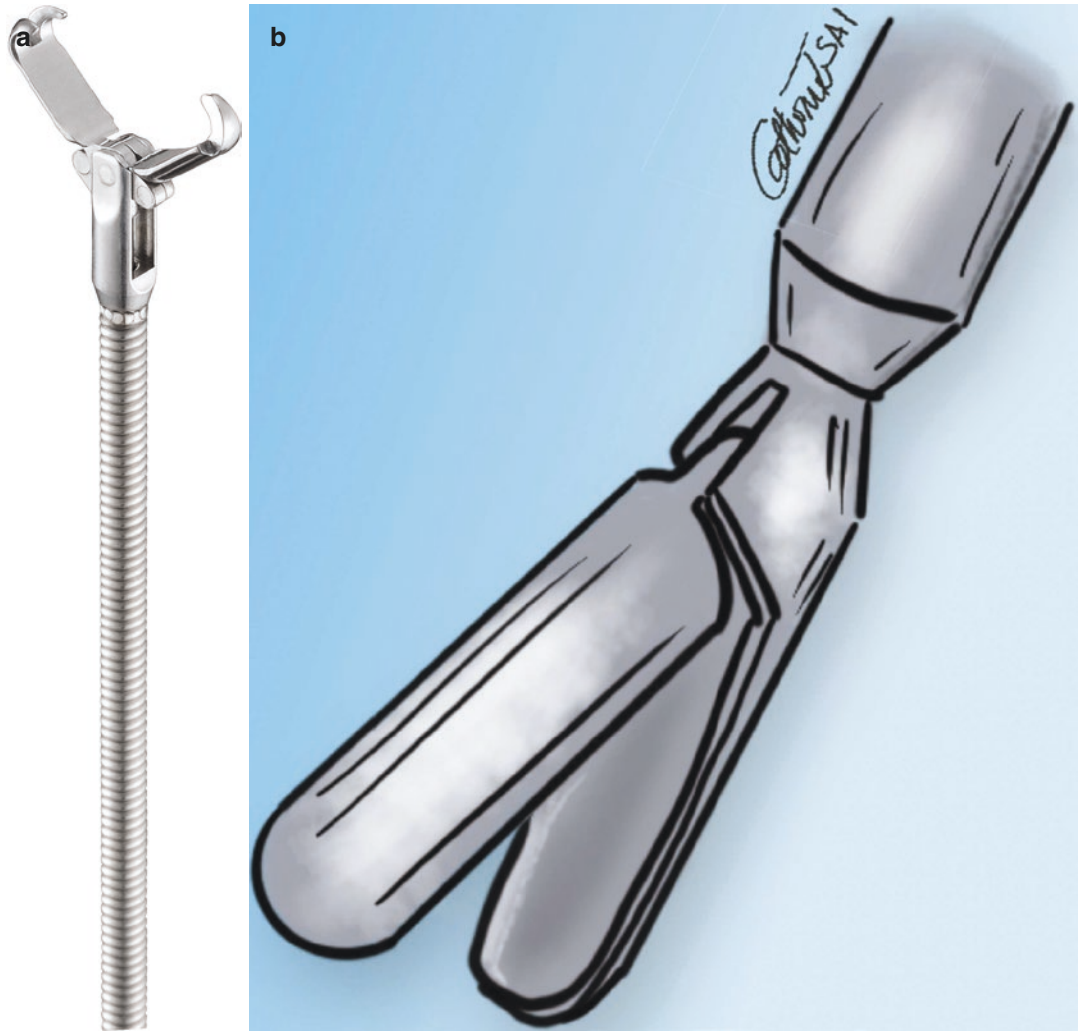

Fig. 22.12 (**a**) Endoscopic grasping device with a small "mouth" (Olympus Deutschland, Hamburg) (small grasping branches, which may be insufficient in traction, but great for biopsies; (**b**) laparoscopic grasper with large branches for traction, which is also needed in flexible endoscopic surgical manipulations. A combination of these thoughts and needs, built in one flexible endoscopic tool, would fulfill unmet needs.

designed originally for diagnostic purposes. A new approach could be to integrate surgical principles in their structure and functionality. A simple example are graspers, which usually follow the flexible endoscopic paradigm of rather small grasping branches, which may lack sufficient power and force of holding to a structure to create enough traction and countertraction (Fig. 22.12a, b). The vast experience in laparoscopic surgery with graspers with longer branches and differentiated surfaces for certain functions may be worthwhile to explore to improve tissue handling (Fig. 22.12b). These could be small steps with substantial effect in moving endoscopic technology forward. Recent endoscopic research is aiming exactly in this direction [46–49].

The principle of minimal access surgery is the reduction of access size and access trauma. The clinical aims are a shorter patient recovery, improved postoperative well-being, better cosmesis, less inhibiting postoperative restrictions in order to get the patient quickly back to full physical and psychological abilities, and pos-

sibly an improved long-term outcome. The latter could be achieved by less wound infections and less incisional hernias over time. The advantage of this concept of minimal access surgery over conventional open surgery has been clearly shown in the past decades.

Whether a further reduction in access trauma can improve the patient's outcome even further has been difficult to prove in the past years. This goal can be reached in two ways. One direction is the development of new technology to facilitate certain necessary surgical steps for endoscopic techniques with endoscopic surgical platforms as pointed out in this chapter. From the surgical standpoint of view, a system is needed that can be transported via the abdominal wall or a natural orifice with a limited diameter into the abdominal cavity, where all surgical functions can be applied such as visualization, traction and countertraction, dissection, hemostasis, and suturing. Robotic technology may enable the desired needs [39–42].

Another approach is the transformation of therapeutic ideas from a surgical concept into an endoscopic concept. An excellent example for this is peroral endoscopic myotomy since the central therapeutic concept of myotomy is kept, but the approach is transferred from a transabdominal pathway to a pure endoscopic transesophageal pathway [4–6].

Further developments in endoscopic, surgical, multifunctional platforms are necessary in the future. Optimal multitasking platforms should have changeable end-effectors, image guidance, possibility of traction and countertraction, as well as sufficient triangulation and at the same time steerable stability to increase precision in manipulations.

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The Fortimedix Surgical Endo-Surgery Platform

23

Ryan C. Broderick, Karl-Hermann Fuchs, Bryan Sandler, and Santiago Horgan

23.1 Introduction

One of the most challenging maneuvers in interventional endoscopy is the resection of lesions in the gut whether it be partial thickness or, if necessary, a full-thickness resection to meet oncologic needs [1–4]. An early technology for performing complex surgical maneuvers for endoscopic rectal tumor resection was the transanal endoscopic microsurgery (TEM-system) [5, 6]. The diameter of the anus and rectum allowed for applications of larger surgical instruments/laparoscopic devices to perform these procedures. However, the upper gastrointestinal tract poses a real challenge for which the TEM system cannot be applied. The diameter and length of the esophagus introduce limitations that require specialized instrumentation for complex endoluminal tasks. The esophageal diameter is limited to about 2 cm while the distance between the mouth and the gastric lumen of 40–50 cm requires miniaturization and lengthening of surgical instruments to create functional end-effectors. These space limitations decrease the mechanical advantage and the ability for triangulation at this distance to perform complex tissue manipulation for resection of gastric lesions; specifically, tradeoffs include decreased grasping force, range of motion, and ability for force application. Many platforms have been developed in the past (refer to prior chapters for endosurgery platform descriptions); however, only a few have achieved clinical application and a stable position in the market, generally at advanced/specialized endoscopic centers [7–14]. Endoscopic robotics has been another avenue recently explored for overcoming the above limitations and allow for intraluminal suturing and dissection. While there is ongoing data being obtained for these platforms, one major limiting step in adoption is significant cost and user expertise and endoscopic robotics is likely still years away from routine clinical use.

Therefore, there has been more recent reflection on simple, mechanical systems, which may be more realistic and expeditious to develop. An endoscopic surgical platform should be able to maneuver within the esophagus, stomach, and gut with its intraluminal restrictions and at the same time carry the potential to perform surgical tasks such as cutting, dissecting, traction, and

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countertraction. Ideally, the system should have an easily understood user interface that allows for comfortable surgery with a short learning curve.

Important clinical applications of an endoscopic platform are endoscopic submucosal dissection (ESD) and endoscopic full-thickness resection (EFTR), which are routinely used in specialized centers for interventional endoscopy [1–4].

Our group at the Center for the Future of Surgery at University of California San Diego established a research program to evaluate a new endo-surgery platform, designed by Fortimedix Surgical BV, the Netherlands. The platform was developed featuring flexible articulating instruments designed to be used with a standard flexible endoscope. The project was performed and supported by Fortimedix Surgical, a company that develops and manufactures proprietary articulating instrument technology.

The system and the instruments were designed and based on an earlier development from Fortimedix Surgical: the symphonX™ single-port surgical platform, a novel, FDA-cleared and CE-mark-approved platform for minimally invasive abdominal laparoscopic surgery [15–17]. Some members of our working group at the Center for the Future of Surgery (UC San Diego) have used and studied this new platform, featuring small articulating handheld instruments, originally dedicated to be used in single-port procedures. Our analysis of use in laparoscopic cholecystectomy was published with promising results [15–17]. Subsequently, an endoscopic surgical platform was developed with similar technology, which can be introduced into the esophagus and stomach alongside any flexible endoscope, allowing for movement within the limited diameter of the esophagus without major friction. The idea was to perform resection of the mucosa and full-thickness wall resections of both the esophagus and stomach under flexible endoscopic guidance and assistance.

23.2 The Fortimedix Endo-surgery Platform

The design of the endo-surgery platform utilized strict criteria to create a familiar interface and function to shorten the learning curve of new technology. Cost was also an important design input, so a system that could be used in combination with commercially available endoscopes was desired (for both cost and familiar interface). The instruments were designed to function and triangulate similar to laparoscopic instruments and end-effectors, but deployed to the target tissue in a similar fashion as endoscopic instruments; thus, a hybrid endoscopic/laparoscopic platform was created.

The system has an external docking station, affixed to the operative table by means of a StrongArm™ Surgical Holder (Mediflex), to stabilize both flexible instruments for the right and left hands of the surgeon. Figure 23.1 demon-

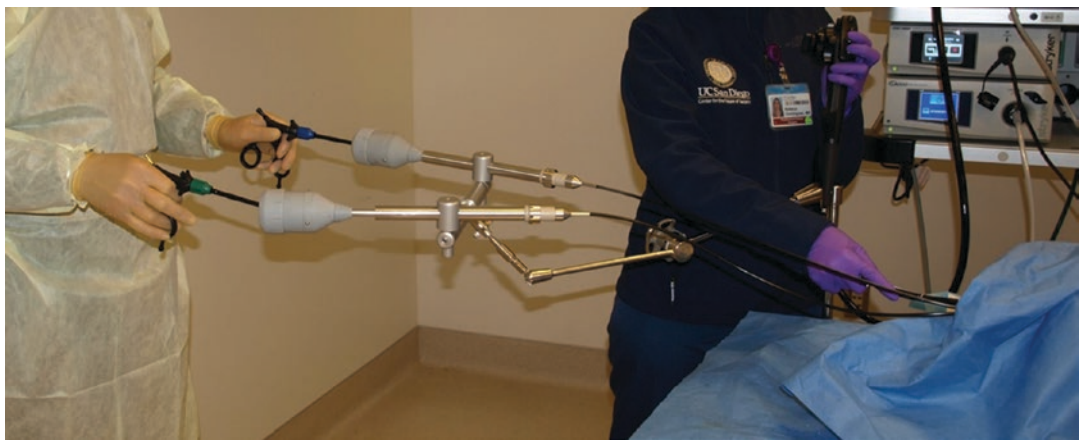

Fig. 23.1 Surgeon A is the primary operator and uses two-hand flexible, articulating instruments to perform tissue handling/dissection. Surgeon B controls a standard endoscope for visualization and tissue targeting.

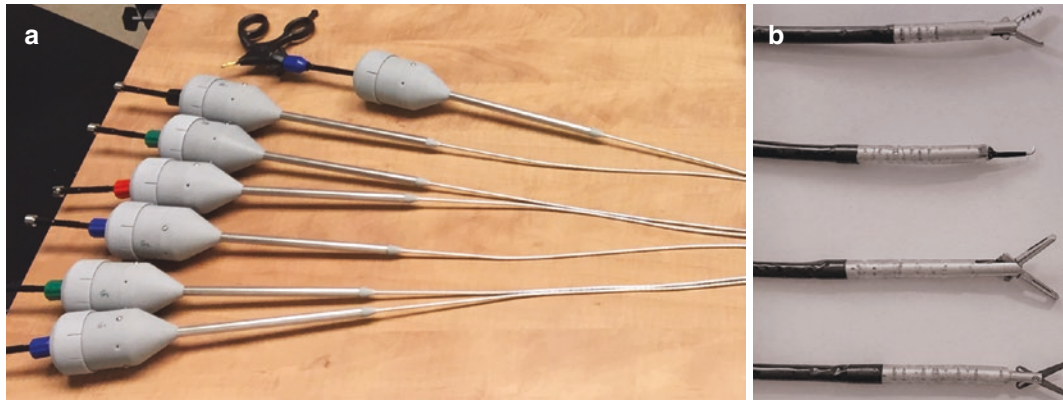

Fig. 23.2 (**a**) Series of instruments tested with standard removable (and reusable) laparoscopic device handles. (**b**) End-effectors include dissector, tissue grasper, scissors, and monopolar hook cautery.

strates the setup of the platform. The flexible, articulating instruments have the ability to create triangulation at the target tissue and provide stability for force transduction (Fig. 23.2). The end-effectors can be manipulated by standard removable and reusable surgical handles. The instruments are inserted into individual instrument lumens, attached proximally to the docking station and distally to the endoscope, to allow advancing and removing the flexible instruments. The surgeon performs two-handed surgery while a second assistant controls the endoscope for visualization and tissue targeting (Fig. 23.1). The handles are designed to mimic the laparoscopic paradigm, with the intent to facilitate the learning process of an advanced laparoscopic surgeon.

The articulating instruments are supported by two individual instrument lumens (left and right) that are attached to the tip of a commercially available flexible endoscope, which is advanced through the esophagus or further into the gastric lumen (Fig. 23.1). In order to facilitate the passage of the system through the pharynx, an overtube (Guardus™, outer diameter 18.5 mm) is used. A specially designed overtube cap was created, which allows instrument and endoscope insertion through individual channels, maintaining the insufflation pressure during surgery (Fig. 23.3). The instruments can be placed with the scope in the esophagus as well as further into the gastric lumen.

In the first series of tests, flexibility/range of motion and grasping capability of the end-effectors were assessed using a box trainer (Fig. 23.4). The experience from these experiments showed a sufficient maneuverability of the instruments and a satisfying direct transfer of movements from the external platform handles to the end-effectors, as could be verified under endoscopic vision. These maneuvers were able to be performed by both novice (resident surgeons) and advanced laparoscopic surgeons.

Additionally, the ability to advance the instruments to the intraluminal target area from the docking station and along the scope was evaluated. Instruments were able to be readily inserted and exchanged without removing the endoscope, mimicking laparoscopic techniques. Further assessment of system/instrument capabilities was evaluated in a porcine model as described later.

23.3 Porcine Model Tests

All necessary requirements for animal testing were requested and granted by the governing body at University of California San Diego (UCSD). After permission was obtained, the testing was performed at the UCSD Center for the Future of Surgery animal training facility in La Jolla, CA, USA. Care was taken to strictly follow the rules for Good Laboratory Practice. The animals were under continuous monitoring and

Fig. 23.3 Overtube adaptor design to facilitate insertion of endoscope and instruments through individual channels, while maintaining insufflation

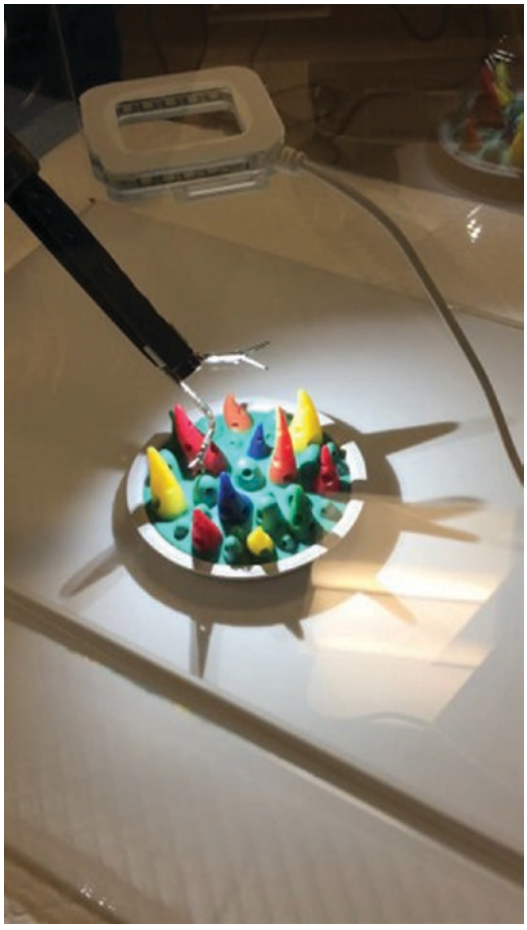

Fig. 23.4 Box trainer view of distal endoscope and end-effectors illustrating instrument lumen attachment to distal tip of the endoscope as well as range of motion capabilities

observation by trained personnel during the entire procedure.

In March 2020, the platform was tested. First, deployment of the system and end-effectors and access to the target tissue was established without difficulty nor injury to the surrounding mucosa.

Range of motion was then tested as well as cutting and grasping of the gastric wall (Fig. 23.5). Endoscopic mucosal resection of the distal esophagus was also completed (Fig. 23.6). These tasks could be performed with success and without major handling problems. Several surgeons participated in the testing, including three novice resident surgeons and three faculty advanced laparoscopic/endoscopic surgeons from UCSD. Subjectively, a satisfying result and proficiency gain within the test phase was demonstrated; the faculty surgeons were each able to complete an endoscopic mucosal resection (EMR) or ESD in its entirety.

Endoscopic dissection of the esophageal and gastric mucosa was able to be successfully completed, with advanced surgeons able to perform the complete procedure and more complex tasks. ESD in the esophagus and stomach as well as EFTR in the stomach were attempted and evaluated. The system setup averaged 5 minutes from entering the esophagus via the Guardus overtube to comfortable endoscopist and operative surgeon positions with end-effector location at the target tissue. The flexible, articulating instruments could be readily advanced in the esophagus to a preplanned position, and a dissection or incision could be performed either with an energy-driven hook or scissors. The grasping forceps provided enough force to pull the mucosal wall and expose the dissection plane in the stomach (Fig. 23.5). There was enough range of motion of the end-effectors to perform instrument crossover for dissection along multiple intended tissue planes (Fig. 23.6). Tip movement could travel in x-, y-, and z-planes for multiple centimeters, providing significant range of motion; this allowed for adequate traction and countertraction forces similar to laparoscopic surgery. The platform was also small enough to work within the confines of the esophagus (Fig. 23.7), but with enough instrument triangulation and range of

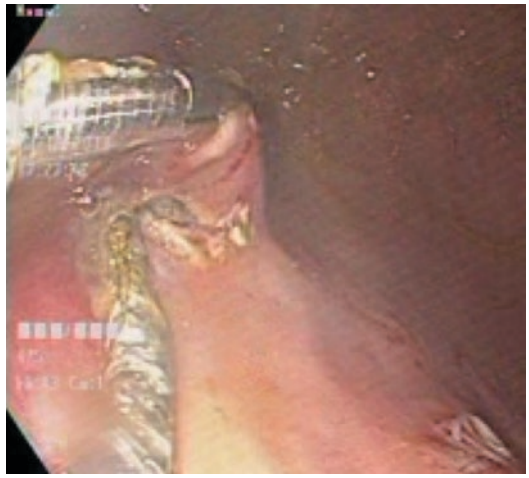

Fig. 23.5 Gastric endoluminal view and performing gastric submucosal dissection. Note left end-effector grasps and lifts the target tissue while right end-effector performs monopolar cutting at the mucosal base. Triangulation achieved by the specially designed instruments.

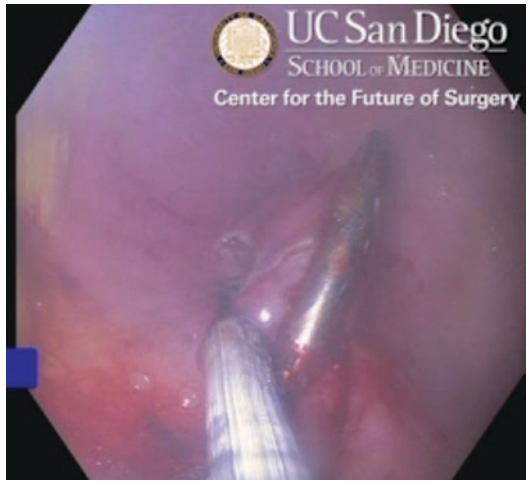

Fig. 23.6 Gastric ESD being performed. Instrument crossover able to be achieved for hook cautery to lateral mucosa with left end-effector providing medial traction.

motion to perform a complete EMR (Fig. 23.8). End-effector visualization was achieved through the entire range of motion/triangulation with direct view from the endoscope.

The system provided a stable platform to perform procedures in the esophagus and stomach. The articulating instruments allowed for precise end-effector manipulations to perform

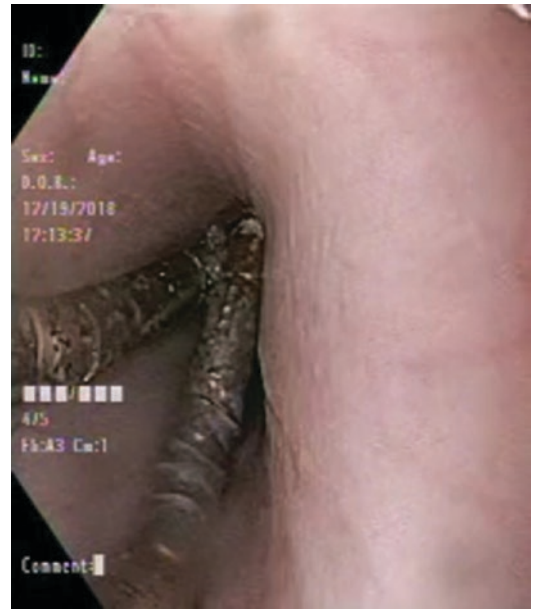

Fig. 23.7 Esophageal endoluminal view

an endoscopic resection procedure of simulated esophageal and gastric lesions with short perceived learning curves for expert endoscopic surgeons.

23.4 Discussion

The trend of minimally invasive therapeutic concepts moves more and more from laparoscopic procedures to flexible endoscopic and/or transluminal techniques (e.g., per-oral endoscopic myotomy (POEM), EMR, ESD, EFTR). Indications for endoscopic dissection include excision of metaplasia/dysplasia of the distal esophagus as well as gastric mucosal, submucosal, and full-thickness tumors. The necessity for improvements in triangulation and grasping forces is obvious when performing EMR and ESD with inline visualization of straight instruments; the learning curve for these advanced endoscopic procedures is long and not applicable to many practitioners.

Furthermore, the advantage of a mechanical, nonrobotic system is the decreased cost, which may have advantage over robotic systems in

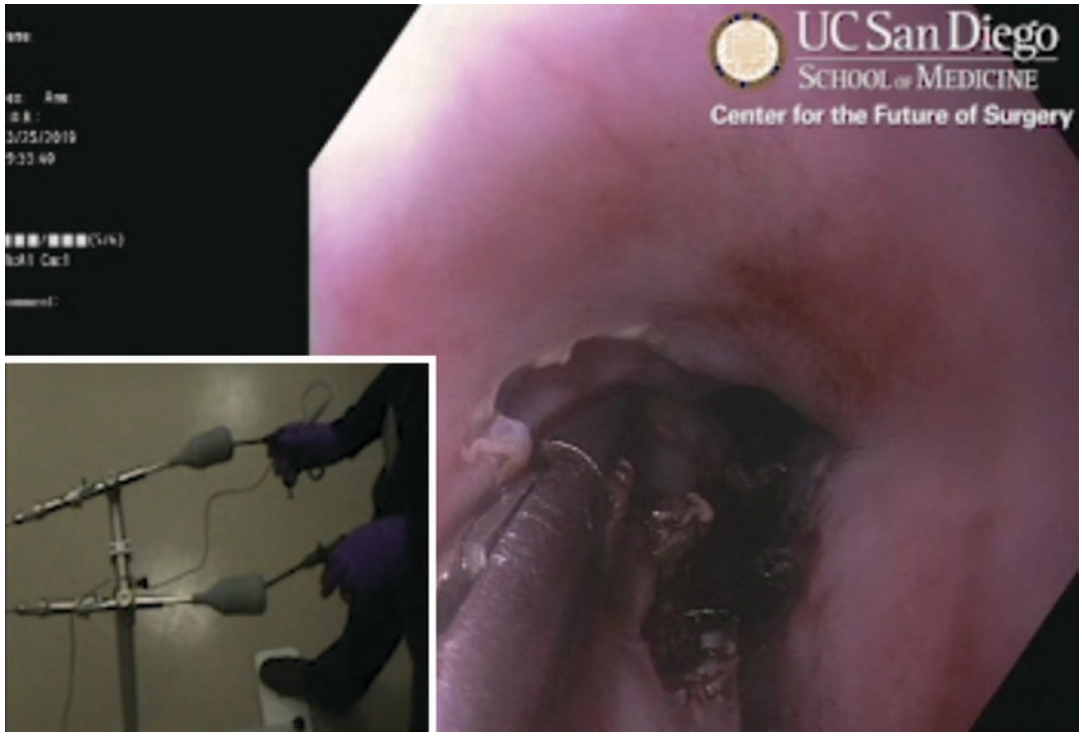

Fig. 23.8 Performing esophageal EMR. Bottom-left picture is surgeon interface during procedure while the main picture shows the endoluminal view of dissection. Left end-effector grasping target tissue for traction, right end-effector performing electrocautery hook dissection of mucosa.

some scenarios [18, 19]. Therefore, our group considered this novel, relatively low-cost endo-surgery solution that may bridge a gap to more advanced robotic solutions. Cost was controlled by relying on existing flexible endoscopes, monopolar generator, and knowledge of articulating instruments from existing laparoscopic technology [15].

Early feasibility tests with the Fortimedix Surgical endo-surgery platform showed that ESD could be successfully performed using flexible scissors, dissection hook, and graspers with good triangulation and sufficient grasping force. Instruments could be exchanged through the system to the target tissue successfully. Despite the narrow space in the gut lumen, the novel endo-surgery platform was able to overcome these limitations with newly designed flexible articulating handheld instruments applied to a standard diagnostic flexible endoscope.

Although the testing sample was small, endoscopic mucosal resection and endoscopic submucosal dissections were able to be performed in entirety with perceived short learning curves. The learning curve is likely partially overcome with prior clinical practice with other advanced endoscopic techniques. The platform seemed to be an easy transition with standard laparoscopic hand and end-effector movements applied to an advanced endoscopic technique.

In the future, both robotic and nonrobotic technologies may be developed in combinations customized for the individual tasks and needs. While robotic systems would provide a potentially more stable platform with many degrees of freedom, current limitations include device and procedural complexity, and high cost. Further development is underway in multiple centers with the potential for advancements in the future.

23.5 Conclusion

The Fortimedix Surgical endo-surgery platform combines a standard flexible endoscope with long, articulating and triangulating instruments. The platform is feasible for use in EMR and ESD of the esophagus and stomach. Further studies are needed and planned to better define the learning curve as well as its efficacy and safety compared to currently available endoscopic techniques.

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24 Techniques and Challenges with the Master–Slave System for Endoscopic Surgery

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24.1 Introduction: Recent Advances in Therapeutic Endoscopy

Over the past four decades, there has been tremendous development in endoluminal therapeutic endoscopy. Since the first performance of endoscopic polypectomy in 1969, therapeutic endoscopy had significant advancement for the treatment of early gastrointestinal (GI) neoplasia [1]. The techniques of endoscopic mucosal resection (EMR) extended endoscopic resection to treatment of early GI neoplasia in upper GI tract as most of these tumors were in flat or slightly depressed morphology rendering simple snare polypectomy not feasible [2]. Despite various techniques of EMR, en bloc resection of early GI neoplasia is limited by the size of specimen obtained using EMR [3, 4]. For GI neoplasia larger than 15 mm, EMR with piecemeal resection would be applied to achieve complete resection, but resulted in high rate of local recurrence as neoplastic cells may remain between resected pieces [4]. The development of endoscopic submucosal dissection (ESD) aimed to improve en bloc resection of early GI cancers through achievement of adequate resection margins [5, 6]. Since the first performance of ESD in Japan, systematic reviews and meta-analysis confirmed the advantage of ESD against EMR for the treatment of early gastric, esophageal, and colorectal neoplasia in terms of lower local recurrence and higher en bloc resection [7–9]. However, ESD resulted in significantly higher risks of complications, including bleeding and perforation. Moreover, ESD is technically challenging as the performance of submucosal dissection was achieved via the ESD device passing over the working channel of the endoscope [10]. There was no countertraction to properly expose the submucosal dissection field, as well as requirement of high skills in steering the flexi-

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ble endoscope to guide the ESD device for precise dissection at the submucosa without damaging the muscularis propria [11]. One of our studies demonstrated that endoscopists encountered more than 60% of perforations during the first performance of ESD training in animal model [12].

To enhance the safe practice of ESD and improve the learning curve, innovative devices and techniques are necessary to achieve exposure of submucosa for clear dissection. Numerous innovative ideas had been applied for the achievement of endoscopic retraction during ESD. Endolifter (Olympus Co Ltd., Japan) was initially developed to allow adequate lifting of the mucosal tumor for ESD [13]. It was not a popular method as after grasping of the mucosa with lifting by device attached to shaft of endoscope, the movement of the endoscope as well as the ESD device will be fixed by the point of mucosal grasping. The use of dental floss attached with a clip aimed to retract mucosa through grasping the cut edge and pulling the dental floss from oral side externally. A prospective randomized study comparing 640 patients on the use of dental floss retraction showed that the use of dental floss significantly reduced perforation after gastric ESD [14]. The pull of dental floss traction to the direction of gastric cardia provided a direct and vertical traction force at the submucosal layer and allowed excellent visualization of dissection line especially for those with dense fibrosis or when bleeding encountered. Other methods to achieve intraluminal traction include the use of clip and rubber band retraction for colorectal ESD [15]. A randomized trial comparing use of SO clip to assist colorectal ESD showed that SO clip retraction significantly reduced procedure time and perforation rate [16]. Although these methods are simple and cost-effective for endoluminal retraction, they are limited by the unidirectional traction as well as inability to reposition. To achieve an adequate repositionable traction through flexible endoscope, it required accurate force translation through tiny manipulators from extracorporeal console deep into the gastrointestinal lumen [17, 18]. Recent developmental and technological advances in flexible endoscopy aimed to achieve endoluminal retraction through mechanically designed platform and robotics-driven mechanisms.

24.2 Novel Endoscopic Platforms for Advanced Endoluminal Procedures

Numerous endoluminal platforms had been developed to achieve tissue retraction and dissection for the performance of endoscopic resections through mechanical design (Table 24.1). Kantsevoy et al. reported a newly developed endoscopic platform (LumenR) (Boston Scientific Co, Ltd., USA) that provides stable intraluminal working space, dynamic tissue retraction, and instrument triangulation to improve visualization and access to the target lesion for en bloc endoscopic submucosal and full-thickness resection [19]. A report demonstrated the feasibility of using this system for ESD of a rectal lateral spreading tumor with excellent exposure and tissue retraction [20]. However, clinical application was limited by the large size of the platform as well as inaccessibility to reach beyond rectum. EndoSamurai, developed by Olympus Japan, was mechanically designed with three working channels targeting at endoluminal tissue manipulation and dissection [21]. Preclinical studies including small bowel resection and anastomosis and endoscopic full-thickness resection (EFTR) were tested with the EndoSamurai [21, 22]. The performance of EFTR was demonstrated to be faster, more precise, and efficient using EndoSamurai compared to conventional endoscope [22]. The Anubiscope was developed at the Institute for Research against Digestive Cancer (IRCAD-IHU, Strasbourg, France) in collaboration with Karl Storz Co Ltd. The design was to achieve triangulation with two mechanically driven flexible arms at tip of a new designed endoscopic platform for the performance of ESD [23]. The Direct Drive Endoscopic System (DDES) (Boston Scientific Co Ltd., USA) adopted similar principles as a mechanical design platform, consisting of three channels with the ability to pass various types of

Table 24.1 Mechanical and robotic flexible endoscopic platforms

Name (company/institution)	Design	Length (cm)	Outer diameter (mm)	No. of instrument channel	Channel size [mm] /(no.)	Preclinical trial	Clinical trial and application
R-Scope (Olympus, Japan)	Mechanical	133	14.3	2	2.8	Ex vivo NOTES (transgastric cholecystectomy/distal pancreatectomy)	Gastric ESD
EndoSamurai (Olympus Japan)	Mechanical	103	15	3	2.8	Ex vivo NOTES (small bowel anastomosis); gastric EFTR	NA
Anubiscope (Karl Storz, Germany)	Mechanical	110	16	3	4.2 (2) 3.2 (1)	In vivo porcine colonic ESD	Transgastric cholecystectomy Transvaginal cholecystectomy
DDES (Boston Scientific, USA)	Mechanical	55	16	3	7 (1) 4.2 (2)	Ex vivo porcine EMR, EFTR, suturing	NA
Incisionless Operation Platform (IOP) (USGI, USA)	Mechanical	110	18	4	7 (1) 6 (1) 4 (2)	Ex vivo porcine NOTES (transgastric cholecystectomy/distal pancreatectomy)	Primary obesity surgery endoluminal (POSE) Transgastric appendicectomy Transgastric cholecystectomy Transvaginal cholecystectomy
STRAS Tele-operated Robot (Karl Storz, Germany, and IRCAD, Strasbourg)	Robotic	55	16	3	4.3 (2) 3.2 (1)	Ex vivo porcine colon ESD In vivo porcine colon ESD	NA
MASTER (NUS & NTU)	Robotic	110	12	2 (dual-channel endoscope)	3.2 (1) 2.8 (1)	Ex vivo porcine stomach ESD In vivo porcine ESD in esophagus, stomach, and colon	Gastric ESD
EndoMaster EASE system (EndoMaster, Singapore)	Robotic	130	14	3		Ex vivo porcine stomach ESD In vivo ESD in esophagus, stomach, and colon	Clinical trial recruiting (clinicaltrial.gov NCT 04196062)
Medrobotics Flex Robotic System	Robotic	25	18	2	4.0 (2)	Ex vivo colon ESD	Transoral ENT surgery
CU Endoscopic Robot (Chinese University of Hong Kong	Robotic	110 (IOP)	18	4	7 (1) 6 (1) 4 (2)	Ex vivo porcine stomach ESD In vivo ESD in stomach	NA

4 mm instruments [24]. The Incisionless Operating Platform (IOP) (USGI Medical, USA) provided four therapeutic working channels with an overtube-like design, allowing passage of an ultrathin endoscope plus large size therapeutic devices such as suturing device for the performance of primary obesity surgery endoluminal procedure (POSE) [25]. At the initial development, clinical NOTES procedures including transgastric cholecystectomy, transvaginal cholecystectomy, and transgastric appendicectomies were performed with IOP [26]. Though these mechanically designed platforms provided the stability and ergonomics to achieve surgical triangulation, there are several limitations in the design [27, 28]. First, the working length of these platforms varies between 55 cm to 100 cm, while the diameter ranged from 14 to 18 mm. The limited length and large size of these platforms are the major constraints for clinical application inside the gastrointestinal tract, which typically has either long length or narrow space. Second, numerous endoscopic platforms were designed to target on natural orifices transluminal endoscopic surgery (NOTES). There are several intrinsic limitations to the performance of NOTES that challenged engineering design. For example, transgastric cholecystectomy required the flexible endoscope to achieve more than 90 degree of angulation in order to reach the target gallbladder through the stomach. Even with the safe access by submucosal tunneling, the ergonomics to operate through flexible endoscopic platform at an angulation was terribly difficult.

Currently, development in endoluminal surgery has been focusing back to the lumen [29]. With the advances in third space endoscopy, per oral endoscopic myotomy (POEM) and submucosal endoscopic tumor resection (STER) had been successful in treating achalasia and gastrointestinal subepithelial tumors, respectively [29–31]. While the performance of advanced endoluminal procedures including ESD, POEM, STER, and EFTR required high skills of manipulation, intensive training is required for endoscopists to master these procedures without complication [12, 32]. The application of robotics-driven mechanisms allows improvement in precise control and force translation to overcome the design constraint of a flexible endoscopy within the gastrointestinal lumen [17, 18]. In one of our ex vivo porcine stomach ESD studies using robotic endoscopy, there was no difference between expert ESD endoscopists, endoscopists, and novice in completing the ESD procedure using Master and Slave Transluminal Robotic System (MASTER)[33]. This demonstrated the advantage of endoluminal robotics for complex therapeutic procedures. The following section explores the current applications of robotics for endoluminal surgery.

24.3 Master and Slave Transluminal Endoscopic Robot (MASTER) for Endoluminal Surgery

The technology of robotics was first introduced to surgical application in 1985 when a robotic system was used to insert needle for brain biopsy under CT guidance [34]. Subsequently, a robotic manipulator named AESOP was developed by Computer Motion for control of laparoscope [35]. In 2000, da Vinci Surgical System was approved by the US FDA for clinical application in general laparoscopic surgery [35]. The advantage of robotic surgical system is the ergonomics and precision in achieving complex surgical tasks within a confined body cavity, as illustrated by the performance of robotic prostatectomy with precision in suturing the urethra within the pelvis [36]. There is similarity in the precision required within the gastrointestinal lumen for tissue retraction and manipulation, hence the development of flexible robotics should be targeting at achieving tissue retraction deep within the gastrointestinal lumen as well as catering for size and physical constraints [37].

The Flex Robotic system (Medrobotics, Raynaham, MA, USA) was developed for the performance of transoral head and neck procedures [37]. Upon modification, it was cleared by the US FDA for clinical application for lesions up to 25 cm from anal verge, in oropharynx, hypopharynx, and larynx. In an ex vivo model

experiment, the system was applied for the treatment of Zenker's diverticulum, robotic-assisted ESD, and endoscopic full-thickness resection with closure by suturing. Most of the clinical procedures reported using the Flex Robotic system were on transoral surgery [38] as the design of Flex Robotic system focused on robotic manipulation of the endoscope while the instruments are mechanically driven. One study reported the feasibility of transanal total mesorectal excision using Flex Robotic system in six cadaveric models [39]. The system achieved TaTME for mid-rectal lesions but failed for low-rectal lesions due to difficulty in maneuvering instruments in close proximity to rigid transanal port, illustrating the limitation.

The STRAS is a robotic endoscopic system designed basing on the Anubiscope platform (Karl Storz, Tuttlingen, Germany) [40]. The design is based on a master console for control of the robotized instruments and slave cart for the attachment of the endoscopic platform. The STRAS system was tested in eight live porcine models for the performance of colorectal ESD. A total of 12 ESD were performed successfully at locations 10–25 cm from anal verge. There were technical issues encountered, including failure of adequate insufflation due to gas leak from instrument channel [41]. The robotic system sustained broken wire in the electric bundle for one of the procedures, while electric insulation failed in two procedures. These are indeed important issues related to flexible master and slave robotic systems upon clinical application.

The first prototype Master and Slave Transluminal Endoscopic Robot (MASTER) was developed with a human–master robotic interface, a telesurgical workstation, and a slave manipulator [42]. This first prototype consisted of two robotic manipulators, one as a tissue grasper and another as monopolar diathermy hook dissector, mounted on a double-channel therapeutic endoscope. The MASTER was developed and tested in numerous preclinical studies for the performance of gastric ESD [43, 44] (Fig. 24.1). In our preclinical testing, we demonstrated that the use of MASTER robotic system allowed even novice with no experience of endoscopy to complete ESD procedure [33]. The first multicenter cohort study on the clinical performance of gastric ESD by MASTER robotic system for the treatment of early gastric neoplasia was done in five patients [45]. The operative time for robotic gastric ESD ranged from 26 to 68 minutes while all resected speci-

Fig. 24.1 EndoMaster EASE system. (EndoMaster Pte Ltd., Singapore)

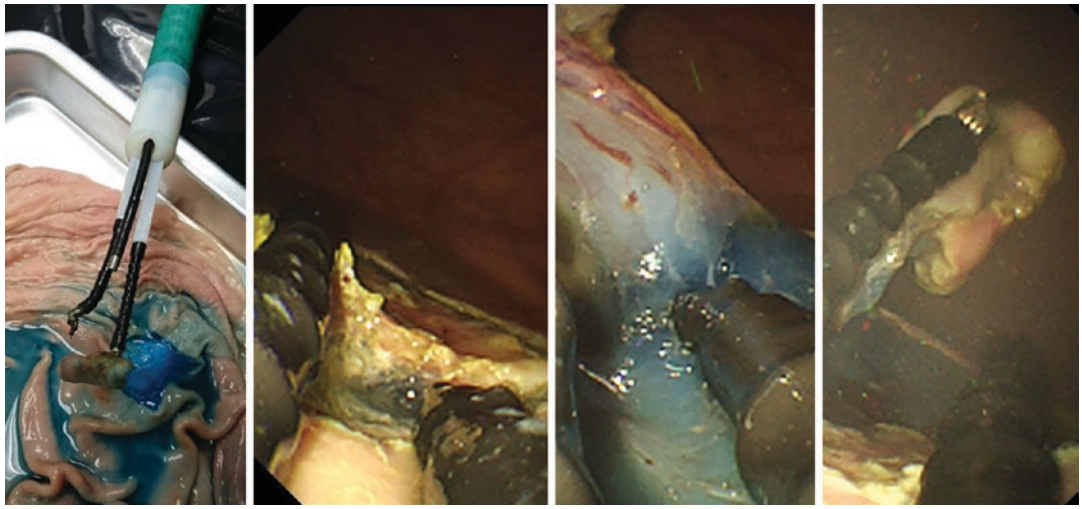

Fig. 24.2 Endoscopic Surgical Robotic System. [Prototype robotic arm (Chinese University of Hong Kong) on Incisionless Operating Platform (USGI Medical, USA)]

mens demonstrated clear resection margins. The feasibility and safety of endoluminal robotics was demonstrated in the first clinical study. However, there are certain limitations with MASTER, including the constraint of building the robotic arms within the conventional double-channel endoscope. The EndoMaster EASE system is developed as a second generation of MASTER where the endoscopic platform was redeveloped with three working channels and build-in optics. The two robotic arms were strategically placed to allow best ergonomics for retraction and dissection. This new EndoMaster EASE system had been tested in preclinical studies to confirm the efficacy and safety in performing ESD within esophagus, stomach, and colon [46, 47]. The system will be further refined and prepared for clinical trial in the performance of robotic colorectal ESD.

Taking a different approach, our team developed a flexible endoluminal robotic system building on the existing platform of Incisionless Operating Platform (IOP, USGI Medical, USA) [48] (Fig. 24.2). The two independent robotic arms consisted of a grasper and dissection knife, which are designed for tissue lifting and submucosal dissection. A flexible ultrathin endoscope would be passed through another channel of the IOP for provision of endoscopic view for submucosal dissection. From the ex vivo model, the mean time for completion of 20 mm ESD was only 23 minutes for expert endoscopists using this robotic endoscopic system.

24.4 Future Development for Endoluminal Robotics

Recent advances in therapeutic endoscopy allowed performance of endoscopic full-thickness resection (EFTR) for the treatment of early gastrointestinal neoplasia with dense submucosal fibrosis as well as subepithelial tumors [49]. A systematic review included 750 patients from 15 studies who received endoscopic full-thickness resection for treatment of gastric lesions. The mean size of tumor was 2.04 cm, and these tumors included GIST, leiomyoma, as well as schwannomas. The analysis showed that conversion to surgery was only 0.8%, while the reasons for conversion include difficulty in endoscopy closure of wall defect, intraprocedural tumor fall into peritoneal cavity, large size, as well as difficult dissection. Some of these issues could be overcome by endoluminal robotics, for example, the difficulty for dissection may be enhanced using a robotics-driven retraction and dissection [50].

Moreover, closure of the defect after EFTR can be technically difficult especially when the defect is large. One of the possible solutions is to perform endoscopic suturing during full-thickness resection [51]. In this cohort of four patients with gastric GIST, EFTR was performed in a sequential manner with endoscopic suturing at the base of the tumor to achieve duplication of gastric wall and avoid perforation. This small case series showed no perforation with 100% complete resection. One of the major difficulties in the manipulation of endoscopic suturing device is the limitation in degree of freedom. The suturing over the defect after EFTR needs to be organized in the optimal position for the needle to pass in catching the full thickness, while the knotting mechanism relied on shortening of the suture rather than the conventional surgeons' knot. Cao et al. reported the performance of endoscopic suturing using a novel-designed robotic platform equipped with separate needle driver and grasper [52]. The robotic instruments had five degrees of freedom, which allowed targeting the tissue cut edge at the right angle without steering of the endoscope, as well as triangulating each other for knot tying. It will have great anticipation on clinical application of endoluminal robotic suturing, especially for the performance of EFTR, endoscopic sleeve gastroplasty, as well as management of gastrointestinal emergencies including bleeding peptic ulcer and perforation [53–55].

24.5 Summary

The technological advancement in flexible robotics allowed the development of master and slave endoluminal robotic systems for the performance of endoscopic submucosal dissection. Preclinical animal studies confirmed the feasibility and safety of these endoluminal robotic surgical systems in the preparation for clinical trials. In future, development of robotics-driven flexible instrumentations including suturing devices should allow the performance of further complex procedures such as endoscopic full-thickness resection and sleeve gastroplasty.

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Transgastric Intra-abdominal Surgery

25

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25.1 Introduction

Upper gastrointestinal endoscopy has developed in the past 50 years from a diagnostic procedure to a major therapeutic option in gastrointestinal diseases [1–4]. Interventional endoscopy has provided technical prerequisites to expand the indications for endoscopic mucosal and tumor resections in the gastrointestinal tract [1–4]. The increasing experience with endoscopic mucosal resections and endoscopic tumor resections has paved the way for more sophisticated endo-surgical procedures. A remarkable step in this development was the introduction of a planned peritoneoscopy and exploration of the abdominal cavity by Kalloo [5]. Subsequently, the hype of natural orifice transluminal endoscopic surgery (NOTES) emerged as a development of ideas originating from interventional endoscopists and gastroenterologists with a "surgical spirit" to move the limits of flexible endoscopy further [6, 7]. On the other hand, the process was supported by gastrointestinal surgeons to expand the possibilities of minimal access surgery and perform many preclinical studies [6–14].

After the initial hype of fantasies about performing intra-abdominal surgery via flexible endoscopes, followed by a critical phase of reflections and of intensive work in several dedicated centers, the concept of NOTES has become a clinical reality despite complex problems and technical limitations [6, 7, 15–19]. NOTES stood for a reduction of access trauma by approaching the abdominal cavity through natural orifices, which further reduced the access trauma [19]. Hybrid solutions enabled additional but limited access via the abdominal wall by reducing number and size of ports [18, 19]. In hybrid procedures, transabdominal trocars are used in limited number and limited size in order to facilitate, assist, and/or enable the maneuvers through the natural orifice via graspers for better retraction, exposure, and/or delivery of rigid energy devices. Despite the fact that transabdominal instruments will limit somewhat the possible positive effects, hybrid procedures increase usually patient safety by facilitating the use of experienced and safe laparoscopic techniques.

These new ideas followed the principle of minimal access surgery, that is, a reduction of access size and access trauma aiming for a shorter patient

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recovery, improved postoperative well-being, better cosmesis, and less inhibiting postoperative restrictions [18, 19]. The transgastric route was the most favorable approach by gastroenterologists and initially also by the surgeons [18, 19].

25.2 The Transgastric Routes and Techniques

In general, transgastric access can be separated in two major access routes: one is the transgastric approach from inside the gastric lumen to the intra-abdominal cavity by flexible endoscopic means as a major focus of this chapter (Fig. 25.1) [9–14]; the second approach is the transgastric route from outside the body through the abdominal wall and in addition through the gastric wall inside the gastric lumen (Fig. 25.2) and sometimes even further, for example, transhepatic into the biliary tree [20–25].

The combined transabdominal and transgastric technique has been initially used in the placement of a percutaneous endoscopic gastrostomy (PEG). This technique is used quite frequently today for special indications such as resection of cardia tumors or procedures at the biliary tree in combination with transgastric and transhepatic access [26, 27] (see other chapters). It has been performed for gastric wall tumors, where laparoscopic techniques and flexible endoscopic techniques are combined in assisting each other in whatever combination is more advantageous for the advancement of the procedure [27].

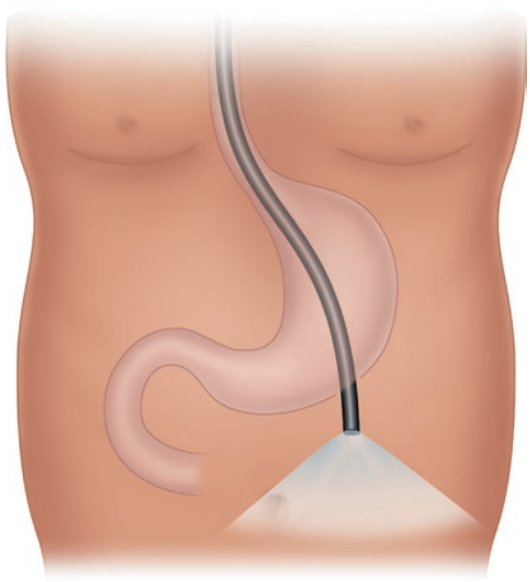

Fig. 25.1 Scheme of transgastric endoscopic technique using a flexible endoscope to advance from intragastric lumen through the gastric wall into the abdominal cavity

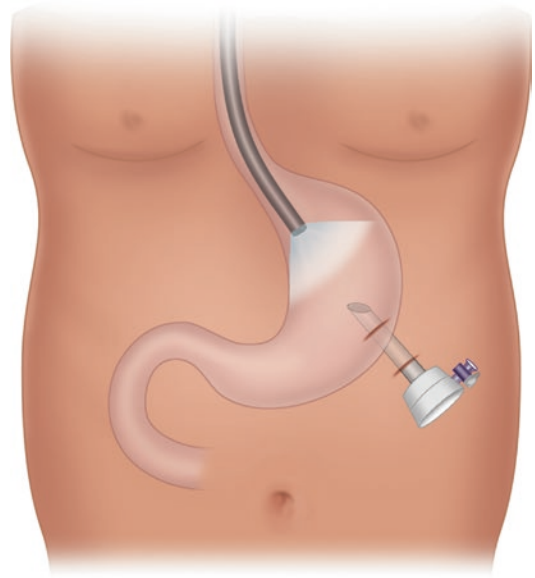

Fig. 25.2 Scheme of combined transabdominal and transgastric technique, using flexible endoscope to insufflate the stomach and subsequently penetrating with a transabdominal trocar into the gastric lumen under endoscopic guidance

A more recent development is the laparoscopic and transgastric route to treat esophageal disease such as tumor resection and myotomy [22, 23]. The transgastric, therapeutic procedures at the pancreas were introduced many years ago; recently, the laparoscopic-assisted and transgastric techniques for the treatment of problems at the biliary system have been added [27–29] (see other chapters).

A major focus of this chapter is the transluminal technique of endoscopic procedures through the gastric wall into the abdominal cavity (Fig. 25.3). Initially, there was a certain fear for contamination of the peritoneum and subsequent

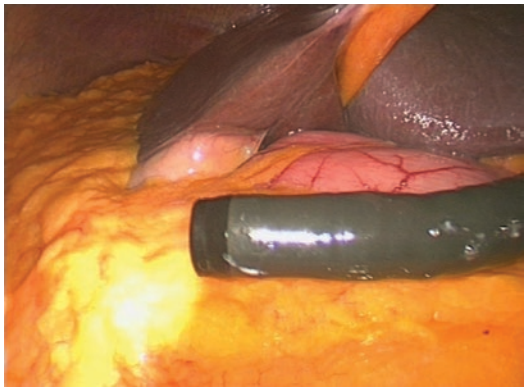

Fig. 25.3 Intra-abdominal view of a transgastric peritoneoscopy, which shows a flexible scope exploring the abdominal cavity. Contamination of the peritoneum is increased, but infection rate is minimal

intra-abdominal infections [5, 6]. Important information came from Narula, demonstrating a rise in bacterial contamination parameters in the peritoneal cavity after opening the stomach; however, no severe complications from infections were observed [30–32]. The infection rate in experimental series ranged between 0% and 16% [30–32]. However, clinical experience showed no increased level of infections if the rules were followed as pointed out in the recommendations for transgastric procedures [17–19]. The endoscopes must undergo a high-level disinfection in a commercial washing machine. Sterile end-effector instruments at the tissue level must be used. In addition, the procedure should be performed under routine sterile conditions with gowns, drapes, and gloves in order to keep contamination low. Prevention of infection is performed by an intravenous antibiotic prophylaxis prior to surgery [17–19]. During the procedures, sterile fluids, water, and tube connections must be used. The acid environment of the stomach must be preserved by discontinuing Proton Pump Inhibitors (PPI) a week before surgery, if applicable.

The transgastric transluminal approach from the gastric lumen toward the peritoneal cavity can be achieved by the penetration of a guidewire from the gastric lumen and subsequently a bouginage widening of the opening until passage of the endoscope is possible. An alternative is an incision of the gastric wall under vision from the scope and subsequent passage of the scope in the abdomen [33].

The transluminal "tunneling technique" was initially introduced by Pasricha as a transgastric and transesophageal access technique to the abdominal cavity [34]. The most popular indication is the per-oral endoscopic myotomy (POEM) and in associated procedures [35–38].

Several closure techniques have been established quite successfully for the different approaches, such as closure with an over-the-scope-clip, closure with laparoscopic mini-instruments, and the overstitch technique [39, 40].

25.3 Indications for Therapeutic Procedures Involving the Transgastric Access

The transgastric access was initially thought to be an ideal way to enter the abdomen since it was thought to be quite easy to have a safe closure of thick gastric wall. The access has been tested for several indications such as peritoneal exploration, appendectomy, cholecystectomy, ovarian tube ligation, small bowel tumor resection, and gastric tumor resection [6–14]. Despite a tremendous effort of many teams to establish these techniques in clinical practice, the latter indications are not established. Reasons for this are the technical limitations of flexible endoscopy in the abdominal cavity. The problem is the lacking strength of traction and countertraction, limitations in movements, and poor steering abilities of the flexible scope [7, 11, 14, 17]. In addition, several multitasking platforms were developed by industry, but never reached the quality level of a commercially available product [19].

As a consequence, the transgastric route and associated techniques are currently only used for full-thickness gastric wall resections with increasing success specially in the Asian countries because of the higher number of cases.

A few clinical studies have been performed with cholecystectomy, staging peritoneoscopy, and appendectomy [41–45]. Transgastric cholecystectomy is quite time consuming and seems to

be technically very demanding compared to the transvaginal cholecystectomy, which has proved to be successful [41–46]. Transgastric appendectomy has been studied in a clinical trial [47]. Table 25.1 demonstrates the published experience, the complication rates, and success rate of transgastric procedures [31, 32, 43–55].

There is no doubt that these new techniques should be trained in the preclinical setting and extensive experimental work is needed, before taking these techniques to the patient [7, 19]. The safe performance of these procedures requires an increased experience and mental work load than traditional minimally invasive surgery [56].

25.4 The Operative Access Technique

The technique of transgastric access was trained in our team very extensively in the porcine animal model with over 100 experimental operations before the first case was done in humans [57]. Prior to the clinical application of this technique, an approval was gained from the hospital directory board and later from the Institutional Review Board of the Hospital.

Extreme care was taken to select patients with an adequate status excluding severe risk factors and a well-balanced indication for surgery. The special circumstances were outlined to the patients, and it was made sure that the individuals understood the explanations.

The first technical step of transgastric procedures is a patient in supine position under general anesthesia. Prophylactic antibiotics are administered with cephalosporins and metronidazole. A flexible endoscope is through the esophagus into the gastric lumen, and it is verified that the upper gastrointestinal tract is empty in order to prevent food and fluid to escape and contaminate the peritoneal cavity.

Then a capnoperitoneum is established in the traditional laparoscopic technique with all safety tests and a 5 mm trocar is placed periumbilical, followed by the positioning of a 5 mm camera to explore the peritoneal cavity. Then the view is focused on the stomach in order to observe the safe penetration of the flexible endoscope through the gastric wall.

With a needle knife, applied through the working channel of the flexible endoscope, a gastrotomy is performed with monopolar current at a preferable site usually in the antrum (Fig. 25.4a and b). The gastrotomy site is best placed in the mid-antrum on the anterior gastric wall, as studied in the experimental model (Fig. 25.5a and b). This position of penetration allows for an optimal position and guidance of the flexible scope to explore the lower part of the abdomen as well as have a sight on the upper quadrants in retroflexion.

Bleeding can occur during the gastrotomy from vessels of the gastric wall. It is important to quickly continue with hemostasis either with the needle knife or with a coagulating grasper. It is also very important to make sure and have laparoscopic guidance for the flexible endoscopist to stay away from the epiploic vessels to prevent major bleedings and damage.

Having finished the gastrotomy, the endoscope should be directly advanced through the opening into the peritoneal cavity because with the opening the stomach deflates and intragastric vision can become difficult. An alternative to direct endoscopic gastrotomy is the penetration of a guidewire into the abdominal cavity and a subsequent dilatation of the opening with a dilatation balloon, followed by the passage of the scope.

If a laparoscope is in position to observe the endoscopic steps, this hybrid approach allows for more safety for the patient. The safety of the laparoscopic component of hybrid techniques has overcome some of the limitations of pure flexible endoscopic technology. In hybrid procedures, transabdominal trocars are used in limited number and limited size in order to facilitate, assist, and/or enable the maneuvers through the natural orifice via graspers for better retraction, exposure, and/or delivery of rigid energy devices.

In the peritoneal cavity, flexible endoscope can be used for exploration of best of the lower abdominal quadrants. Upper quadrants are hard to reach with flexible endoscopes in retroflexion

Table 25.1 Results of transgastric NOTES procedures

Authors	Transgastric procedure	*n*	Complications	Access problems	Successful completion; number of Trocards
Narula 2009 [24]	Peritoneoscopy	10	0	0	100% 1
Dallemagne 2009 [61]	Cholecystectomy	5	0	0	100% 1
Salinas 2010 [62]	Cholecystectomy	27	Morbidity 18% Mortality 0	0.0	100% 1
Nikfarjam 2010 [32]	Peritoneoscopy	9	1 infection at gastrotomy	0	100% 1
Nau 2011 [25]	Peritoneoscopy	40	0	0	100% 1
Zheng 2011 [33]	Peritoneoscopy	5	0	0	100% 1
Dotai 2012 [63]	Sleeve gastrectomy + organ extraction	28	7,1%	14%	100% 1
Perry 2012 [64]	Peritoneoscopy in obese	10	0	20%	80% 1
Kähler G 2013	Appendectomy	15	13%	6,6%	93% 1
Harnsberger C, 2014 ()	Appendectomy cholecystectomy	10	0	20%	80% 1
Breithaupt W 2014 ()	Small bowel/gastric tumor resection	10	10%	10%	90% 1
Wang x 2016 ()	Liver cyst fenestration	4	0	1	75% 1
Hornemann 2017	Salingectomy	6	0	1	100% 1
Schwaitzberg S 2018	Cholecystectomy	4	0	1	75% 1
Li Y 2020 ()	Gall bladder polypectomy	1	0	0	(100%)

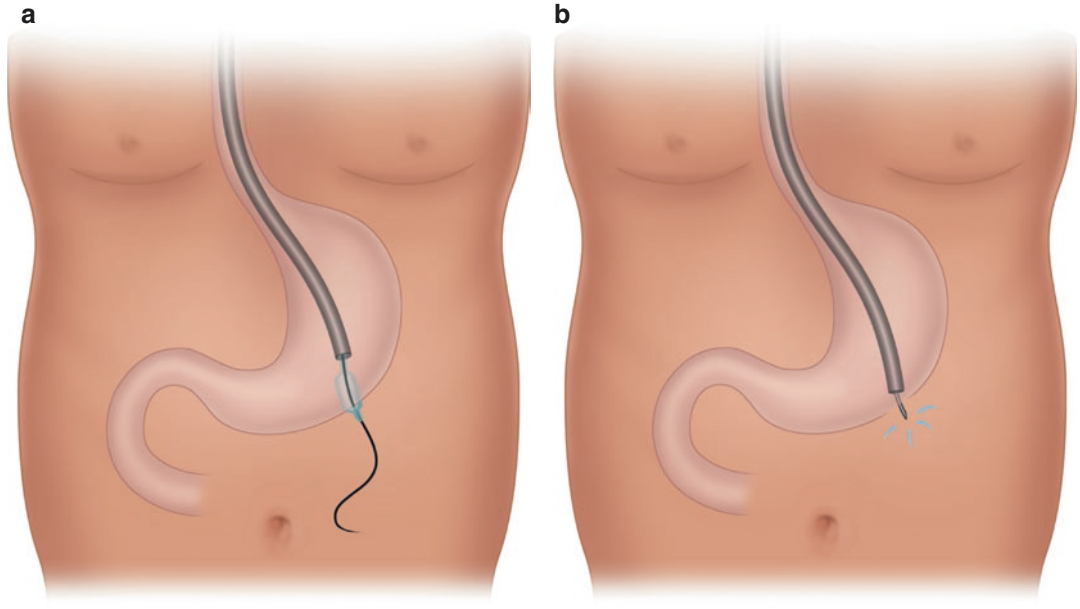

Fig. 25.4 Scheme of two different techniques of endoscopic gastrotomy: (**a**) first, a guidewire is placed through the gastric wall, followed by a balloon dilation to facilitate the passage of the scope; (**b**) a direct incision is performed under endoscopic vision with a needle knife and then the endoscope is passed through the opening into the abdominal cavity

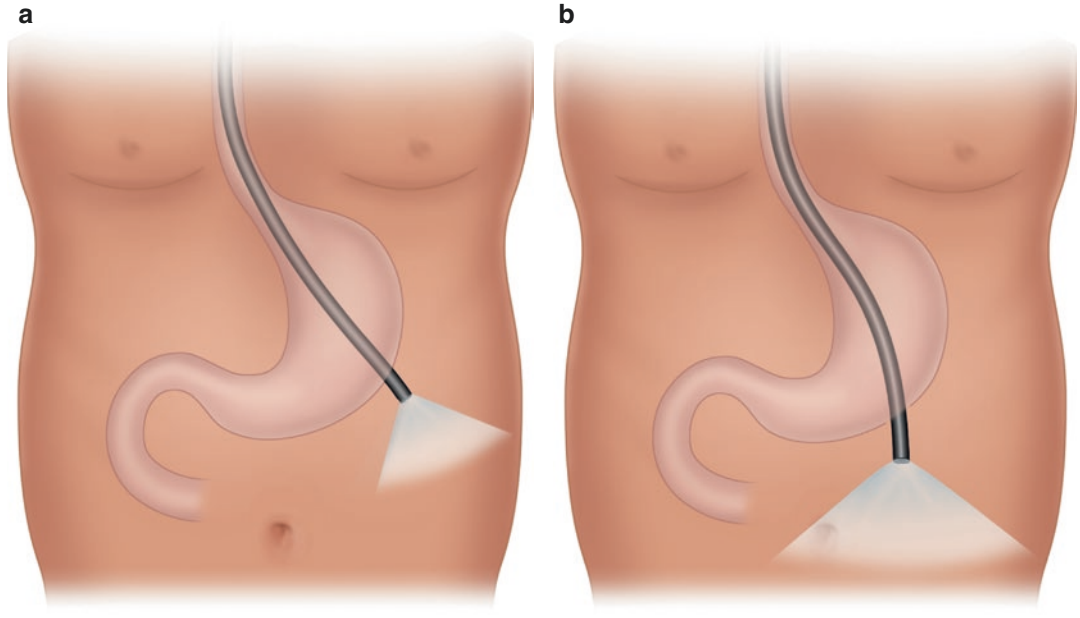

Fig. 25.5 Scheme of two different sites of transgastric penetration of the flexible endoscope, which will lead to possible different target areas of exposure within the abdomen, since the penetration site at the greater curvature will influence the pathway of the flexible scope. (**a**) left lateral penetration will best allow for left lower quadrant exploration and limited exploration of the left upper quadrant; (**b**) penetration in the lower portion of the antrum will enable exploration of both lower quadrants

and hybrid endoscopic antireflux procedures, cardiomyotomies, and other procedures investigated in the upper quadrants of the abdomen, but have been abandoned in this technique.

With changing position of the operation table and the patient, the exploration can be expanded. Indication for therapeutic procedures can be resection of small tumors of the stomach, the small bowel and other locations, the ovarian tube ligation, and/or resection of pelvic lesions. Bowel resection can always be performed in the hybrid technique with transabdominal stapler applications and transoral specimen retrieval.

The closure of the stomach is the crucial technical step for the safety of the patient. Contamination of the peritoneal cavity occurs with the transoral use of the endoscope. However, experimental and clinical experience has shown that contamination has only a very limited influence on intra-abdominal infection and the most important issue in the field is a safe and dependable closure technique of the gastric wall [7, 19, 30–32].

25.5 Transgastric Peritoneoscopy

The most thorough investigations and preparations to establish the transgastric endoscopic technique were performed by the group from the "Ohio State University" [58]. This group has very systematically investigated open questions around technique, risk of contamination and infection, and possible safeguards in the initial years. Based on the technique of Kalloo, they have used a single-channel flexible endoscope to advance into the stomach [5]. Next, a needle knife papillotome was used after the selection of an appropriate spot for penetration of the endoscope. Usually a small gastrotomy is sufficient to pass a Jagwire through the opening into the abdominal cavity. Using the Jagwire, a wire-guided balloon dilator was passed and fitted into the opening during dilation, followed by the passage of the endoscope into the abdominal cavity.

The muscular wall of the stomach is adequate to take the forces of the passing and moving shaft of the endoscope within the gastric opening, associated with the procedure and, in addition, allowing for a sufficient closure later on.

Important to the indication of peritoneoscopy is the possibility of total exploration of the peritoneal cavity and all organs. A few studies showed a sufficient visualization of the abdominal structures by a flexible endoscopic peritoneoscopy compared to a laparoscopic exploration [32, 59].

25.6 Transgastric Cholecystectomy

Several groups of investigators have trained and performed a transgastric and transvaginal cholecystectomy [17–19, 41–45]. However, transgastric cholecystectomy turned out to be technically very demanding with the insufficiencies of available flexible endoscopes [41–45]. The introduction of transvaginal cholecystectomy was quite successful and led to a halt in any further clinical investigations regarding transgastric cholecystectomy [60–62]. After this initial experience, it was very hard to establish a randomized comparison between the routine, state-of-the-art laparoscopic cholecystectomy with transgastric version.

A working group of NOSCAR® established a study protocol and performed the initiation of a prospective randomized clinical trial comparing NOTES® cholecystectomy as an alternative procedure to laparoscopic cholecystectomy [54]. Ninety patients were randomized with the primary objective of demonstrating noninferiority of the transvaginal and transgastric arms to the laparoscopic arm. In the initial design, there were both transgastric and transvaginal groups to be compared to the laparoscopic control group. However, after enrollment and randomization of six laparoscopic controls and four transgastric cases turned out to be not practical due to lagging enrollment, the arm was closed. The limited transgastric approach was performed and compared with nine laparoscopic control cases enrolled through the transgastric arm. In total, 41 transvaginal and 39 laparoscopic cholecystectomy controls were randomized into the study with 37 transvaginal and 33 laparoscopic chole-

cystectomies being ultimately performed. The results were basically only relevant for the transvaginal group since there were too few patients after transgastric cholecystectomies. There were no major adverse events such as common bile duct injury or return to the operating room for hemorrhage. The technique of transgastric cholecystectomy was not continued worldwide since it was too cumbersome and time consuming with the available technology.

25.7 Transgastric Small Tumor Resection

The resection of small tumors in the gastric wall or the wall of the small bowel can be considered as a quite valuable indication for minimal invasive therapies. Today, many of these tumors are resected by flexible endoscopic techniques such as endoscopic mucsal resection (EMR), endoscopic submucosal dissection (ESD), and endoscopic full-thickness resection (EFTR) [4, 40]. In somewhat larger size tumors, a transgastric approach is justified often with the intention to resect a complete segment of the bowel [52, 57].

Tumors within the stomach area, even an unfavorable position at the posterior wall or at the smaller curvature, can be resected by transgastric endoscopic techniques using a full-thickness resection technique, if necessary, under laparoscopic assistance and the tumor can be removed transorally. Closure could be performed in combination with endoscopic and laparoscopic techniques.

Tumors in the small bowel could be identified and localized by transgastric endoscopy. A standard endoscope is used to incise the gastric wall with a needle knife and subsequently the endoscope is passed into the abdominal cavity, exploring the situs and identifying the tumor at the small bowel. A combined transabdominal, endoscopy-assisted stapler resection of a small bowel segment is probably advisable depending on tumor size and location as well as the anastomosis (Fig. 25.6). Specimen retrieval can be managed transesophageally and transorally.

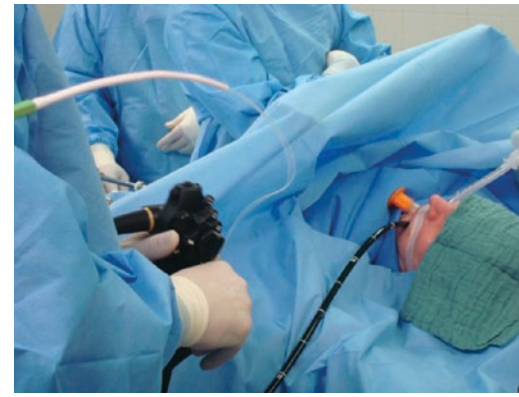

Fig. 25.6 Scene of a hybrid laparoscopic-assisted, endoscopic, transgastric resection of a small bowel tumor. A surgeon is helping with transabdominal stapler application via a trocar, while the endoscopist is dissecting via transgastric route the small bowel mesentery

25.8 Transgastric Appendectomy

An appendectomy can be usually a rather simple surgical procedure since it does not require a major organ resection nor a sophisticated dissection. However, a transgastric procedure requires a rather complicated technique with flexible endoscopy, in which the surgeon is often not trained. The latter creates a number of difficulties. The nonelective character of an appendectomy is also a limiting factor. In preparation of a randomized trial, the Mannheim study group did substantial preclinical testing [47, 63]. For ligation of the tubular structure of the appendix, an absorbable loop for flexible endoscopes was developed and could be applied through a flexible scope. All patients diagnosed with acute appendicitis were screened for contraindications for transgastric appendectomy. The diagnosis of acute appendicitis was based on clinical examination, laboratory tests, and ultrasound investigations.

Details of the procedure were published [47, 62, 63]. After induction of a general anesthesia, the patient was positioned on a vacuum mattress to facilitate extreme positioning during the procedure. Prior to the operation, a single-shot anti-

biotic prophylaxis was administered, consisting of 500 mg ceftriaxone and 500 mg metronidazole. The procedure was performed using a double-channel therapeutic gastroscope (Karl Storz PV-TG 2).

The procedure began with a gastroscopy to exclude abnormalities in the esophagus and stomach. Then a passage was created via guidewire and a balloon at the anterior wall of the gastric corpus. The gastroscope was advanced into the peritoneum and a capnoperitoneum established. Patients were positioned in a Trendelenburg position for better exposition of the caecum. A trocar was inserted in the umbilicus under endoscopic control. The appendix was then pulled with a grasper and the dissection of the mesoappendix was performed using a needle knife. Ligation of the appendix was carried out using specially developed loops [63]. The appendix was then grasped and extracted via the esophagus. The closure of the stomach was performed with an over-the-scope-clip (Ovesco Endoscopy AG, Tübingen, Germany). In a series of 36 patients, there were no problems with gastric access. No damage of neighboring organs occurred. Due to severe inflammation or a different diagnosis, conversion was necessary in five cases to laparoscopy and in two cases to laparotomy [63].

The authors concluded that their experience series suggests transgastric appendectomy to have the potential of a routine procedure in an academic hospital after an adequate preparation [47, 62–66].

25.9 Comments

Since training is an important issue, training programs must be established to educate surgeons and gastroenterologists in these new procedures. Training is important to explore the technical difficulties and find solutions. One can start a training program with commercially available instruments to gain experience in navigating with a flexible endoscope in the abdomen, exposing different organs in the abdomen as well as retracting and dissecting tissue [7, 16–19, 33, 57]. The team can train operative techniques, which are daily indications in gastrointestinal surgery. From the limitations and problems of these training sessions, one can learn to improve the operative steps as well as improve the currently available instruments. Mechanical support to create a stable platform for action of the flexible scope, for example, to retract the fundus of the gall bladder can be a large problem. It could be overcome by an additional rigid segment in the endoscope. This can be compensated for by using hybrid technology with laparoscopic-assisting forceps. The technical shortcomings of flexible endoscopic technology are summarized in several articles and chapters [16–19].

Great concern was involved regarding a safe closure of the gut, and there was initially a substantial fear for possible complications similar to the infection issue [6, 7]. Several prototypes of suturing devices were developed by industry and experimentally evaluated [7, 8, 11, 13, 14, 19]. Unfortunately, some of the promising tools such as the flexible stapling devices were withdrawn from the market. Some startup companies with interesting products went out of business. Other developments such as the over-the-scope-clip have emerged toward valuable instruments with a well-established role in clinical practice [11, 18, 39, 40]. Some suture devices and preliminary platforms were used successfully in selective centers [39, 40].

As a consequence, safe closure is possible today in all access routes with rather simple technical and new conceptional means [39]. The complication rate of the clinical experience with transluminal procedures is quite low, indicating a safe closure for the different approaches [19].

For the transgastric technique, there is no real "killer application" such as myotomy for the esophagus. The limited gastrotomy can be closed quite safely with the over-the-scope-clip technology [40]. If there is a larger opening in the gastric wall after resection of a gastric wall tumor, either endoscopic suturing devices or hybrid technology with laparoscopic stapling closure is necessary [39]. In Asia, gastric wall

tumors are more frequent. Therefore, a growing experience exists in Japan, Korea, and China on these rendezvous procedures between endoscopic and laparoscopic techniques. More complex procedures such as partial bowel resection can be performed via the transgastric approach with current available techniques and instruments [19, 44, 47, 49, 52]. In recent years, also clinical experience with gynecological procedures emerged using the transagstric route for endoscopic salpingo-oophorectomies [67]. In addition, experience with transgastric-assisted gastrojejunostomy was published using a magnetic system for anastomoses [68].

Transgastric procedures are new for laparoscopic surgeons as well as for gastroenterologists. Gastroenterologists expand their endoscopic repertoire by using the transgastric route for endoscopic techniques at the biliary system [69]. Both can benefit from learning these techniques together, especially from encountering certain problems that require a solution, which can have elements from surgical and endoscopic background. Transgastric access techniques and intra-abdominal procedures are very complex and will need extensive training in order to apply in a safe way to patients. The potential of this approach has not been explored and exploited sufficiently and will need further work in the future.

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Endoscopic Platforms

26

Alexander Meining

26.1 Background

Endoscopic resection of lesions larger than 2 cm in size or early stages of cancer can be challenging for the interventional endoscopist. Endoscopic mucosal resection (EMR) has been widely accepted as an effective and minimally invasive treatment for patients with large gastrointestinal adenomas. Endoscopic submucosal dissection (ESD), can be considered for en bloc resection of early cancers in the gastrointestinal (GI) tract. However, ESD is very time consuming, difficult to learn, and bears a higher risk for perforation. To overcome these limitations, bimanual resection enabling traction and countertraction during resection appears helpful. To enable these tasks, several versions of endoscopic platforms have been developed, designed, and manufactured. These include very simple tools, such as dual-channel endoscopes or additional working channels (AWC) attached to an endoscope, but also rather complex versions such as robotic master–slave systems. All these platforms are aimed to enable a more effective resection of early lesions [1, 2]. Some of these devices have been already proven effective in a clinical setting; however, overall data are sparse and there are still several limitations. The present review mentions available systems and summarizes their respective pros and cons. Finally, future perspectives with room for potential improvement in developing endoscopic platforms will be discussed.

26.2 Currently Available Platforms

26.2.1 Nonmechatronic Platforms

If endoscopic platforms were defined by enabling traction and countertraction for endoscopic resection, the simplest platform would be a dual-channel endoscope. However, dual-channel endoscopes are limited due to the fact that despite two instruments may be introduced these can only be moved very close to each other in a parallel manner. Hence, although the so-called grasp-and-snare technique has been introduced decades ago [3], the wider distribution of the technique has been hampered by the fact that due to the limitation as mentioned before resection remains clumsy, risky, and far away from ideal surgical principles such as holding the lesion with one instrument and simultaneously cutting the lesion with another instrument.

The next step to overcome these limitations was to develop, design, and manufacture an additional working channel (AWC, Ovesco, Tübingen, Germany) that might potentially enable a more

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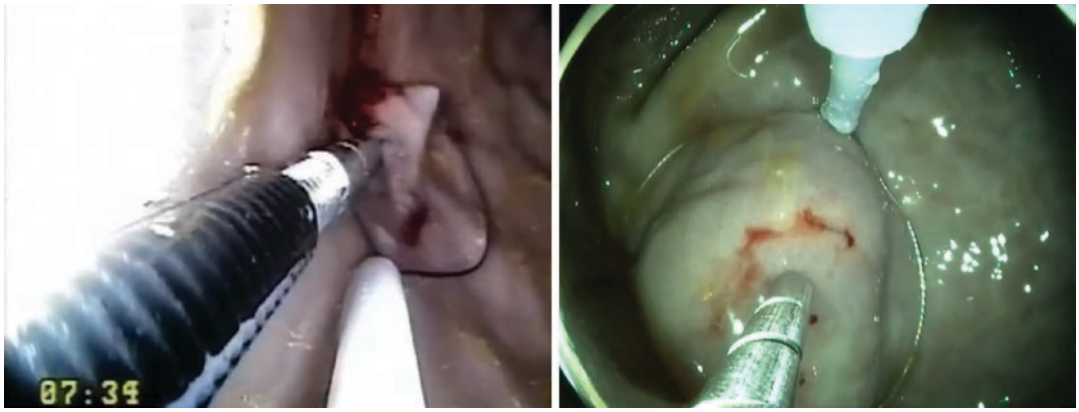

Fig. 26.1 Grasp-and-snare technique using a conventional dual-channel endoscope (left) and the additional working channel (AWC) attached on a conventional endoscope (right). The AWC offers a greater distance between both channels, thereby enabling to some point the concept of traction and countertraction.

effective grasp-and-snare technique. The AWC enables introduction of an additional tool for a distinct traction and countertraction of tissue (see Fig. 26.1). The device is mounted onto the tip of the endoscope. In comparison to a narrower diameter of dual-channel endoscopes, a larger distance between the channels could enable the endoscopist to make better use of the traction and countertraction principle and enable more effective use of leverage effect [1].

However, both instruments can only be used parallel in one horizontal level. Further development of a bendable bimanual grasping device might be reasonable as a next step. This has been achieved with a prototypic hand-held device (Fig. 26.2) [4].

Other platforms that have meanwhile been introduced are the ORISE Tissue Retractor System (TRS, Boston Scientific, Marlborough, MA, USA) and a double-balloon platform (Dilumen, Lumendi, Westport, CT, USA).

The ORISE TRS is a dedicated overtube system that has a retractor cage at its end helping to stabilize the intraluminal space for submucosal dissection. Since instruments may be introduced through separate and bendable instrumentation channel through the overtube, it allows independent movement of scope and tissue grasper [5]. There have been several case reports published that show that the ORISE device can facilitate ESD by supplying constant tension and allowing

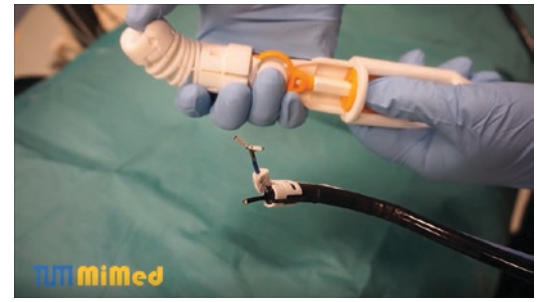

Fig. 26.2 Prototype of a hand-held device for tissue traction via an additional working channel

for effective visualization of the dissection field [6]. Nevertheless, one of the shortcomings of the device is that resection is limited to the sigma and upper rectum.

In contrast, the Dilumen device may also be used proximal to the descending colon. It consists of a soft flexible sheath that fits over standard and small diameter endoscopes. The device employs two balloons, one behind the bending section of the endoscope and the second in front of the tip. When both balloons are deployed and inflated, the area in between is stabilized and two instruments can be introduced. So far, data have been very sparse on these concepts and data on the use of mentioned overtube platforms in the upper GI are still missing. Potential shortcomings of all overtube-based platforms will be that the increase in diameter will limit their use in a narrow and bended lumen.

For non-overtube-based systems the Anubiscope from Karl Storz and the EndoSamurai from Olympus should be mentioned. Both platforms have in common that dual-channel endoscopes with dedicated manipulators have been used. However, although these platforms have been introduced already more than 10 years ago, none of them has been used in clinical routine practice and published studies were more or less only preclinical cases in the animal model. Reason is that steering and handling of instruments that have been introduced through one of the two channels is cumbersome once the endoscope is in a bended position (so-called whipslash phenomenon).

26.2.2 Mechatronic Platforms

Since the introduction of robotic system to surgery, there has been an increasing demand to transfer the concept of rigid mechatronic platforms to flexible, endoluminal endoscopic surgery. Endoscopic robots may be able to simplify procedures. To overcome the limitation of mechanical platforms as mentioned above, it is aimed to locate motorization of devices used for traction and countertraction at the proximal side, which makes the robotic system easily compatible with medical constraints. Furthermore, instruments are controlled with master interfaces to intuitively control all degrees of freedom. At present, many different types of endoscopic robots have been developed. However, most of them are still in a preclinical phase. So far, registered human trials (clinicaltrials.gov) have only been performed with the EndoMaster (EndoMaster, Singapore). The EndoMaster consists of a modified two-channel endoscope that is used as a vehicle to bring two dedicated manipulators to the target lesion. Manipulators can be used for grasping or cutting, offer eight DOF, and are controlled by a platform similar to the DaVinci system. Results showed that complex endoscopic procedures such as gastric ESD have been successfully performed with the device [7]. Nevertheless, none of these mechatronic platforms has been commercially available so far. Comparison of endoscopic robots with standard techniques or already available nonmechatronic platforms is lacking. Hence, although technically fascinating, the main hurdle for robotic flexible endoscopic systems will be to show clear superiority taken under consideration the complexity and potential costs of robotic systems.

26.2.3 Future Perspectives

Due to its minimal invasiveness, endoscopic platforms used for endoluminal therapy of gastrointestinal lesions will become more and more attractive. Endoscopic resection has already been implemented in many national and international guidelines. However, despite these aspects, most endoscopic equipment is outdated and not ready for digital medicine. Devices used for GI endoscopy are still controlled manually, interventions are often imprecise or clumsy, and are therefore not sustainable.

The key is therefore to develop, design, and evaluate new emergent devices and technologies well suited to be adopted for endoscopic resection.

At present, several strategies are followed: the simplest one is to further develop new tools that may be used via standard endoscopes. The second strategy is to use conventional endoscopes and devices but to integrate those into dedicated platforms to enable traction and countertraction. Finally, the most complex strategy is to develop endoscopic robots that will not only enable better endoscopic detection of neoplastic tumor growth but also improve delineation prior to precise and safe resection of such early lesions.

It remains unclear which strategy is best to follow and whether this may be regarded a sequence in the evolution of endoscopic platforms. Furthermore, it should also be considered that there is probably not one solution for all types of resections. There are still some lesions where a simple snare is enough to enable a safe and accurate resection, whereas for other lesions – in particular, when early cancers are suspected – an R0 resection is mandatory and an endoscopic submucosal dissection with standard

endoscopes and instruments is too risky or the respective examiner is not adequately trained with such complex procedures. In addition, location of the lesion might also be relevant. It makes no sense to use a 180-cm-long flexible colonoscope to perform an endoscopic resection in the rectum. The approach to perform endoscopic resection in this region is different from performing such a resection in the cecum or the duodenum. Hence, there is a demand allowing patient-specific (e.g., length, workspace, max. forces) and task-specific (e.g., access route, flexible vs. rigid) configurations for various procedures. Disposable endoscopic manipulator systems might be a solution to overcome these problems rather than one super, high-end endoscopic robot. Disposable endoscopes made for diagnosis have just recently been introduced into the market. Indication-specific modification of these disposable endoscopic platforms should be quite simple to be achieved. Furthermore, individualized 3D-printed platforms have also been successfully evaluated in a preclinical setting [4].

26.3 Summary

Endoscopic platforms used for endoscopic intraluminal resection have been developed to enable traction and countertraction inside the lumen to decrease the risk of perforation and enable a higher R0 resection rate in comparison with standard techniques such as mucosal resection or submucosal dissection. There are currently several strategies followed, from modification of devices to over-tube-based platforms and endoscopic robots.

All these concepts are attractive since they potentially limit current shortcomings. Nevertheless, the data available so far is very sparse. The true benefit of such new devices and concepts remains unproven. Further studies are mandatory. Finally, new concepts should also focus on patient- and task-specific disposable therapeutic platforms.

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Transanal Microsurgery TEM and TEO

27

Mario Morino, Alberto Arezzo, and Edoardo Forcignanò

27.1 Introduction

The conventional surgical therapy for rectal cancer is represented by total mesorectal excision (TME). This technique is burdened by not negligible mortality and morbidity in the postoperative course and also by genitourinary and bowel habits alterations, hence the need to identify characteristics of the tumor that indicate a local treatment. Transanal endoscopic microsurgery (TEM), conceived by Buess in 1983 [1], has become a standard procedure during the last years [2]. Initially the technique was adopted slowly as the surgical procedure was perceived as complex and the equipment expensive. Transanal endoscopic operation (TEO) [3], equipped with a monitor offering high definition, and, more recently, transanal minimally invasive surgery (TAMIS) [4], using a system designed for single-port surgery, have simplified the technique and reduced the cost of the equipment. Several demonstrations proved that transanal endoscopic microsurgery results more accurate and effective than traditional transanal excision (TE), for a higher rate of clear margins, of nonfragmented specimen and fewer recurrences [5]. It has been demonstrated that "en bloc" resection of up to T1sm1 tumor, according to the classification by Kikuchi [6], is oncologically radical, with a minimal recurrence rate. In fact, the risk of lymph node metastases increases with the increase of submucosal layer infiltration, corresponding to 2% for sm1, 8% for sm2, and 23% for sm3, respectively [7]. Considering these data, it is possible to say that the risk of lymph nodes invasion can be neglectable if the tumor is an in situ carcinoma. Moreover, there is a minimal risk when well-differentiated colorectal adenocarcinomas invade the submucosa layer superficially. In the other cases, a radical treatment such as rectal anterior resection (RAR) or abdominoperineal resection (APR) with TME is indicated. The oncological outcomes after "salvage surgery" are as good as those of primary surgical resection [8, 9]. This is most probably due to the respect of the integrity of the mesorectal fascia, one of the principles of oncological appropriateness for rectal cancer treatment. According to this consideration, it is essential for the preoperative staging of the lesion to correctly assess the indication to local excision.

27.2 Preoperative Staging

27.2.1 Biopsy

The ordinary use of tissue sampling by multiple biopsies has some limitations related to

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superficiality and inaccuracy of sampling [10]. The application of the revised Vienna classification to biopsy specimen might correctly assess the probability of finding a tumor invasion in the lesion excised [11]. In our experience, nearly 50% of specimens resulting in invasive cancers at definitive histology had a preoperative assessment of dysplasia by histology of biopsy sampling, even low-grade dysplasia in about 8% of cases. Therefore, it can be said that any grade of dysplasia assessed by biopsy sampling could be regarded as free from malignancy.

27.2.2 Lifting Sign

If the lesion does not completely lift after endoscopic injection of saline solution into the submucosal space, this might indicate invasion of the submucosal layer, impeding a complete endoscopic resection of the lesion. This is called the "no-lifting sign," that is, a reliable endoscopic sign to assess the possibility of cancer invasion, which may impede a radical oncological resection of the lesion. Unfortunately, not all the cancers that invade the submucosa are a good indication for a local resection. Furthermore, the possibility of infiltration of the deep margin of the specimen increases. Therefore, the lifting sign of the lesion does not guarantee that the endoscopic resection might be finally curative [12, 13].

27.2.3 Digital Examination

Digital examination, possible for lesions located in the lower part of the rectum, can easily assess the solidity of the tumor, the location, and the gap from the anal verge. This information can be useful to the surgeon to evaluate the feasibility of the TEM [14, 15].

27.2.4 Endoscopic Ultrasound (EUS)

Marone et al. [16], in a recent systematic review, showed that endoscopic ultrasound has a diagnostic accuracy of 84% (range 63–96%) for evaluating the cancer depth through the layers of the rectal wall. Marusch et al. [17] performed a comparison between ultrasonography T stage (uT) and pathology T stage (pT). They demonstrated a uT–pT correspondence of 65%, showing that, in clinical practice, the accuracy of the diagnosis assessed by endoscopic ultrasound while staging a rectal cancer does not achieve yet acceptable results. To determine correctly the indication for a local resection, it is preferable to understand whether the neoplasm infiltrates the submucosa, and, when it does, if the invasion grows >1 mm under the lamina propria. Today, this is not possible for any in vivo diagnostic instrumentation.

27.2.5 Magnetic Resonance Imaging (MRI)

Rectal cancer study based on MRI study has a fundamental role in the advanced stages, but is known for limited accuracy and value in early lesions [18]. Recently, in a population-based study by Detering et al. [19], the accuracy of MRI was assessed among individuals affected by T1–T2 rectal cancer who underwent both local excision or TME. In the study, the overall performance of MRI in staging rectal cancer was disappointing, with 54.7% of overstaging for pT1 lesions and 17.3% for pN0, even if they showed some improvements in tumor and nodal staging over time. The authors concluded that preoperative MRI has the defect of overstaging the lesions with the consequence of losing the possibility of organ preservation strategies.

27.3 Indications

Transanal endoscopic microsurgery is employed to treat a number of different benign and malignant diseases. The main indication is represented by endoscopically unresectable rectal adenomas. Endoscopic mucosal resection (EMR) does not guarantee an en bloc excision in the presence of a large adenoma so that a piecemeal resection might happen. As a consequence, the pathological

evaluation could be demanding, in the end leading to a higher risk of local recurrence. Twenty years ago, the endoscopic submucosal dissection (ESD) technique was introduced to permit a resection en bloc of the lesions, especially when lesions were larger than 20 mm [20]. Compared with EMR, ESD is technically demanding and time consuming, obliging to extensive training for a steep learning curve [21]. As a consequence, ESD did not reach a large diffusion in Western countries, so that transanal surgery is still the most common procedure for the excision of large rectal adenomas. The role of TEM for the treatment of early rectal cancer (T1) is still debated, mainly due to an inadequate lymphanedectomy. The invasion of the submucosal layer (sm), together with the lymphovascular invasion, is one of the main predictors of lymph node metastasis and local recurrence. T1 sm1 cancers have a very low incidence of lymph node metastasis, about 1%, increasing up to 15% T1 sm2–3 and even 25% for T2 cancers. Thus, rectal carcinomas confined to the superficial submucosa layer (pT1 sm1), without lymphovascular invasion, are good indication for TEM. Here, TEM offers the same oncological outcomes compared to radical abdominal surgery with extensive lymphadenectomy. On the contrary, TEM is not recommended for pT1 sm2–3 and pT2 cancers as unique treatment because of the high risk of lymph node dissemination. Furthermore, TEM could be also used for other indications than the oncological ones, such as high supralevator and rectourethral fistulas repair, transrectal drainage of pelvic collections, and transrectal excision of extrarectal masses [22]. TEM might serve also for palliation of individuals with extended metastases and for unfit for radical surgery.

27.4 Extended Indications

Preoperative staging might be challenging to select patients suitable for TEM due to low accuracy of the available technique. T1 cancers that penetrate the submucosa for >1 mm (T1 sm2–3) and T2 cancers have an incidence of lymph node metastasis up to 15% and 25%, respectively, that requires a subsequent TME. After a local resection by TEM as full-thickness excision, conventional anterior resection might be a difficult operation with the consequence of a higher risk of abdominal perineal resection [23]. Full-thickness TEM could be considered curative in 75% of patients with the right indications. Thus, it would be preferable to identify a method to achieve the complete "sterilization" of the mesorectal tissue, this way improving the oncological result of local resection.

Lezoche et al. have verified the possibility to expand the indication of TEM to T2 tumors, applying a neoadjuvant chemoradiotherapy before a local excision [24]. In their trial, they randomized patients undergoing either radical surgery or neoadjuvant long-course chemoradiation therapy followed by TEM. Even if this treatment is demonstrated to be effective in terms of oncological outcomes, it is quite uncomfortable for patients and, not least, concerns have been raised regarding the leakage rate after neoadjuvant chemoradiation therapy [25]. Based on the experience of Lezoche et al., we performed a study to verify the feasibility of a short-course regimen radiotherapy (25 Grays in 5 fractions) 4–10 weeks before TEM in selected individuals affected by rectal cancers staged T1–T2 N0 [26]. The study was aborted after only 14 patients for unexpected discouraging results. Although no radiotherapy-related complications occurred, leakage of the suture was reported in seven patients at 30 days. During the follow-up, we recorded one local recurrence occurring 6 months after index surgery, which required abdominoperineal resection. The conclusion of the study was that short-course neoadjuvant radiotherapy with subsequent TEM is burdened by a high leak rate and should be carefully reconsidered. More recently, the results of the GRECCAR study became available. This randomized trial compared neoadjuvant chemoradiotherapy and local excision to chemoradiotherapy followed by TME in individuals affected by rectal cancer stages T2–T3, who were good responders to neoadjuvant chemoradiotherapy [27]. In this study, no difference was observed between groups in terms of complications and long-terms oncological

outcomes. Thus, the authors concluded that local excision is suitable in selected patients presenting with a small T2 or T3 tumor of the mid–low rectum who achieved a good response after neoadjuvant therapy. However, it must be emphasized that 37% of the patients in the group receiving initially local excision after neoadjuvant therapy, in fact, received, had at a second stage a total mesorectal excision based on the pathology result and stage of the local excision. Thus, better selection criteria of the patients are mandatory to avoid unnecessary completion of TME.

27.5 Technique

TEM is a standardized procedure easy to reproduce; below, the technique is described as it is performed at our institution [28].

Patients are advised to start a low-fiber diet 5 days prior to surgical procedure; in addition, 12 and 2 h before surgery, they receive a rectal enema. A one-shot antibiotic is administered intravenously before the insertion of the rectoscope. Prophylaxis of deep venous thrombosis is generally not required.

27.5.1 Equipment

Currently, there are two fully reusable platforms to perform transanal endoscopic surgery: one is the original TEM equipment (Richard Wolf, Knittingen, Germany) (Fig. 27.1), the other the transanal endoscopic operation (TEO) instrumentation (Karl Storz GmbH, Tuttlingen, Germany). Some technical advantages of the original TEM device consist of a peristaltic CO_2 inflating pump-stabilizing pneumorectum, an evacuating surgical smoke system from the rectum and stereoscopic vision. The main convenience of the TEO equipment is its compatibility with standard laparoscopic tower and its lower cost than the Richard Wolf device. For these reasons, we use the Storz's equipment since early

Fig. 27.1 The original Richard Wolf (Knittingen, Germany) TEM equipment

Fig. 27.2 The transanal endoscopic operation (TEO) instrumentation by Karl Storz GmbH (Tuttlingen, Germany) and the holding arm to fix the rectoscope to the operating table

2008. TEO device includes a 7.5, 15, or 20 cm rectoscope that is also 4 cm in diameter; it has three working channels of 12, 5, and 5 mm, respectively, for either dedicated or standard laparoscopic instruments; a 30° 2D optic is inserted through a further 5 mm channel. The rectoscope is fixed to the operating table via three joints arm stiffened by a single screw (Fig. 27.2). Standard endoscopic units for CO_2 insufflation, light source, and camera processor are used while imaging is projected on a HD monitor. A CO_2 thermo-insufflator allows the insufflation and the creation of the pneumorectum. The tip of the rectoscope is shaped as a very short flute beak that permits both tissue manipulation and suturing at 360°.

27.5.2 Anesthesia

TEM was traditionally performed under general anesthesia due to the duration of the operation that requires bowel distension and complex positioning of the patient. TEO procedure can also be successfully and safely performed under spinal anesthesia as shown by a pilot study [29]. Since 2013, we use spinal anesthesia as a standard type of anesthesia.

27.5.3 Positioning of the Patient

Depending on the lesion's location, the patient is positioned prone or supine in order to observe the target the closest to 6-o'clock position. In case of lateral lesions, we do not position the patient in the lateral decubitus, but we adopt the supine position, except for the neoformation located in the left and right upper quadrant. In case of circumferential lesions, there is a high occurrence of opening the peritoneum, so the individual is always in prone position, this way preventing the ileal loops from dropping into the surgical field and facilitating the surgical closure of the defect.

27.5.4 Surgical Technique

27.5.4.1 Step 1: Dissection

First, the rectoscope is introduced transanally; the lesion is found and the device is fixed to the operative table in the right position. The position of the rectoscope is dynamically changed along the operation to maintain a good visualization and an easy orientation toward the lesion. CO_2 insufflation is used, and the pneumoperitoneum is kept stable starting with a minimum pressure of 8 mmHg, which might be necessary to increase up to 16 mmHg when supine, and even more when prone. A 5 mm minimum lateral margin is dotted with monopolar hook cautery in order to direct the dissection. Excision is commonly begun at 4 o'clock or the right distal border of the tumor. Monopolar hook is usually used to perform the dissection, although in the more complex cases, especially if partial excision of the perirectal fat is performed, advanced devices such as Ultracision ACE™ (Johnson and Johnson Medical, Cincinnati, OH) or Ligasure™ (Covidien, Tyco, Medtronic, Minneapolis, MN)

could be used. Excision is then extended all around the tumor with or without inclusion of some perirectal fat. A full-thickness excision with lateral and deep-free margin is recommended, in those cases in which uncertainty of the preoperative diagnosis and stage remain. In selected cases, a submucosal dissection may be preferred. Finally, the specimen is extracted through the anus and fixed upon a rigid support highlighting and pinning with spikes the margins of the normal mucosa around the tumor.

27.5.4.2 Step 2: Suture of the Defect

First, the wall defect is disinfected with iodopovidone solution; the rectal wall is always sutured after a full-thickness excision while the closure of the defect might be unnecessary after a submucosal dissection. We usually performed suture with one or more Maxon 3-0 (Covidien, Tyco, Medtronic, Minneapolis, MN) running sutures locked with dedicated silver clips (Richard Wolf, Knittingen, Germany). These clips are useful to anchor the suture in place since knotting during TEM might be difficult. As an alternative, a barbed suture V-Loc™ (Covidien, Tyco, Medtronic, Minneapolis, MN) might also be used, avoiding the need of clips or knotting. If the peritoneum was opened, the defect might be closed as a single layer being careful to include the serosal layer in the stitches or as two layers running suture. During the suture, the pneumoperitoneum could be reduced to permit better compliance of the rectal wall. At the end of the suture, patency of the rectum is checked through the rectoscope.

27.5.5 Postoperative Management

Mobilization generally occurs on the same day of the procedure. The urinary catheter is removed at 24 h, 48 h in case the tumor is located on the anterior wall. Analgesic drugs are generally not requested, so that occasional intravenous paracetamol is sufficient in the first 24 h. Fluid oral intake is administered the same day of surgery, while solid intake the day after. Discharge generally takes place within 3 days after the procedure if no complications occur.

27.6 TEM Versus ESD

With the introduction of ESD in the year 2000, flexible endoscopy allowed a surgical-like technique with the aim to resect en bloc superficial lesions of the digestive tract bigger than 2 cm. First used in the upper gastrointestinal tract [30], then ESD was indicated also for lesions of the lower gastrointestinal tract showing some consistency [31]. ESD can be employed in any tract of the colon in replacement of EMR, while in the rectum it represents an alternative to TEM for aims. A meta-analytic study [32] considering 21 series (11 ESD and 10 TEM) for a total of 2077 patients demonstrated that the rate of en bloc resection was 87.8% in the ESD group versus 98.7% in the TEM group ($P < 0.001$). Similarly, the rate of R0 resection was 74.6% after ESD versus 88.5% after TEM ($P < 0.001$). Complications were similar in the two groups, 8.0% following ESD and 8.4% following TEM ($P = 0.874$). The recurrence rate was lower after ESD, 2.6% only versus 5.2% after ($P < 0.001$), although this was surely influenced by a much longer follow-up in the TEM series. In fact, nonetheless, the overall need of further abdominal treatment, including both oncological indications and postoperative complications, was 8.4% for the patients undergoing ESD versus 1.8% for those undergoing TEM ($P < 0.001$). In these meta-analyses of case series, TEM seems to guarantee better oncological outcomes compared to ESD, with comparable complications rate. In the past, the major advantage of the ESD was that it can be performed without general anesthesia, but nowadays, we routinely performed TEM under spinal anesthesia. Considering the low preoperative diagnostic accuracy, it is reasonable to think that the TEM with a full-thickness excision is the technique of choice in those lesions with risk factor for malignancy.

27.7 Future Perspectives

The opportunity to expand the indications of transanal endoscopic microsurgery is connected with the capacity to evaluate lymph node status,

either preoperatively or intraoperatively. Our group tried to apply the concept of sentinel lymph node (SLN) biopsy to identify positive lymph nodes in those cases suspected to be invasive cancers [33]. Indocyanine Green Solution (ICG) is injected endoscopically in the submucosal layer below the lesion before the beginning of the procedure. After the resection of the lesion, the perirectal fat is exposed and a near infrared (NIR) camera is introduced inside the rectum through one of the TEM's working channels. NIR fluorescence emitting ICG previously injected show an exact map of lymphatic vessels and nodes in the mesorcetum, first resected, then examined by the pathologist. In this preliminary report, the pathologist confirmed the presence of lymph nodes in the resected specimen without evidence of neoplastic invasion. This was only an initial report testing the feasibility of a technique that now requires to be validated. With the described technique, it is possible to preserve the integrity of the mesorectal fascia, allowing, if necessary, a subsequent total mesorectal excision without compromising the oncological outcome.

27.8 Conclusion

Since its introduction, TEM has been a real innovation in rectal surgery allowing to apply the concept of rectal sparing surgery; by doing this, it is possible to decrease the short- and long-term complications of the conventional TME. TEM, even more than ESD, should be the standard treatment of the early lesion of the rectum, but on the condition that it is able to guarantee an excision that can be considered both radical and curative. Thus, selection of correct indications needs to be improved as well as innovative multidisciplinary therapies must be implemented. Therefore, a significant improvement in the staging of rectal cancer will allow a therapy truly tailored on the single individual, this way contributing to a significant decrease of invasiveness of the therapeutic procedure.

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28 Transanal Endoscopic Colon Resections

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28.1 Introduction

The principle of minimal access surgery is the reduction of access size and access trauma possibly resulting in a shorter patient recovery and improved postoperative well-being with less inhibiting postoperative restrictions as well as a better cosmetic result [1–4]. This could be achieved by less wound infections and less incisional hernias over time. Subsequently, this all may lead to better overall outcome [1–4]. The transanal access has been used for rectal surgery since many decades [5]. Gerhard Buess has introduced endoscopic transanal tumor resections by transanal endoscopic microsurgery TEM) [5, 6]. The transanal route has been explored and investigated for colorectal resections with remarkable success [7–11]. Transanal minimal invasive surgery (TAMIS) is an increasingly performed technique in colorectal surgery [9–11]. The concept of using a natural orifice as an access route to the intra-abdominal cavity can provide a relevant reduction of access trauma by reducing number and size of necessary ports. However, the risk of complications is substantial, and therefore, a detailed training program is necessary. In addition, the technical requirements to perform complex transanal tumor resection and transanal colon resections are also substantial [11].

The transanal or transcolonic technique was initially considered dangerous because of the infection issue and the bacterial load of the colon [3, 4, 12–15]. Clinical experience does exist for transanal endoscopic procedures [transanal endoscopic microsurgery (TEM)], which showed convincing clinical evidence that the infection issue should not be a major problem in transanal procedures [5, 6].

The introduction of more complex transanal-assisted hybrid procedures such as colorectal tumor resection and colon resection for benign disorders was followed by a rather quick acceptance by many surgeons [15–20]. The most important idea behind the transanal/transcolonic route is the use of the anastomotic site as the access point into the peritoneal cavity [3–5, 8, 9].

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There is no additional risk of access site infection and complications, compared to a regular laparoscopic colorectal resection, since there is no additional site of transmural passage [19, 21–26].

28.2 Technical Issues for Transanal Approach

There are different concepts regarding transanal procedures and colorectal resections. The first is a hybrid solution, in which transabdominal trocars are used as necessary. An example is the transanal rectal resection or transanal total mesorectal excision (ta-TME) [9–11] (see dedicated chapter). Some authors use two teams, who operate simultaneously from the transanal situs and the other team from the abdomen, using several transabdominal ports [9]. The dissection work is split between the transabdominal and transanal team using energy tools and staplers also transabdominally. The specimen is usually retrieved via the anus.

The second concept is a very limited use of transabdominal ports (usually only small camera optics for safety views and graspers for assistance). The main dissection work and resection is performed via the transanal trocar as well as the specimen retrieval. Care is taken to limit the transabdominal access to maximum 3–5 mm instruments.

Indications for transanal colorectal surgery in this project were based on benign colorectal disorders such as chronic sigmoiditis, severe slow transit constipation, and pelvic floor disorders with rectal prolapse [16, 19]. All patients received a detailed diagnostic workup and a critical discussion followed regarding the necessity to perform surgery or decide for further conservative therapy.

Prior to colorectal surgery, patients received a bowel preparation in order to have a clean colon and rectum for transluminal work. Preoperative antibiotic prophylaxis was administered. Patients had to deliver an informed consent to agree to this surgical technique after several sessions of information, questions, and answering.

28.2.1 The Hybrid Transanal Technique

After establishing a capnoperitoneum via a Veress needle and after necessary safety tests, a periumbilical port was introduced in the abdominal cavity [19]. Two additional 5 mm ports were brought in the right lower quadrant for dissection of the colon and rectum (Fig. 28.1). Via these ports also, the dissection of the anastomotic site, all necessary hemostasis, as well as all energy devices were applied. The dissection of the mesentery was stepwise performed under careful laparoscopic control to ensure that the pelvic nerve plexus was not in danger and the dissection planes could be followed. The dissection and mobilization of the colon segment (sigmoid) were completed according to the necessities of the indication of the procedure. Then bougies were introduced into the anus, rectum, and sigmoid colon. A careful bougienage of the rectum facilitates the following maneuvers. Then, a transanal endoscopic applicator (TEA) was introduced into the anus and rectum, which allows for safe introduction of endoscopes, linear staplers, grasping devices, and specimen removal (Fig. 28.2) [19, 27]. Afterward, a 28 mm anvil of a circular stapler was inserted with a rigid grasper and positioned more proximal in the descending

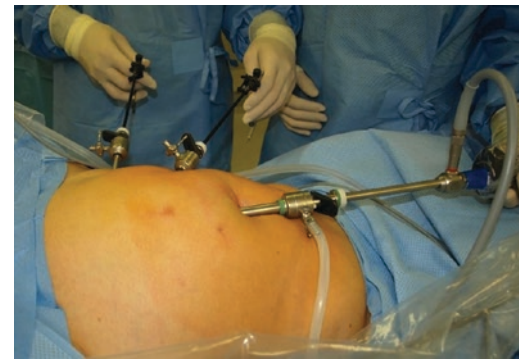

Fig. 28.1 Overview of trocar positions in a transanal-assisted hybrid colon resection with 2 5 mm ports for dissection and grasping and 1 camera port (5 or 10 mm). The transanal endoscopic applicator (TEA) carries all instruments >5 mm

Fig. 28.2 Transanal endoscopic applicator (TEA) with a diameter of 3 cm. The device has different adaptors to work with either on 12 mm opening and one 5 mm opening. Alternatively, there is an adaptor with three 5 mm openings

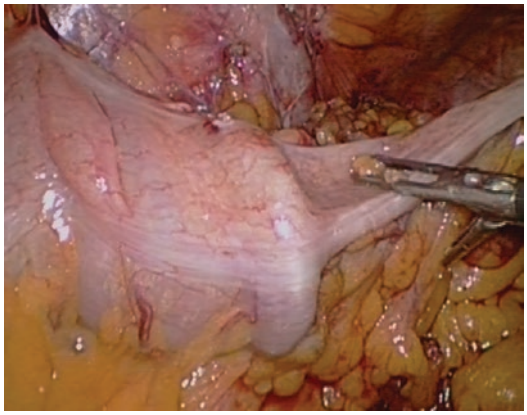

Fig. 28.3 The anvil of a circular stapling device is positioned transanally with a grasper prior to resection at the proximal anastomotic site

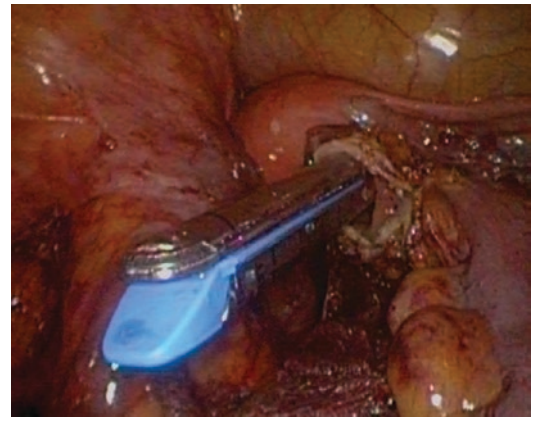

Fig. 28.4 A linear stapler is passed via the TEA after opening of the colon into the abdominal cavity to transect the colon

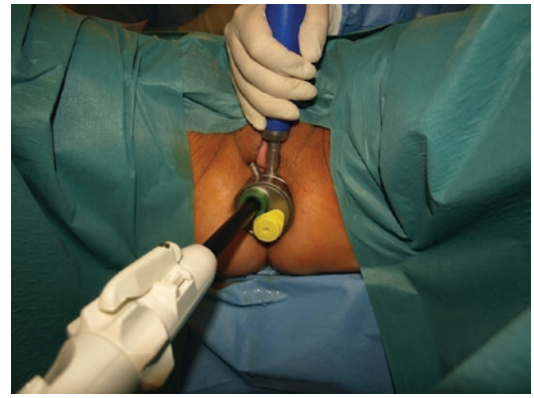

Fig. 28.5 The linear stapler in the TEA can be quickly moved in and out and can be reloaded as required. It is important to keep the hand-operated handle of the TEA free to follow the necessary movements of the platform. This will avoid unnecessary mechanical forces on the anal sphincter and will ensure good maneuverability of the transanally inserted instruments within the abdominal cavity

colon to the future anastomotic site (Fig. 28.3). This was followed by an incision of the colon – usually the distal sigmoid – at the distal anastomotic site. Here, a transanally introduced linear stapler can exit the colon into the abdominal cavity and was used to transect the proximal end of the sigmoid segment, which needs to be resected (Fig. 28.4).

Via the transanal positioned TEA instrument, the application, removal, and change of stapling cartridges could be technically easily performed (Fig. 28.5). At the proximal colon stump, the intraluminal anvil was grasped through the bowel wall and stabilized. The central pin of the anvil was penetrated through the bowel wall at the stapled line to be available for later anastomosis [19].

Once the sigmoid segment was resected and free, a grasper was advanced via the TEA to reach for the specimen in the abdomen. Then, the

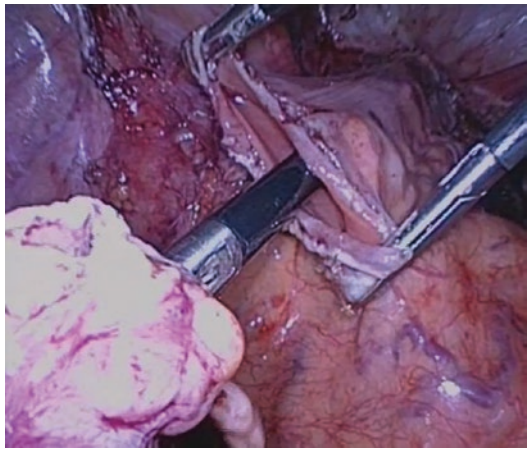

Fig. 28.6 The resected colon will be grasped transanally and removed with care

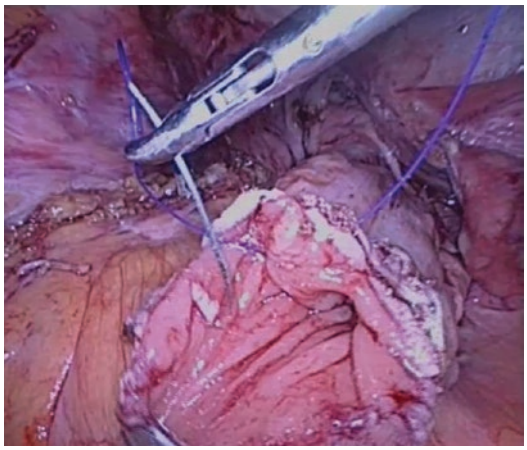

Fig. 28.7 At the end of procedure, the rectal stump will be closed with a purse-string suture as usually in the abdominal cavity with 5 mm instruments to prepare for a safe circular stapler anastomosis

specimen was pulled through the luminal opening at the distal rectosigmoid stump via the rectal lumen and the TEA transanally to the outside (Fig. 28.6).

After removal of the specimen transanally, a purse-string suture was placed at the distal rectosigmoid stump in order to complete the anastomosis with the circular stapling device. The TEA was removed and a circular stapler was inserted transanally and advanced to the distal rectosigmoid opening, carrying the purse-string suture (Fig. 28.7). The central pin was opened and the purse-string suture was tied down around the central pin. Furthermore, the anvil was connected to the stapler, followed by approximating and firing the device in the usual manner under laparoscopic visual control. Thus, the anastomosis could be performed under the same optimal conditions that laparoscopic surgery can provide [21].

28.2.2 The Transanal Technique with Special Rectoscope System

Driving the idea of minimal access therapy further requires the reduction of access trauma to an absolute minimum [3, 4]. For the transanal approach, this means that the access to the abdominal cavity and the target organ during surgery should be just the anus and a transluminal pathway through the rectum and colon. If one follows this line of thinking, the transanal approach requires a new operative endoscope system for the anus and rectum, which can carry several instruments, a camera system, and space for the passage of energy devices, stapling devices, and other specialized tools. These tools and devices may need to be steerable and may need to have a certain length to be able to reach all colon segments in the abdomen.

We have developed such a system with Fortimedix Surgical BV (Geleen, The Netherlands) as a platform for transanal endoscopic operations. The system is based on a single-site platform, developed by Fortimedix Surgical BV (FMX-platform) and used for laparoscopic single-site cholecystectomy and hernia surgery [28, 29] (Fig. 28.8). Using a box-training model, we tested together with the engineers from the company the technical necessities to create a novel designed platform, which can be applied through a special transanal trocar, using the TEA. The FMX platform can take a camera system and at least two further instruments for dissection and hemostasis within the bowel lumen (Fig. 28.9). This surgical platform (FMX-TEA system) for purely transanal colorectal surgery is currently a preclinical investigational

Fig. 28.8 Box-training with the transanal prototype platform with the Fortimedix™ and TEA system. The Fortimedix™-introducer can be easily inserted in the TEA

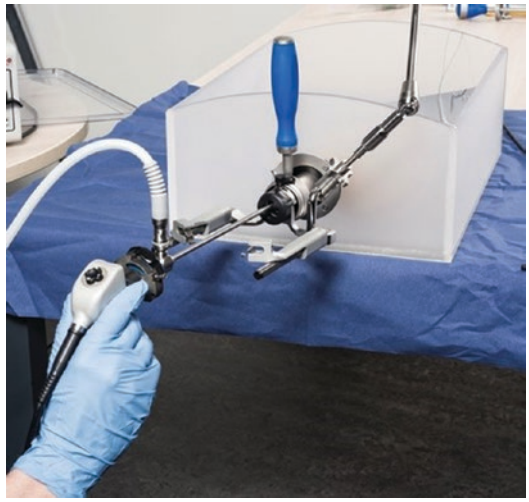

Fig. 28.9 Box-training with the next-generation transanal Fortimedix™ platform through the TEA. The articulating instruments are inserted through the FMX-introducer, which can be used intraluminally and in the intra-abdominal cavity

Fig. 28.10 View of the Fortimedix Surgical™ telescope platform for transanal application, which allows for dissection and manipulations within the transanal trocar as well as far up in the abdominal cavity to mobilize the colon

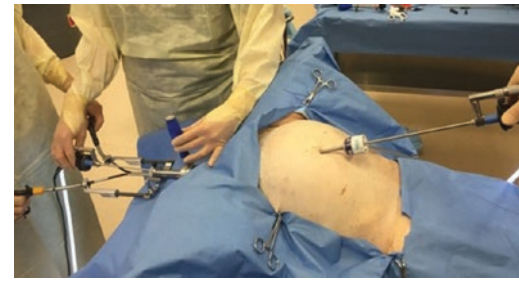

Fig. 28.11 Overview of the setting of all access trocars in transanal colon resections with the Fortimedix™ platform. Transanally the FMX-TEA system is inserted as well as all operative active instruments for dissection and resection. Transabdominally there is a 5 mm camera port for safety reasons in the right lower quadrant of the patient. In addition, one may use a 3–5 mm grasper without a trocar for assistance

device that is constantly being updated. It features articulating surgical instruments for the purpose of achieving triangulation after insertion through a multiple-use introducer with a diameter of currently 25 mm. A telescope was designed to allow a maximal axial working range (Fig. 28.10). In addition, the system allows an instrument flexibility to work either in the narrow endoscopic lumen as well as in the rectum and also further orally in the sigmoid or transluminally in the abdominal cavity (Fig. 28.11). This goal is achieved by carrying the instruments based on a stronghold in a sliding system, which allows for these extensive movements.

Several preclinical training sessions were performed to gather experience and develop the methods around this technique (Fig. 28.11). The concept of using a natural orifice as an access route to the intra-abdominal cavity can provide a relevant reduction of access trauma by reducing number and size of necessary ports.

The transanal instrument manipulations are supported by one transabdominal 3-5 mm grasper (with or without port), which can be introduced

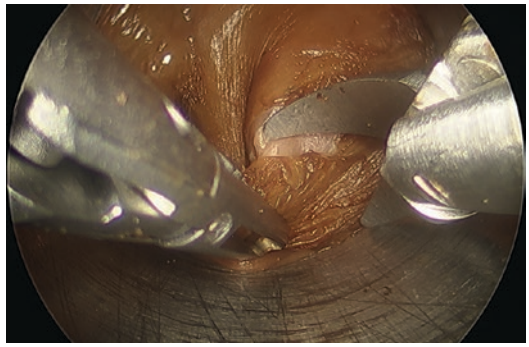

Fig. 28.12 Intraluminal view through the FMX-TEA platform in the rectum, observing the incision of the rectum on the posterior wall with articulating scissors

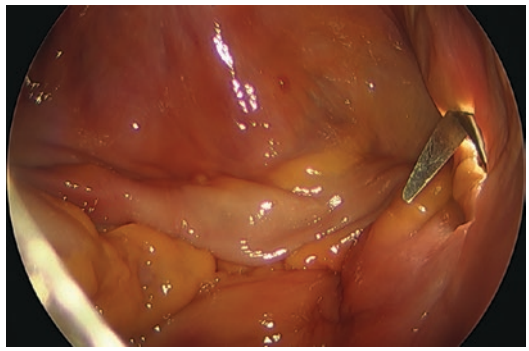

Fig. 28.13 Intra-abdominal view on the FMX-TEA platform, dissecting the proximal rectum. After this step, the dissection of the sigmoid and mesosigma can be performed, using articulating scissors, graspers, and energy devices

via the umbilicus, in order to assist with traction and countertraction, if necessary (Fig. 28.11). In addition, a 5 mm camera may be used from the right lower quadrant to provide a safety view for checking the transanal dissection manipulations and anatomical landmarks.

Figure 28.12 demonstrates the view inside the new platform, when severing the colon to get access to the peritoneal cavity. Figure 28.13 shows the view inside the abdominal cavity during dissection of the colon. Figure 28.14 demonstrates the dissection of the sigmoid mesentery on the way up to the proximal anastomotic site. A set of in vitro sessions and cadaver studies have been performed in Europe and the United States introducing the updated platform through a commercially available applicator for transanal surgery [transanal endoscopic applicator (TEA)]. A training pathway from in vitro models and human cadaver models was created before a "first-in-human" use has been performed after the appropriate administrative procedures of legitimations. Feasibility of transanal approach for colon transection, suturing, and range of the instruments was investigated.

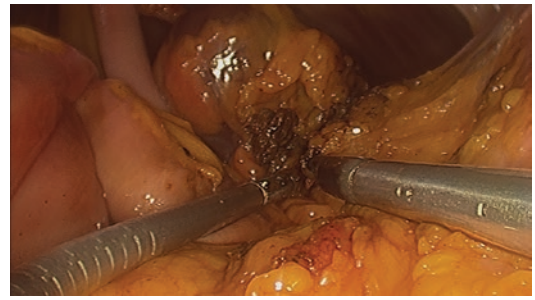

Fig. 28.14 Intraluminal view within the Fortimedix Surgical™ telescope platform for transanal application, advancing the dissection in the abdominal cavity on the sigmoid mesentery

Initial clinical application was performed in patients with benign colorectal disease and indications for sigmoid resection. The patient was placed in lithotomy and head-down position at the edge of OR table. After draping, the perianal and abdominal regions need to exposed. The anus of the patient should reach several centimeters over the rim of the OR table in order to later move the TEA and FMX system in any direction necessary. After all preparations for the procedure and technical check of the platform, a capnoperitoneum is established by a Veress needle. A 5 mm trocar is placed in the right lower quadrant at lateral position for observational (i.e., scope) and assisting purposes (e.g., grasper). Then a 5 mm laparoscopic camera for transabdominal safety view is inserted and the abdominal cavity is checked for any special finding, which may prevent the program of the procedure. Especially the pelvis and the rectum is explored since this is the area of access later on. A transabdominal needlescopic grasper for assisting purposes is also inserted at the site of the Veress needle access at the umbilicus.

Now the TEA system is inserted in the rectum, followed by the FMX-Introducer in TEA

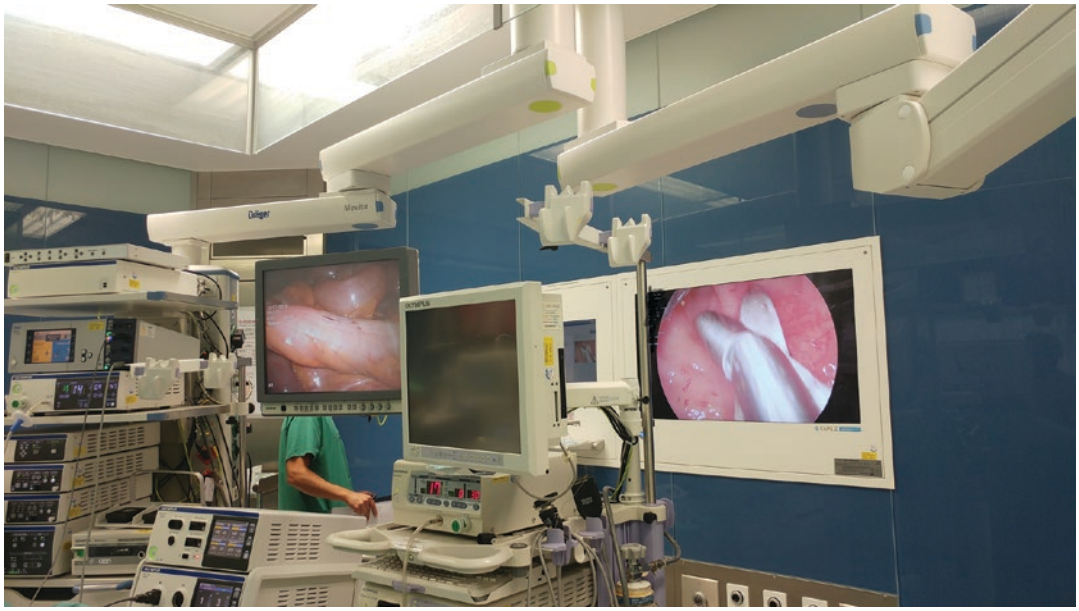

Fig. 28.15 A clinical case of transanal colon resection with the Fortimedix Surgical™ telescope platform for transanal application

(Fig. 28.15). A 5 mm 0°angeled laparoscope (bariatric length) is inserted in the system's scope lumen. Care is taken to position the platform in the anus and rectum exactly at the level, where subsequently the transluminal penetration and dissection will have to be performed to continue the procedure representing also the later site of anastomosis.

Under vision of the lateral safety scope, a holding suture using a regular straight needle purse-string suture is placed through the abdominal wall from the suprapubic region toward the uterus to withdraw the retroflexed uterus from pelvis (if applicable) toward the ventral abdominal wall. The latter allows a free sight into the plevis during the entire procedure.

Now the FMX-TEA platform is mounted with several semi-flexible instruments. A FMX grasper is inserted in the left instrument channel, and the FMX scissors are inserted in the right instrument channel. The instruments are advanced to the end of the TEA to inspect the rectal site, where the dissection should start (Fig. 28.16). For this purpose, the proximal rectum is inspected with the internal scope and instruments, while an additional checkup should be done with the lateral

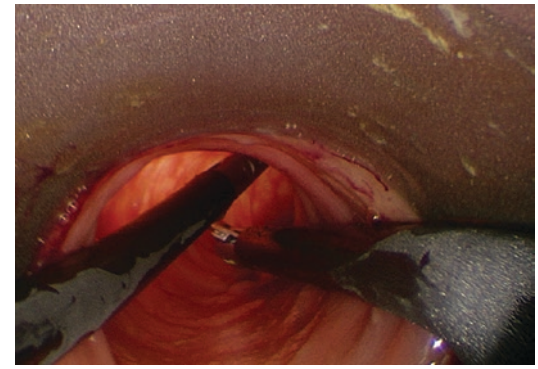

Fig. 28.16 A clinical case with the Fortimedix Surgical™ telescope platform for transanal application. The system is inserted in the rectum and the dissection can be started intraluminally

scope to double-check the corresponding landmarks of the intra-abdominal anatomy with the vision from inside the rectum. Before starting the dissection of the rectum, it is important to preserve sufficient length of bowel rim above the TEA for the necessary purse-string suture application at a later stage.

The dissection of the rectal wall can be started with an energy device, while the line of incision should be under observation both transabdomi-

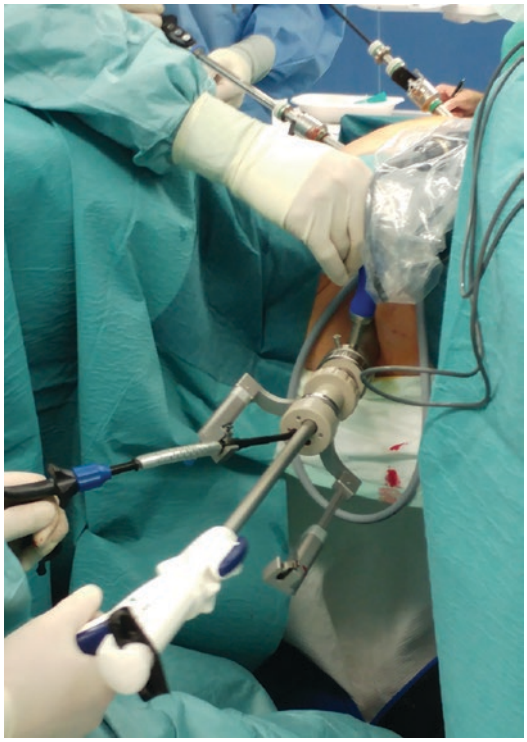

Fig. 28.17 A clinical case with the Fortimedix Surgical™ telescope platform. A linear stapler is inserted through the FMX-TEA system

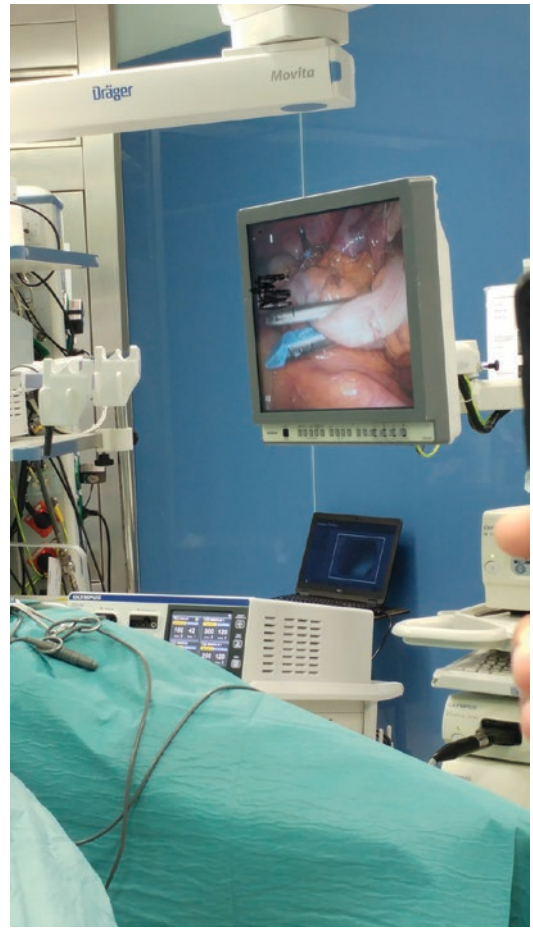

Fig. 28.18 The view from outside shows the application of a stapling device through the FMX-TEA system to transect the colon and complete the resection of the sigmoid

nally and transanally, both on the anterior and posterior aspect of the rectum or colon. Usually it is best to start incision on posterior side (to stay initially in the mesorectum and keep the intraluminal air) and proceed in a circumferential manner. It is important to proceed layer by layer to maintain dissection planes and orientation. The intra-abdominal safety view should be used continuously to make sure to stay on the optimal incision line until the circular separation of the colon is completed. Now the proximal open colon stump is mobilized for safe closure either by stapling or by sutures.

Then the scissors and laparoscope are removed from the FMX platform. A linear stapler is inserted in the optic channel of the FMX platform (Fig. 28.17). The remaining grasper in the left channel is used to manipulate the distal end of rectosigmoid segment inside linear stapler under transabdominal observation. After firing, the stapler is removed again and replaced by the laparoscope. Now the dissection of the mesosigmoid is performed using scissors and an energy device. The dissection and mobilization of the colon are continued until the proximal anastomotic site. Again a linear stapler is inserted after removal of the laparoscope and the resection of the colon is performed, closing the proximal opening temporarily to prevent contamination (Fig. 28.18).

Now the specimen is pulled out transanally removing the FMX platform from the TEA to allow for enough space for passage (Fig. 28.19). Then an anvil of a circular stapling device is delivered with a grasper through the TEA into the inner pelvis. The tip of the anvil carries a small loop of suture. This is followed by the insertion

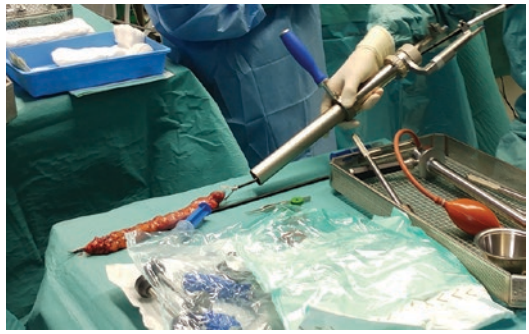

Fig. 28.19 In this clinical case, the colon resection is finished and the system has been removed from the anus, grasping the specimen for retrieval

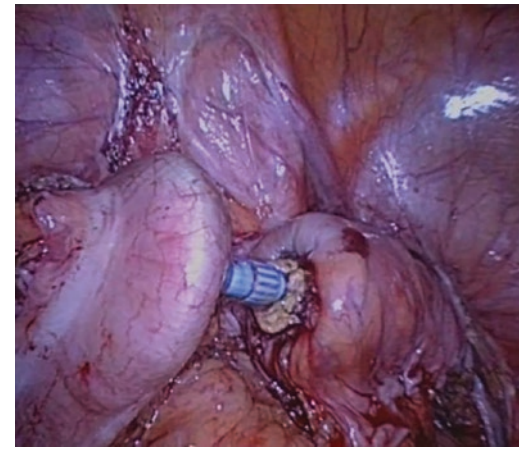

Fig. 28.20 The colorectal anastomosis is performed with the similar quality after classic laparoscopic surgery with a circular stapling device

of the FMX platform again. Now, the staple line of the proximal colon is cut away and small tissue strip is removed. Then the suture and the needle are picked up with the needle holder and the needle is penetrated through the antimesenteric wall of the colon followed by the tip of the anvil, thus creating the basis for a side-to-end anastomosis. The needle is cutoff and secured for later removal via the TEA. The bulky end of the anvil is pushed also into the colon lumen. Afterward, the open colon stump is closed by a linear stapler in the fashion described above. Now the proximal colon stump with the anvil is ready for anastomosis with the rectum, which needs to be prepared.

A purse-string suture is applied through a 10 mm scope lumen of FMX-Introducer and the scope is repositioned. The purse-string suture is performed, which is quite cumbersome from inside the platform and the lumen. Now, both camera systems are used to have a comprehensive sight at all times on the progress of the purse-string suture to prevent inadvertent locking of the suture. At the completion of the purse-string suture, the end of the thread is pulled outside for closure. The distal stump is closed by pulling on the untied purse-string via the scope lumen. With a grasper, the central pin of the anvil is connected with the transanal placed circular stapler. The stapling device is approximated and fired, thus completing the anastomosis (Fig. 28.20). The anastomosis is checked for air tightness.

This procedure has been trained in experimental preclinical testing as well as in cadaver training. Our experience shows a quite steep learning curve from 5 hours to 150 min within five training cases. It must be emphasized that the procedure is demanding and requires an experienced and dedicated team to perform this procedure safely. After the appropriate steps and preparations such as IRB-consultation, this procedure was introduced clinically in four patients in a pilot phase.

28.3 Comment

Transanal endoscopic surgery has a large potential in representing the future method for a number of indications in colorectal surgery [4, 5]. The technological basis of these procedures needs to be developed further and optimized to facilitate the work of the endoscopists and surgeons in order to provide the adequate safety for the patients.

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The Medrobotics Platform for Transanal Surgery

29

Mario Morino, Alberto Arezzo, and Edoardo Forcignanò

29.1 Introduction

Despite considerable advancements, it is recognized that current robotic devices are somewhat limited in dexterity. Hence, conducting delicate tasks in remote locations, such as endoluminal surgery in the depth of the colon, is beyond the scope of today's robotic systems, which are predominantly fabricated from rigid components. In contrast to rigid robots, flexible robots allow for increased dexterity and adaptability to accomplish tasks, as well as improved safety when working around or even within humans, with huge potential for use in medicine [1]. Aiming to reduce the invasiveness of theranostics (therapeutics and diagnostics), Medrobotics (Medrobotics, Raynham, MA, USA) introduced recently a novel, versatile robotic system with the aim to advance with minimal invasiveness, through narrow cavities and along hollow organs, to diagnose and treat diseases, so far out of reach.

According to the report "Against Cancer" on *Cancer Screening in the European Union* (2017) [2], CRC is one of the three most common cancers in the world, with about 1.85 million new cases each year, a figure expected to double by 2030 [3–6].

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29.2 State of the Art

Only small, flat polyps (< 2 cm) can be removed using the standard colonoscope. Attempting to resect larger tumors (> 2 cm) by endoscopic mucosal resection runs the risk of dividing the tumor into pieces and spreading cancer cells, which requires retreatment in up to 20% of the cases, and impedes correct pathology tumor staging (severity analysis), often resulting in radical surgery as a precautionary measure [7, 8]. Endoscopic submucosal dissection was conceived 20 years ago in an attempt to resect tumors in one piece, reducing the risk of cancer spreading and allowing correct pathology staging. It is performed by an electrified knife inserted through a working channel of the colonoscope. The tissue is cut by moving the scope tip, impacting negatively on the clinician's visual perception as the camera moves with the knife and making tissue manipulation virtually impossible. This leads to unsafe oncological resection margins in almost half of the cases and a high risk of complications [9]. Transanal endoscopic microsurgery (TEM) is a rigid endoscopic platform designed about 35 years ago, proving effective in appropriate local excisions of early rectal cancer [10], but unfortunately applicable only up to 15 cm into the rectum and cannot reach polyps often situated in the upper colon. Colonic resection, although preferably performed through laparoscopy, is burdened by a consistent perioperative morbidity

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of up to 30% [11] and should be limited to those cases unsuitable for endoscopic resections. Even the combination of laparoscopy and endoscopy to reduce the extent of resection is affected by consistent complications and oncological inadequacy requiring radical surgery (11.5%) [11].

29.3 New Techniques for Endoluminal Theranostics

Recently, there has been a remarkable trend in new robotics driven by an interest in creating robotic structures that can interact with the environment in an inherently natural way [12–15]. Soft robotics draws heavily from the way in which living organisms move and adapt to their surroundings [39], but they are far from any clinical application today. Technological developments include snake-like robots, reconfigurable and self-assembling robots, robot capsules, self-propelling robots, and soft and inflatable robots [1, 16, 17]. Many of these technologies have been developed to solve the fundamental challenge of reaching a remote target inside an inaccessible hollow space, such as the colon. All of these have their merits in their own right but suffer from shortcomings when considered for operating inside a long and narrow colon. We find that soft and inflatable robots show particular promise, yet their use for colonoscopy is in its infancy, and most cannot reach far enough inside the colon.

Over the last decade, extensive efforts have been made to miniaturize surgical devices to improve endoluminal theranostics. Nowadays, three main endoscopic platforms use the principles of soft or flexible robotics.

- Endo-Master (University of Singapore) is a flexible endoscope, with two robotic arms, allowing triangulation, controlled by handles at a user console but requiring an overtube for insertion into the bowel [18].
- Anubis Scope (Karl Storz Endoscope) is a flexible endoscope with a tulip-shaped tip avoiding the use of an overtube. Flexible instruments for dissection with 4 degrees of freedom (DoFs) are introduced through dedicated channels [19].
- Flex® Robotic System (Medrobotics) consists of a robotic steerable endoscope advanced into the bowel ignoring gravity due to an inner mechanism creating a stable surgical platform, with two flexible mechanical arms running next to the endoscope. In the current version it can only reach up to 25 cm from the anus into the bowel.

Of these, the Flex® Robotic System (Medrobotics) is the only one available on the market and we had the privilege to use it since now almost 2 years.

29.4 Medrobotics Flex® Robotic System

The system is mainly composed of two units and a flexible robotic endoscope (Fig. 29.1):

(a) *Flex® control console*. The control unit of the Flex® Robotic System is equipped with a haptic controller, joystick type, which can be moved in space in three dimensions

Fig. 29.1 Flex® Robotic System consisting of two transportable main units and a flexible robotic endoscope

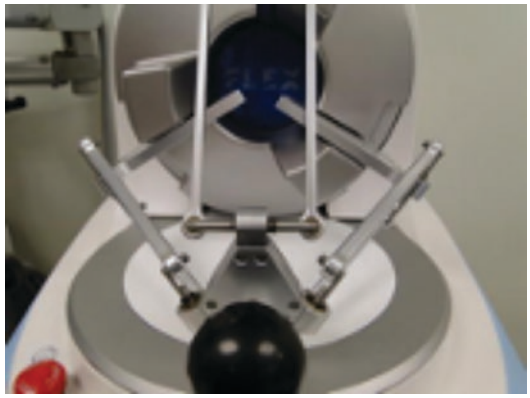

Fig. 29.2 The control unit of the Flex® Robotic System is equipped with a haptic controller, joystick type, which can be moved in space in three dimensions. The movement of this device operated by the surgeon determines an exact excursion of the Flex® Drive

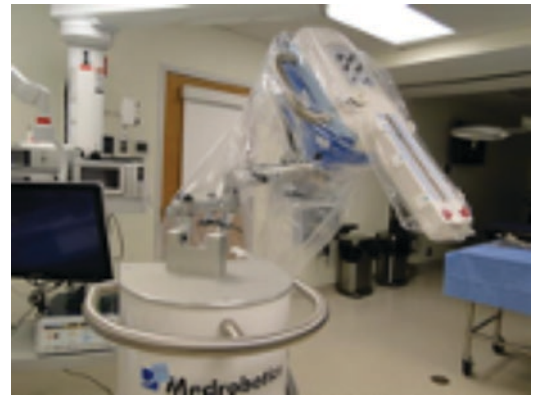

Fig. 29.3 The Flex® Cart is the other unit that makes up the Flex Robotic System that contains the Base and serves to give stability to the Flex® Drive, to transfer commands from the console to the flexible robotic arm. This system is compatible with both Flex® Drive flexible robotic endoscopes for transanal and transoral surgery

(Fig. 29.2). The movement of this device operated by the surgeon determines an exact excursion of the Flex® Drive.

(b) *Flex ® Cart and Base*. The Flex® Cart is the other unit that makes up the Flex Robotic System that contains the Base and serves to give stability to the Flex® Drive, to transfer commands from the console to the flexible robotic arm (Fig. 29.3). This system is compatible with both Flex® Drive flexible robotic endoscopes for transanal and transoral surgery.

(c) Flex® Drive. The working sides of the two variants of the Flex® robot are displayed (Fig. 29.4): on the right, the instrument utilized in the ENT field (Flex® Drive), on the left the version used in the colorectal surgery field (Flex® CR Drive). Note that the Flex® CR Drive is equipped with a disposable cap, which is set up with the robotic system and is used to produce an airtight seal when it mates with the reusable rectoscope. At the end of the flexible robotic arm, there is a miniaturized camera that can be sterilized for multiple uses. All the constituents are intended for single use, except for the camera that is reusable. The two white tubes on the sides of the camera are operating channels located at 3 and 9 o'clock. These host flexible 3.5 mm or 2 mm instruments used to perform surgery and triangular with the camera lens 0°.

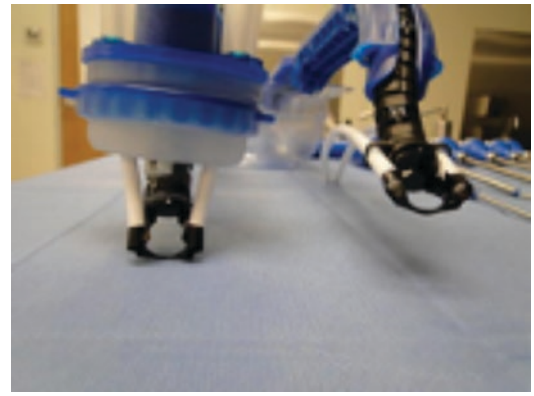

Fig. 29.4 The working sides of the two versions of the Flex® Robot are shown: on the right, the instrument used in the ENT field (Flex® Drive), and on the left, the version used in the colorectal surgery field (Flex® CR Drive)

In the operating setting, the surgeon, close to the patient, works with two dedicated flexible instruments introduced through the operating channels placed on the sides of the camera, which allow surgical manipulation of the tissues (Fig. 29.5).

29.4.1 Features

The Flex® Robotic System received the CE mark for Transoral applications in 2015 and for transanal applications (rectum and distal colon) in

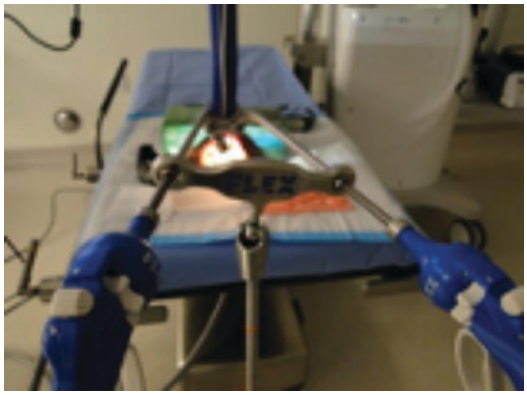

Fig. 29.5 Operative setting: the surgeon, close to the patient, works through two dedicated flexible instruments introduced through the operative channels placed on the sides of the camera, which allow the surgical manipulation of the tissues

2016. The system also has FDA clearance for the two specialties, respectively, from 2016 and 2017.

The Flex® Robotic System was conceived in two mobile units, transportable by an operating room (OR) to the other. This allows to optimize the operating times, being able to move the robotic units as soon as the surgical act is finished, to make the robot immediately available in another OR, also passing from one surgical specialty to another without waiting for the patient change and OR cleaning.

The average setting time of the Flex® Robotic System, calculated from totally inactive to "ready for surgical use," is about 5 minutes.

The Medrobotics company envisages a development of the system in the orifice (scar less surgery) and single port (minimal invasive surgery) fields; the technological positioning is to allow patient treatments in difficult to treat areas, exploiting the unique characteristic of a flexible robotic arm and dedicated flexible instruments.

In the distal part that houses the camera, the Flex® Drive has a diameter of 28 mm and is controlled via the haptic controller placed on the console, straightly by the surgeon at the patient's bed, and not in a remote location. The disposable Flex® Drive flexible robotic arm is mounted on the Flex® Base placed on the Flex® Cart unit before use and transanal coupling with coupling to the dedicated multipurpose rectoscope. In the version for transoral use, however, thanks to the use of a particular retractor, the Flex® Retractor, the oral cavity is kept open and the Flex® Drive is accessed up to the target area to be treated. Essentially, a control knob operated by the surgeon can be used to remotely transfer the endoscope in spatial coordinates. The surgeon then operates at the patient's bedside using flexible, laparoscopic-style pistol-grip instruments, specially designed for exclusive use with the Flex® Robotic System.

These non-robotic tools reach the distal part of the flexible robot, where they can be disposed to generate working angles away from the tool axis, otherwise very narrow radius, thus allowing triangulation. The system hosts different bending 3.5 mm or 2 mm instruments, such as needle holders, grasping forceps, and monopolar tipped or laser holder coagulation instruments. The undisputed advantage of having non-robotic tools, compared to other robots on the market, is to preserve 100% tactile feedback, a benefit that translates into full control of the manipulation of anatomical tissues and discrimination of soft tissues from cartilage and bone. A reusable HD-3D camera with light-emitting diodes permits a clear illumination and definition of the operating range that is viewed on an HD monitor in a similar way to surgical endoscopy.

The Flex® Robotic System with Colorectal Flex® Drive is transanally anchored. In this setting, the Flex® Drive is positioned at 12 o'clock and an 8 mm AirSeal trocar is located at 6 o'clock and is connected to a high-flow insufflator for stable pneumatic distension. At 3 and 9 o'clock, metal pipes are placed through which the flexible instruments are advanced. The entire system is fixed to the operating table rail by means of supports in order to guarantee the stability of the platform. In the transoral operating setting, however, the Flex® Drive is stabilized through a different dedicated multipurpose instrument support and does not need to operate in a pressurized environment.

The system is designed for use by a single surgeon. The operator first creates a field of view by positioning the Flex® Drive with the built-in HD camera, then handles the flexible devices to per-

form the excision. The Flex® CR Drive is transanally coupled to a dedicated metal anoscope, anchored to the operating table, while the two operating channels are anchored outside the endoscope. Once the system is anchored, the operator uses the control console to navigate and move up the instrument toward the area where the target is located. The Flex® Drive advances with controlled movements of 3 or 5 cm at a time, in maximum safety, until the visualization and exposure of the target area to be treated. Once the operative field is defined, the surgeon uses the flexible instruments to complete the dissection to the side; the position of the optic persists stable during this period, but can be adjusted at any time from the console. Two 3.5 mm or 2 mm flexible instruments are then used simultaneously, introduced into the flexible operating channels located at 3 and 9 o'clock with respect to the instrument axis. The Flex® Drive has suction, irrigation, and lens-cleaning capabilities performed by manual irrigation of saline.

This flexible robotic system is principally suitable for the local excision of rectal neoplasms and potentially for ones located in the sigmoid tract. The maximum excursion of the endoscope from the anal margin/plane of the teeth is currently 17 cm. Closure of the breach can be accomplished with a 3.5 mm flexible needle holder suture.

One of the most promising aspects of the Flex® Robotic System is that it can allow for greater proximal reach with respect to the entry orifice compared to rigid instruments. The ability to manipulate the Flex® Drive allows the operator to navigate beyond barriers, such as those placed by the sacral promontory or the tongue base onward. This consents surgeons to access locations not otherwise accessible and consequently lead to new applications via the transanal route.

29.5 Personal Indications for Use of the Medrobotics Flex® Robotic System

The main indication to use the Flex® Robotic System is the dissection and excision of colorectal neoplasms at an early stage. In fact, although endoscopic submucosal dissection (ESD) offers a higher en bloc resection rate compared to endoscopic mucosal resection (EMR), it is technically demanding, time consuming, and bears high adverse event risks compared with other endoscopic methods [20], including risk of perforation up to 10% for colorectal tumors [21]. This is mainly due to the lack of tissue manipulation and, as a consequence, of countertraction [22] that is only partially compensated by extensive training and a wide range of accessory devices including distal attachment caps, electrosurgical knifes, external forceps, suturing devices, magnetic anchor, and cannula-guided snare used in combination with standard flexible endoscopes [23]. In fact, they lack dexterity, triangulation of instruments, and force transmission to point of action. Moreover, the visual field is in-built with the direction of the tool, which is moved together with the endoscope.

We were personally able to remove superficial neoplasms up to 7 cm in maximum diameter, entailing up to half of a circumference and extending up to 18 cm from the anal verge, measured by rigid endoscopy. The precision of HD-3D visualization and the smooth gestures of the dedicated grasper and spatula, although mechanical but flexible, allow to opt either for an endoscopic submucosal dissection, in case a clear plane above the muscle layer is recognizable, or for a full-thickness excision if not.

In case an endoscopic submucosal dissection is intended, the mucosal incision is performed after submucosal injection of saline solution and methylene blue drops. Under countertraction with a grasper, submucosal dissection is performed using a monopolar spatula. A high-frequency generator is used under the same settings used for conventional endoscopic surgery. The spatula allows blunt dissection just above the internal muscle layer, which is fully respected and integer (Fig. 29.6). After standardization of the technique, a common procedure used to last about 1 hour, if suturing was not required. In these cases, suturing is considered not necessary but sometimes preferred to limit postprocedural bleeding and prevention of postprocedural perforation, although today we are

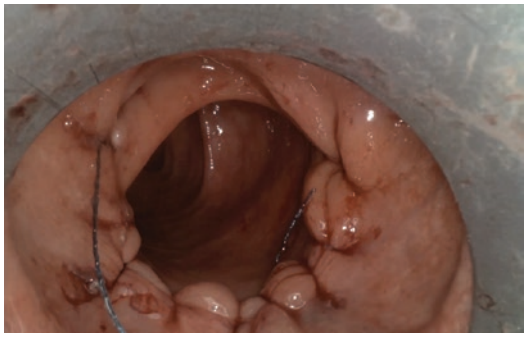

Fig. 29.6 Result of an endoscopic submucosal dissection in the upper rectum anterior wall

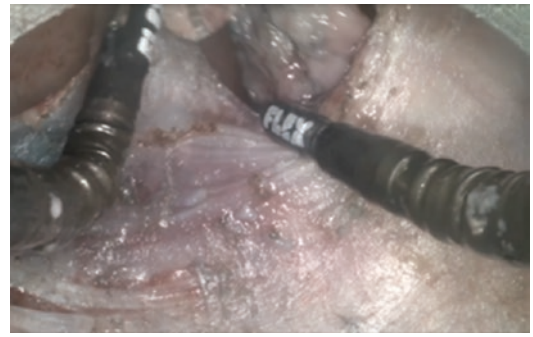

Fig. 29.7 Final image of a running suture with barbed suture after a semi-circumferential full-thickness excision

currently testing hemostatic powders to prevent postoperative bleeding in an effective way. Depending on the preoperative assessment of the position and extension of the neoplasm, the patient can be placed either supine (much more comfortable) for posterior lesions or prone (less comfortable but safer) in case of anterior lesions, especially if potentially above the peritoneal pouch. This is because, in case a perforation of the rectal wall occurred, you avoid small bowel loops dropping inside the rectum, as we learned from the transanal endoscopic microsurgery (TEM) experience. As we still consider the procedure part of our learning curve, we prefer general anesthesia, although selected cases could be performed under spinal anesthesia, as we routinely do for TEM [24]. The patient is generally discharged 24 h after the procedure.

As said, an evident advantage of using such a robotic system with a surgical approach compared to standard endoscopy is that you can switch to a full-thickness excision in case the submucosal layer is suspected for infiltration. In this case, we switch to a robotic colorectal full-thickness excision. It is common experience that the reliability of preoperative imaging workup is unfortunately quite low, so that about 10% of supposed benign lesions turn out to be invasive cancers. Here, after converting the procedure into a full-thickness excision, the Flex Robotic System allows a reliable full-thickness defect suturing. The wound is secured by 3/0 V-lock barbed suture (Fig. 29.7). A perfect closure of the wound is always possible in these cases, preventing the risk of bleeding and reducing the risk of late perforations. Although this is generally just a monolayer running suture, possibly a double-layer suture may be performed reinforcing the reliability. Hereto, after a short learning curve and standardization of the technique, a common procedure used to last an average of about 1 hour and a half including suturing.

We confirm the impression of what recently demonstrated [25, 26] that the robotic ESD is able to significantly reduce procedure time and augment the complete resection rate for ESD. While today the gain compared to TEM is limited, longer systems currently under development will hopefully allow these complex procedures to be performed at least up to the left side of the colon.

29.6 Discussion

The above-mentioned platforms all have the limitation of being just therapeutic devices, with considerable dimensions allowing just limited maneuverability and dissection, due also to lack of control. Typically, the controller's task for surgical robots is merely to aid surgeons in a master–slave architecture by scaling motion, reducing tremors and enhancing precision, as in the da Vinci system. The step forward is to use active perception for shared control mode [26–28] as an enhancement of the teleoperation mode to address additional tasks such as redundancy utilization, constraints generation, and stiffness modulation. Furthermore, semi-autonomous control

of micro-manipulators moving in a small, hard-to-reach and fairly inaccessible workspace will entail the success of the polyp excision procedure that otherwise could not be done except in a partial manner causing recurrence and collateral damage [29–31].

Today, da Vinci robot (Intuitive Surgical, Seattle, USA) makes it possible to perform laparoscopic surgery with great accuracy, limiting the use of standard "open" surgery in particular situations. The limit of this technology, however, is in a certain sense to technically improve what is already possible with the existing technology for endoscopic surgery. The Flex® Robotic System (Medrobotics), on the other hand, represents, in a complementary way, a miniaturized endoscopic surgery system that allows to perform surgical maneuvers in areas that are currently not accessible except to flexible endoscopes without surgical characteristics as they are not stabilized and with a restricted visual field. This allows to bring a miniaturized HD-3D surgical platform inside the body by passing through the natural orifices, therefore first of all oral or anal (and transvaginal in the future). This is why the Flex® Robotic System represents the opening of a new frontier of surgery. It represents the world's first robotic surgical platform with an orientable and shapeable robotic telescope for scar-less surgery. The Flex® Robotic System offers surgeons the unique ability to explore complex anatomy in a minimally invasive way and to operate in hard-to-reach anatomical points that might otherwise be inaccessible with straight, rigid surgical instruments. This allows more patients to access the benefits of minimally invasive endoluminal surgery.

Today, ESD has created a bridge between endoscopy and surgery, providing access to "surgical" and "oncologic" values, such as R0 resection and complete remission of cancer. To our knowledge, this is the first robot-assisted, single-operator, ESD for a large sessile upper rectal lesion including suturing on living human [32]. An evident advantage of using such a robotic system with a surgical approach compared to standard endoscopy is that you can switch to a full-thickness excision in case the submucosal layer is suspected for infiltration. Our personal experience supports the evidence that flexible robotic technologies can enhance the performance of complex dissection within the gastrointestinal lumen applying a surgical technique based on tissue manipulation, traction, and countertraction.

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The Potential of Single-Site Surgery

30

Christof Mittermair and Helmut Weiss

30.1 Timeline

The development of single-site laparoscopic surgery (SIL) is attributed to the first decade of the current century by the majority of surgeons. However, the idea to gain access to the abdominal cavity through one incision dates back to 1902, when the German surgeon Georg Kelling performed the first one-port laparoscopy in dogs [1]. It was a Swedish gastroenterologist, namely Hans Christian Jacobaeus, who did the first single-port laparoscopy in humans in 1910 [2]. For reasons of technical and general medical limitations, including but not restricted to the lack of sufficient anesthesiology, it took until the final two decades of the last century for minimally invasive surgery to be accepted as a matter of clinical routine. Again, technical limitations mandated the use of multiple incisions, at least for therapeutic indications. The concept of SIL was then adopted by gynecologists for tubal sterilization using a single incision and a specially adapted instrument [3]. Further surgical and technical developments allowed modified adaptation of the SIL concept in more demanding procedures. Again, gynecologists pioneered the field with the first SIL hysterectomy [4] as well as the first SIL appendectomy in 1991 [5]. At that time, the concept did not meet with great enthusiasm on the part of general surgeons, and so our predecessors either developed extraumbilical one-trocar techniques [6] or gradually reduced the number of incisions for appendectomy by applying a transumbilical laparoscopically assisted technique [7]. The first case series of SIL cholecystectomies using a technique that was similar to what we now know as SIL was published by Navarra and colleagues in 1997 [8]. It took another 10 years for surgeons around the globe to become comfortable with this "new" idea, and subsequently the concept gained momentum and a majority of surgeons busied themselves with this technique. The synonyms of the SIL concept are given in Table 30.1. The number of performed procedures and published reports exploded within a few years and peaked in 2012 and 2013 (Fig. 30.1; publications). The technique spread to all surgical subdivisions and new applications were created.

30.2 SIL Concept

The aforementioned modern developments in reducing trauma to the abdominal wall stem from tremendous progress in all fields of minimally invasive surgery, targeting every organ in the abdominal cavity. As it was possible to perform these procedures in a technically safe manner with the concept of minimally invasive surgery

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achieving a breakthrough in the surgical field, the focus shifted to the minimized approach to the abdominal cavity. There was considerable interest in omitting every visible scar in the abdominal wall, thus fostering the concept of transumbilical single-incision laparoscopic surgery.

Table 30.1 Most commonly used synonyms of single-site laparoscopy (SIL)

SILS™	Single-incision laparoscopic surgery
LESS (U-LESS)	Laparoendoscopic single-site surgery
SIES	Single-incision endoscopic surgery
E-NOTES	Embryonic NOTES
TUES	Transumbilical endoscopic surgery
SPA	Single-port access surgery
SPL	Single-port laparoscopy
SAS	Single-access-site laparoscopic surgery
SSA	Single-site-access laparoscopic surgery
SSUL	Single-site umbilical laparoscopy
OPUS	One-port umbilical surgery
NOTUS	Natural orifice transumbilical surgery
TULA	Transumbilical laparoscopic assisted
SIPES	Single-incision pediatric endosurgical techniques

The underlying physical concept is based on a simple comparative calculation of the incisional length required to pass a 10 mm inner diameter trocar (outer diameter 11 mm) versus the delivery of three instruments with an outer diameter of 5 mm each. Irrespective of the elasticity of the skin and the fascial sheets, this calculation yields a minimal incisional length of more or less 17 mm for a "10 mm" trocar and three SIL instruments. The prejudice voiced against an increased intrinsic risk for wound complications with SIL as compared to conventional multi-trocar surgery was fed by publications that reported early learning curve data and misleading calculations such as described in [9]. The benefit from minimizing the incision is of special interest when no specimens or very small specimens have to be removed, or small, foldable implants (e.g., meshes in hernia surgery) have to be applied in the abdominal cavity. A low rate of incisional hernias (less than 1% in long-term follow-up) was achieved in our patient cohort using a multichannel port or homemade "glove-port" with wound protection foil and thorough closure of the single fascial incision with non-absorbable monofilament running sutures.

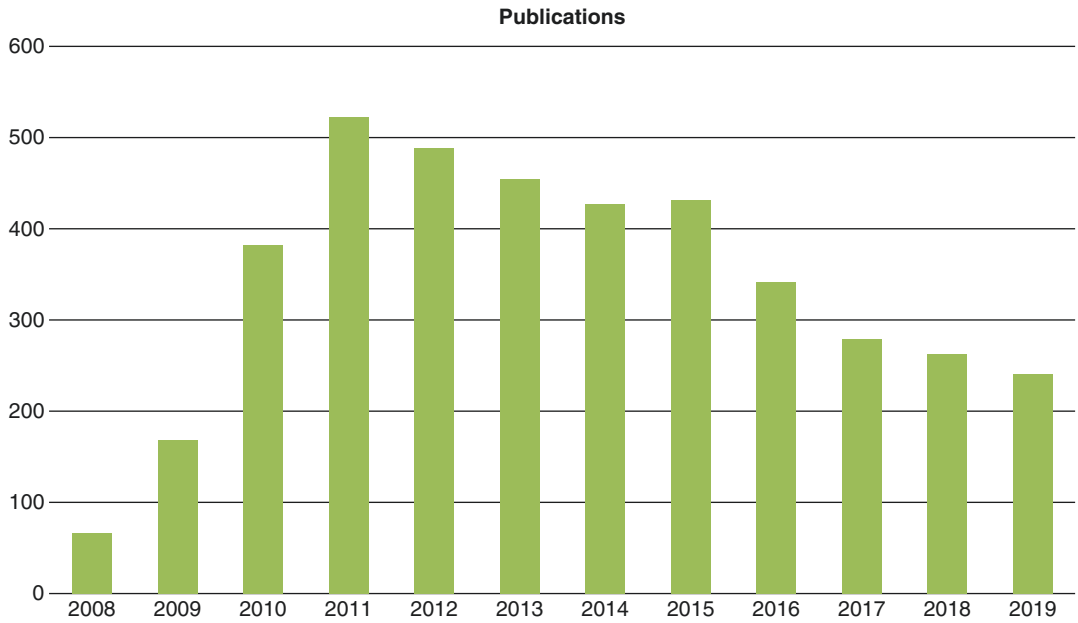

Fig. 30.1 Publications in numbers regarding single-site laparoscopy

Another circumstance supporting the idea of SIL via the umbilicus is its natural shape. This frequently pleated structure allows incision lengths of up to 40 mm to be hidden almost invisibly in the pit of the bellybutton.

When larger specimens need to be retrieved, the incision can easily be enlarged. We recommend that this lengthening of the incision be performed at the caudal end because it permits the cranial fold of the belly button, which is responsible for its shape, to be preserved, thus giving a better cosmetic result. During the past decade, it became obvious that almost all visceral pathologies that require specimen retrieval can be performed entirely through one incision that is needed for harvesting. In all such cases, the ideal incisional site is more important than the incision length, as in many situations (e.g., liver resection of posterolateral segments, metabolic surgery) the intra-abdominal targets cannot be reached by instruments delivered through the navel (Fig. 30.2, left).

Another undoubted advantage of SIL is the fact that it can be performed with standard laparoscopic instruments and follows well-known strategic surgical steps. Therefore, surgical outcomes and safety steps are unaffected when it comes to the ease of immediately converting single-port surgery to multiport conventional laparoscopy.

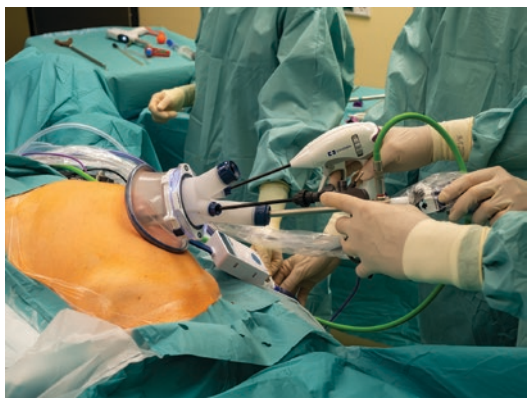

Fig. 30.2 Arrangement of instruments in transumbilical SIL left colectomy. An extralong camera is guided without clashing with the operator's straight (right hand) and bent (left hand) instruments.

Natural orifice transluminal endoscopic surgery (NOTES) could be seen as the direct opposite of SIL as it was developed at a similar time and follows the same goal, namely that of the utmost reduction of trauma to the abdominal wall. However, in contrast to SIL it has several disadvantages and limitations: first, there is a high risk of spilling gastric, urinary, or colonic contents into the abdominal cavity, depending on the site of instrument delivery. Second, many newly designed and unfamiliar instruments are required. Third, spatial orientation is more difficult than in standard percutaneous laparoscopy. And fourth, there remains discomfort with the challenging closure of the viscerotomy with the potential for leakage from gastrotomy or colotomy. These factors have favored broad clinical implementation of SIL and vice versa have hampered further application of NOTES in clinical routine.

As early adopters of SIL, we have enthusiastically standardized a variety of procedures at our department during the past decade, but also observed the standpoint of various colleagues on our team that led to a renaissance of conventional laparoscopy mainly because of the procedural comfort for the surgeon: the EAES statement on ergonomics reads SIL is associated with a more neutral posture of the surgeon's head and trunk but a higher workload and higher wrist range of motion. After passing the learning curve with SIL, the better patient recovery and the astonishing cosmetic results together with the comparable procedural time and costs encouraged us to routinely offer SIL for a variety of surgical treatments (Table 30.2; procedures).

30.3 Technical Prerequisites

As mentioned above, incisions of up to 40 mm can easily be hidden in the pit of the U-shaped umbilicus. A vertical incision is associated with a small number of wound complications and a pleasing cosmetic result [10]. However, horizontal incisions are advocated by other groups [11] because they provide good cosmetic results and low postoperative pain scores. In our experience,

Table 30.2 SIL procedures/SJOG Hospital Salzburg, Austria (September 8, 2008, to August 24, 2020)

SIL procedures	Number	
Cholecystectomies	2115	ERCP/cholangiography
Inguinal hernia repairs	1691	TAPP/TEP/SILAR
Colorectal resections	757	TME/APR/ ta TME
Appendectomies	845	
Liver resections	105	Minor/major
Small bowel resections	88	Crohn/ileus
Gastric resections	46	GIST/metabolic surgery
Pancreas resections	28	Oncologic/spleen preserving
Adrenalectomies	25	Trans/retroperitoneoscopic
Fundoplications	21	Nissen/Toupet
Other	242	
Total	5963	

the complete mobilization of the umbilical skin allows good vision of the fascia and therefore facilitates safe fascial closure under direct vision after SIL. This might outweigh the risk of a longer incision as in conventional laparoscopy, even more so because in up to 40% of our patients we observe a clinically relevant fascial defect, which can be repaired during the same SIL procedure. This is supported by the data of Asakuma, who found a fascial defect in 100% of examined cadavers [12].

The skin incision can then be closed virtually without a scar; it regains its natural shape at the end of the procedure by refixing both skin flaps to the fascia with a three-point suture. The skin incision can be closed either with a running suture or with single-button sutures.

The lack of SIL platforms or trocar systems at the beginning of the modern SIL era in 2009 caused most surgeons to use three umbilical trocars inserted into the abdomen via three small fascial incisions. Fascial closure and instrument movement were considerably complicated with this technique. Furthermore, permanent air leaks aggravated surgical procedures. The subsequent development of SIL platforms by various companies produced noticeable relief. For the surgeons, the SIL technique entails a negative characteristic feature that is experienced when instruments collide inside and outside the body due to the pivot point at the umbilicus. To diminish this awkward effect while establishing triangulation, several different strategies can be pursued:

- First, crossing the instruments results in a virtual exchange of the right and left sides, meaning that the instrument that is deployed with the right hand is positioned on the left side of the operative field and vice versa. In this situation, the use of at least one articulating or bent instrument reestablishes triangulation and prevents the hands from clashing outside the body. Furthermore, deployment of longer graspers to reach the target is an advantage. Handling pre-bent instruments seems easier for surgeons starting out with SIL. However, articulating instruments with rotating tips enable greater degrees of freedom for complex movements in advanced procedures. The bent or articulating instrument should always be used in the supporting hand, whereas the straight instrument is held in the operating hand to facilitate more demanding performance tasks such as dissection, sealing, clipping, or suturing.
- Second, double-curved instruments have been used. These instruments provide correct instrument orientation with respect to the right or left side for both hands. However, this advance in handling is counterbalanced by the reduced freedom of instrument movement as all tasks have to be performed in an almost linear axis.
- Third, a variety of different retracting devices have been developed to alleviate exposure of the surgical targets. Of these, various suspending sutures have proved to be easy to use in

standard SIL procedures. Self-made devices composed of percutaneous sutures or wires allow flexible or static retraction in a string puppet-like fashion, while intra-abdominal retractors (EndoGrab, EndoLift, Virtual Ports, Israel; VERSA Lifter, TPEA Lifter, Surgical Perspective, France), whose versatility of positioning permits them to act as somewhat mobile virtual ports, are also available.

- Along with the selection of useful working instruments and retraction devices, the choice of an appropriate camera system with a corresponding optic plays a crucial role. The insertion of an extralong camera system with a 30° or 45° telescope connected to the light cable at an angle that is not perpendicular to the axis of the camera reduces interference with the camera holder outside the body. Laparoscopes with a flexible tip have proved to be helpful in various situations by facilitating triangulation and exposure, but require subtle guidance.

The following paragraphs summarize the current status and the potentials of SIL with regard to specific surgical applications.

30.4 Appendectomy

The first SIL appendectomy was reported in 1991 by Wolenski and Pelosi [5]. This early report of a few cases was followed by sporadic reports until 2009. With the beginning of this modern SIL era, the number of performed procedures and published reports grew enormously. This may be a consequence of a steep learning curve [13] as well as the fact that minimally invasive surgery increasingly became the standard access for appendectomy in the treatment of appendicitis.

The appendectomy in uncomplicated appendicitis indeed seems to be the perfect role model for SIL for a variety of reasons: the procedure is usually not very demanding, triangulation plays a minor role compared to other surgeries such as cholecystectomy, procedural time is not extensively long, and the presence of a specimen entails the need for a retrieval site. Data from the first larger case series were encouraging and were followed by randomized, controlled trials and meta-analyses. Shorter hospital stay, earlier return to work, and better cosmesis in the SIL group stand vis-à-vis shorter operating time and fewer conversions in the standard three-port groups [14, 15]. These outcomes are encouraging, and hence the procedure is recommended by the EAES for patients looking for a better cosmetic result and earlier return to work [16].

Over the last 10 years, our group has acquired experience with more than 800 cases including perforated and abscessed stages. Our observation that the SIL appendectomy is a very suitable teaching procedure in uncomplicated cases and in expert hands can be performed even in complex cases including ileocecal resection is in agreement with the experience of other groups with a wealth of experience.

30.5 Inguinal Hernia Repair

Contrary to other procedures or indications, SIL inguinal hernia repair has not gained wider acceptance in the surgical field. This stands in contrast to its potentially intrinsic benefit since it is possible to keep the only incision at the umbilicus shorter than that needed for a conventional 10 mm trocar. Patients with a proven loss of structural integrity at the musculotendinous layer and thus an increased risk of wound complications including incisional hernia [17] should per se benefit from this minimized incisional trauma. However, the first SIL TEP procedure was performed in 2008 by Filipovic-Cugura [18] and since then numerous case reports and case series have confirmed the feasibility of the procedure. Various factors account for the moderate adoption rate among surgeons: SIL inguinal hernia repair is regarded as a technically demanding procedure requiring advanced skills in both SIL and hernia surgery. SIL is likely to increase procedural time, which is confirmed by a meta-analysis analyzing data from 10 studies [19]. Conventional laparoscopic inguinal hernia repair in a three-port technique is regarded as one of the most common procedures performed in minimally invasive surgery. It has undergone a

multitude of technical improvements over the last 30 years and ensures high standards. This high level of expertise allows only marginal improvements that can only be measured with a high case load. This may also explain the lack of high-level data supporting any clinical benefit other than cosmesis in this generally intensively studied area [20].

At our department, we have acquired experience with both SIL TAPP and SIL TEP in recent years. With the aim of keeping the incision as short as possible, the "homemade" glove-port system has come into standard use. For patients who are concerned about the cosmetic result, the international expert consensus recommends that SIL TEP be offered as a safe and feasible approach when performed by experienced surgeons [16].

30.6 Diagnostic Laparoscopy and Small Bowel Resections

In keeping with the primary idea of SIL being employed for diagnostic reasons, widespread use of this technique for this indication would be the logical consequence. However, there is only scarce literature with few patients on this topic. Again, gynecologists adopted the technique early and used SIL for diagnostic purposes in patients with suspected ovarian cancer [21]. Within the surgical community, Najah and colleagues reported a series of 183 diagnostic SIL procedures for suspected peritoneal metastases, of which 90.2% were successfully completed. In contrast to most other groups, they used a supraumbilical incision to gain access to the abdominal cavity, simply to allow easy excision of the trocar site as part of the future midline incision during cytoreductive surgery due to the potential risk of port site metastasis. Another series of 42 successful SIL diagnostic surgeries out of 1700 overall procedures was reported by Dapri [22]. In contrast to these fairly modest numbers among a multitude of performed SIL procedures worldwide, this indication is given high priority by our group. We have performed 187 SIL procedures for diagnostic purposes and acquired positive experience with this technique in all kinds of unclear abdominal pathologies. The approach ensures sufficient overview of all four quadrants of the abdominal cavity and allows a multitude of therapeutic options, depending on and increasing with the individual surgeon's experience. Even in patients with intra-abdominal adhesions, the approach is safe and feasible as adhesiolysis can be performed under direct vision.

SIL naturally plays a minor part in the treatment of bowel obstruction. This is not due to an inferiority of the concept by comparison to standard laparoscopy, but is a result of the general refusal of minimally invasive techniques by these patients. Arguments frequently stated against minimal invasive surgery in small bowel obstruction are inferior intraperitoneal vision, a higher risk for bowel injury, and increased costs as compared to open surgery. However, a report on 34 successful SIL cases in patients with bowel obstruction demonstrates its feasibility in experienced hands after very careful patient selection [23]. We have also been able gather some experience in patients with small bowel obstruction and had a low complication rate in these selected patients. However, advanced experience with SIL surgery is recommended for this indication as there is generally very little space for instrument handling and movement in the abdominal cavity. This increases the risk for unrecognized bowel injury with potentially life-threatening consequences.

30.7 Upper Gastrointestinal Tract Surgery

Application of SIL at the esophagus for malignant indications is a rarity in the literature and clinical medicine. A few case series have demonstrated a fundamental feasibility [24, 25]. However, the technique has not been able to garner any importance in the clinical routine setting as the technical difficulties posed by the anatomical obstacles do not outweigh any increased procedural risk. This is clarified as follows: access via a thoracoscopy implicates instrument han-

dling and application in very tight conditions, which further diminishes the natural technical disadvantage of instrument handling in SIL, in particular when advanced skills are required to perform an intrathoracic anastomosis. On the other hand, instrument application solely through the abdominal cavity is, in most cases, not technically expedient.

The situation at the gastroesophageal junction is a different one. First successful reports of SIL fundoplication date back to 2010 [26], and substantial literature and clinical cases have been published since then. Here the group of Rosemurgy and Ross deserves to be mentioned as they have booked considerable experience in this field. Although high patient satisfaction and excellent cosmetic results have been reported [27], the procedures are technically demanding and careful patient selection appears to be mandatory. Intrathoracic preparation of the esophagus is aggravated by a potentially long distance from the incision and narrow spatial conditions. The synopsis of the aforementioned factors may explain the low acceptance of this technique among laparoscopic surgeons. These factors and an iterated intraoperative clash with the body of the pancreas prompted us to return to a conventional laparoscopic technique. However, according to the current literature SIL anti-reflux surgery (Nissen fundoplication) is offered as a procedure that is performed safely in select patients (ASA 1 or 2).

The implementation of SIL in gastric surgery is broader and more common. Despite its use in bariatric procedures (see next paragraph), some groups have acquired considerable experience with SIL for gastric surgery. As expected, the initial application was restricted to small case series and the resection of GIST tumors or benign indications. These resections are generally well suited for SIL and provide a good introduction to SIL gastric surgery. With the increasing experience acquired in recent years, some groups started to target malignant cases with oncological resections requiring lymphadenectomy. However, technical limitations have caused the focus here to be clearly on early stage carcinomas and D1+ lymphadenectomies. The status of D2 lymphadenectomy in SIL has to be scrutinized and critically analyzed today. This technique is promoted and successfully implemented by two very experienced minimally invasive surgical groups in Asia [28, 29]. Other numerically noteworthy reports do not exist to date. The available literature focuses on technical feasibility and the oncological equivalence to conventional laparoscopic resections. Nevertheless, the small number of cases leads to a well-founded statement on generalized oncological outcomes to seem untrustworthy to date. Furthermore, it has to be critically remarked that from a worldwide perspective the role of minimally invasive gastrectomy with D2 lymphadenectomy is insignificant and the available literature does not allow a conclusion to be drawn as yet. Concise lymphadenectomy, especially at the pancreatic body and the splenic vessels (regions 11 and 12a, p), is technically extremely demanding in every kind of minimally invasive procedure, but is ontologically necessary. The correct dissection in this crucial step, inter alia, has caused our group to continue to perform this procedure with a conventional laparoscopic technique.

Another technically interesting application with a clinical impact is the use of intragastric SIL. Here, the stomach is fixed to an incision in the abdominal wall and a SIL device is introduced. This permits intragastric surgical (resection) techniques to be applied without destroying the integrity of this organ with extensive resections. Moreover, this procedure can easily be performed as a rendezvous procedure with standard flexible transoral gastroscopy. The technique is already used to resect GIST, which is difficult to reach via standard access paths [30]. Further indications incorporating intragastric suturing and other demanding techniques are easily anticipated, and some groups have started to investigate this technique in animal models, including bariatric procedures [31]. We have acquired some experience with the resection of intragastric GISTs and one case of the complicated removal of a foreign body. While the results are encouraging and the complexity of the procedure is manageable, the rarity of these cases means that only scarce experience exists.

30.8 Metabolic Surgery

As in all other areas of minimally invasive surgery, SIL has made its way into bariatric/metabolic surgery. In addition to the aforementioned arguments supporting SIL, there is still another factor that plays a key role in these patients: As the abdominal wall remains virtually scar-free, there is no trace of a metabolic procedure. Consequently, there is less stigmatization of patients in the community. The first reports of SIL sleeve gastrectomy and gastric band application at an early stage [32, 33] are in line with a notorious innovativeness among bariatric surgeons. Procedures including anastomoses were implemented only 2 years later, which evidences the complexity of suturing in the SIL technique. It must be stated that for these difficult procedures in critical patients the use of articulating instruments and sometimes even articulating camera systems is advocated by all groups who regularly perform SIL bariatric procedures.

Most data are published on SIL sleeve gastrectomy, which is a direct result of two factors. First, the number of sleeve gastrectomies has steadily risen, with this intervention being the most common bariatric procedure currently performed, at least in the United States [34], and second, the procedure is relatively simple with the SIL technique. However, careful patient selection has been seen to be indispensable for successful surgery. The transumbilical approach offers the possibility to hide the scar and make it almost invisible, but the distance to the stomach and the fundus differs from patient to patient. In tall and very obese patients, the gastroesophageal junction is difficult to reach from the navel, and thus a different access point or a classical laparoscopic approach has to be chosen.

Gastric banding has also proven to be possible with the SIL technique. In addition to cosmetic advantages, a relatively small number of complications and, in some series, a pleasing body weight loss have been demonstrated [35]. However, with the trend to lower rates of implanted gastric bands, no large series on this indication exist.

The Roux-en-Y gastric bypass is considered an advanced laparoscopic technique and is even more demanding when performed with the SIL technique. The required two anastomoses are a significant technical hurdle, being crucial for the success of the procedure and potentially life-threatening if not executed accurately. This factor and, again, the advance of sleeve gastrectomy may explain its relatively hesitant implementation. Nevertheless, existing data provide encouraging results in terms of weight loss and superior cosmesis, in expert hands [16].

Our personal experience is limited to 31 gastric sleeve resections, Roux-en-Y gastric bypasses, and single-loop bypasses with appropriate results. This is due to the fact that we run only a small bariatric surgery program that also comprises teaching and robotic surgery.

30.9 Colorectal Surgery

The implementation of SIL in colorectal resections is a logical step in various respects when developing this technique. For all SIL colorectal resections, the umbilicus is suitable as the site of port placement and can provide access to all parts of the colorectal frame. Only dissection at the splenic flexure can be challenging in some patients because of its considerable distance from the navel. Additionally, specimen retrieval is mandatory in almost all colorectal procedures, and, as described earlier, an incision length of 4–5 cm can be easily hidden in the umbilical arch while allowing removal of bulky colonic specimens, as in sigmoid resection for recurrent diverticulitis. Last but not least, when access to the abdomen is established through only one incision, movement to another quadrant inside the abdominal cavity is not hampered by impending unfavorable trocar positioning (Fig. 30.2, SIL left colectomy). Thus, as expected, the first SIL colorectal procedures were conducted and published much earlier than for other indications [36, 37] and initially comprised mainly resections in benign diseases. These first cases were immediately followed by numerous case series, and the indication was extended to malignant cases and

the rectum. The advantages of the technique, namely an improved cosmetic result, less postoperative pain, and earlier return to normal life, were proven in randomized controlled trials. Some recent data suggest even a lower postoperative complication rate with the SIL technique as compared to multiport laparoscopy [38]. However, when performing surgery in malignant cases, oncological safety comes into focus. With regard to key parameters for oncological safety in the short term, the number of resected lymph nodes and the rate of R0 resection are regarded as standard indicators. With regard to the aforementioned criteria, this oncological safety has been demonstrated in some randomized controlled trials, the first published in 2012 [39, 40]. These data were followed by other randomized controlled trials confirming the oncological safety. Finally, a meta-analysis of randomized controlled trials in 2018 [41] did not show any statistical difference in oncological safety by comparison with multiport laparoscopy. Over the last 10 years, we have gained experience with 757 cases of colorectal resection in benign and malignant disease. The consensus paper on SIL concludes that in select patients (<T4 or tumors <5 cm, BMI <35, no previous abdominal surgery) SIL colonic resection was offered to patients as an equally safe and effective alternative to multiport colonic surgery with comparable histological surrogate outcome [16].

With a short learning curve, we were able to switch all cases from multiport laparoscopy to SIL with an additional trocar occasionally needed in complex cases.

In contrast to the large body of data available on SIL colonic surgery, reports on SIL surgery of the rectum are scarce. Some small case series have demonstrated its feasibility in select patients, but larger case series or conclusive RCT do not exist in sufficient quantity. Several reasons are decisive for this fact: the complexity of the procedure is high and the learning curve is extended. Thus, the recommendation that rectal resections be performed with the SIL technique is cautiously limited to select patients and experts only: single-incision endoscopic rectal surgery in select patients (tumor size <4 cm and BMI <30) has been safely performed by experienced laparoscopic surgeons with less postoperative pain and comparable histological surrogate outcome than for multiport laparoscopy [16].

Parallel development of techniques such as the trans-anal total mesorectal excision (TaTME) has shifted the focus to this promising approach and, finally, it must be mentioned that the acceptance for minimally invasive resections at the rectum is still unexplainably low among surgeons. In contrast to these developments, we have successfully integrated SIL rectum resections into our clinical routine among all procedures. We generally use the site of the planned ileostomy to gain access to the abdominal cavity as the only incision in these patients. However, for low and ultra-low rectal malignancies TaTME has gained high significance and we usually combine the technique with a trans-abdominal SIL approach.

30.10 Cholecystectomy

Cholecystectomy is still regarded as the most commonly performed and doubtlessly the most discussed SIL procedure. Its first report dates to 1997 by Giuseppe Navarra [8]. He published a case series of 30 patients operated between May and October 1995 using three suspension sutures to handle the gallbladder and two umbilical 10 mm trocars for the camera and one working channel. In this early series, no complications were reported and the operating time was 123 min. The authors reported good vision of the organ as well as shorter hospital stay, less postoperative pain, and a superior possibility to remove the specimen as compared to the multi-trocar technique. The publication was greeted by some criticism from the surgical community concerning the safety and feasibility of the procedure. Supported by the fact that at that time conventional laparoscopic cholecystectomy was still the subject of controversy, the time was not ripe for another innovation in this field. The SIL technique fell into oblivion for this indication until it was rediscovered in 2008 and 2009. Thanks to the technical and surgical progress made since the first report by Navarra, case series conducted

10 years later provided encouraging results [42] and the surgical community took up the technique in no time at all – some of the surgeons even without obtaining the pertinent skills. This, however, led to some hair-raising case reports at surgical conferences among other, more serious surgeons who were able to integrate this technique thoroughly and safely in their surgical armamentarium. Part of the long-lasting reluctance to implement SIL may be explained by these disquieting examples of surgical pioneering spirit and the awkward necessity to invest in further skill training in order to efficiently manage the SIL technique.

Subsequently, a multitude of case series and first randomized controlled trials were published that confirmed the feasibility and showed better cosmesis, less postoperative pain, and shorter recovery time. In contrast to these findings, some criticism was voiced concerning incisional hernia and data assuming a higher hernia rate after SIL [43, 44]. However, these findings could not be confirmed by other data from high-volume centers [10, 45]. Another concern is a possible larger number of adverse events [46]. These findings have to be taken seriously, however, and a closer look is worth taking. When patients from early case series and trials are included in these analyses, indeed a comparatively large number of adverse events can be observed. A recent multicenter study from Korea shed some new light on this circumstance and revealed a relatively constant and low rate of adverse events in the chronology of the last 10 years despite a considerable increase in acute cholecystitis treated with SIL [47]. Additionally, and, again, this group demonstrated a relatively low rate of 0.5% incisional hernias.

A survey of 600 surgeons from around the world reported that surgeons would prefer standard four-port CHE or mini-laparoscopy if the procedure were being performed on themselves. However, the main factors guiding the decision-making procedure are the surgeon's experience with this technique and the safety of the procedure [48]. As in other fields of visceral surgery, the optimal approach for each situation is chosen at the surgeon's discretion. Consequently, a publication announced that dual-incision laparoscopic cholecystectomy has the advantage of the shortest procedural time combined with the lowest complication rates and good cosmesis as compared to SIL or multi-trocar laparoscopy. Our own experience differs slightly as all surgeons on our team are free to perform a SIL, dual- or multiport laparoscopic cholecystectomy, and we have not observed any difference between these techniques with regard to time or complication rates. However, as adequate triangulation and sufficient exposure are mandatory in these procedures, we have a low threshold for implementing suspension sutures and additional trocars in difficult patients or pathologies. The published consensus statement advises that in patients with a BMI <35 SIL cholecystectomy can be performed if a patient desires better cosmesis and less pain than for conventional four-port laparoscopic cholecystectomy [16].

30.11 Pancreas Resection

Single-incision laparoscopic pancreas resection is a very exotic application of this technique. As standard laparoscopic pancreas surgery is among the most demanding procedures in minimally invasive surgery, the incorporation of SIL pancreas resections into clinical routine has, understandably, not progressed without conflict. Reports on SIL and the pancreas are limited to a few cases and case reports on resections at the pancreatic tail. First reports go back to 2010 [49] and describe individual cases of distal pancreatectomies. The available literature is scarce, and no generally valid conclusions can be drawn. However, the procedure appears to be safe and oncologically suitable if performed by expert SIL surgeons. The data have to be interpreted restrictively as some groups including ours have meanwhile abandoned the concept of pure SIL pancreatic resections for dual-incision laparoscopy, providing an additional trocar for better handling and the use of an extraumbilical drainage site [50, 51]. Our group has gone through the same development over recent years. We started with a pure SIL approach and changed to a

dual-incision technology for technical reasons combined with the need for an extraumbilical drain. Our experience with this technique started in 2009 and comprises 28 cases with no technical restrictions and a good oncological outcome. International consensus recommends that SIL distal pancreatic resections be offered as a procedure that is equally safe and effective as multiport laparoscopy, when performed by experienced surgeons [16].

30.12 Liver Resection

Again, the very demanding technique of minimally invasive liver surgery hampered comprehensive introduction of SIL hepatectomy. Because of this, the step forward to SIL was taken very cautiously although the larger incision required for specimen retrieval speaks in favor of the SIL concept. The first hepatic procedures performed with the SIL technique were deroofing of cysts and minor resection of small benign tumors as well as ideally located malignant tumors [52–54] in 2009. The technical feasibility was established and indications expanded to more complex cases. Some evidence was gathered on left lateral sectionectomy as it is regarded as a technically simple standard procedure in minimally invasive liver surgery [55]. For this indication, SIL was seen to be superior to multiport surgery with regard to cosmesis and postoperative pain control. Consequently, the implementation of SIL in minimally invasive hepatectomy is making progress and some groups have successfully acquired experience with major liver resections performed with this technique [56]. We have performed more than 100 SIL liver resections in the last ten years. Starting with minor resections in highly selected patients, we little by little expanded the indications to more complex cases including 36 major liver resections. The use of inline radiofrequency pre-coagulation has proven effective in our hands [57], which facilitates resections even in complex cases. Currently, SIL minor liver resections have been offered as safe and effective surgical procedures when performed by experienced surgeons, as compared to the conventional laparoscopic approach [16].

The umbilicus is the preferred site for port placement when operating on the left and anterior segments, whereas an incision in the right upper abdominal midclavicular line has proven ideal to reach the posterolateral segments (Fig. 30.3; approach for posterolateral segmentectomy). With regard to the use of SIL, it is

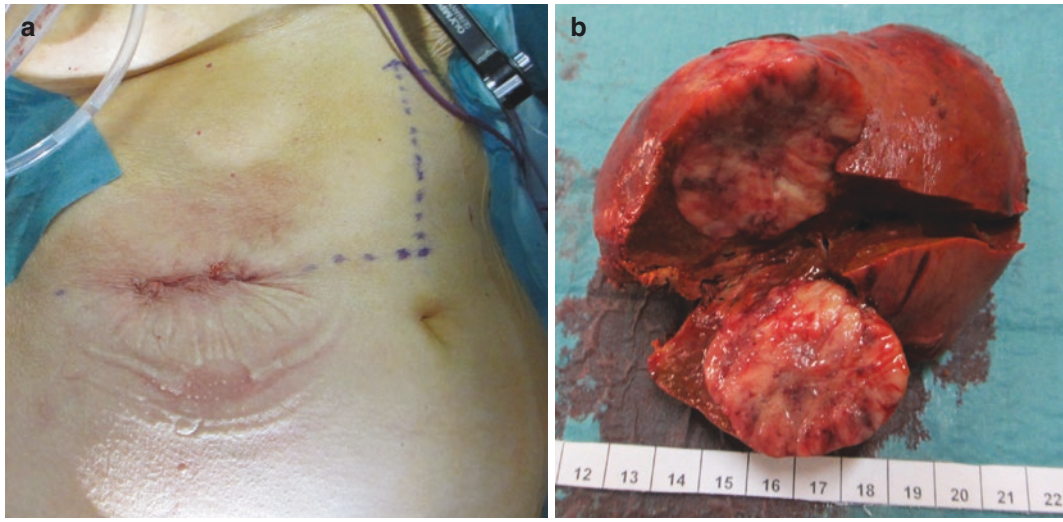

Fig. 30.3 External view of subcostal SIL approach for right lateral hepatic resection (**a**) and corresponding liver specimen (**b**)

clearly understood that every surgical procedure, and in particular complex interventions such as major hepatic resections, requires the utmost safety precautions, which can never be compromised by poor surgical performance or lenient patient selection.

30.13 Conclusion

Modern SIL has been on the market for more than a decade. It was initially enthusiastically introduced by the surgical community and promoted by the industry, but then encountered unjustified disdain in the face of disappointing results from ill-conceived use. The early learning curve became a strenuous obstacle course, but ultimately brought forth new and safe standards for advanced minimally invasive surgery that offers a procedural performance combined with aesthetic integrity that is unrivaled by any other technique of trans-abdominal surgery.

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New Single-Site Platforms

31

Hans Friedrich Fuchs, Rabi R. Datta, Dirk L. Stippel, and Christiane J. Bruns

31.1 Introduction

The advent of minimally invasive surgery [or minimal access surgery (MAS)] was characterized by a massive switch of the majority of surgeons from open cholecystectomy to the laparoscopic technique, often pushed by the patients, who required this less invasive approach [1–3]. This "killer application" built a major portion of the success of MAS [1–3]. In the subsequent 30 years, several alternative, possibly even less invasive access techniques to classic laparoscopic cholecystectomy emerged and some of them also disappeared again. The initial success story of classic laparoscopic cholecystectomy could never be repeated. An early alternative technique was mini-instrument cholecystectomy, which is still used in certain centers quite successfully [4–6]. With the hype around natural orifice surgery, transgastric cholecystectomy was investigated, but obvious limitations in available technology inhibited clinical applications [7–9]. Transvaginal cholecystectomy went through a hypes especially in Germany, but did not stand the test of time [10–12].

Single-port access was introduced during the phase and several investigations were performed [13–15]. The obvious advantage was the reduction of access trocars; however, the procedure through the limited "single" port was quite cumbersome because of the nature of the technique [13–15]. Initially the special instruments needed to curved and crossed inside the abdominal cavity, increasing the level of complexity of the procedure [13–16]. These latter disadvantages were soon followed by an increasing number of complications due to complexity of the technique and inexperience of the surgeons [14].

As a consequence, the popularity of single-port surgery (SPS) and cholecystectomy decreased in the past 5–10 years again. Today, SPS is not the standard of care in most institutions. The technical difficulties lead to an increased operative time and even possibly increased complication rates [15, 17–24]. Furthermore, the incision usually at the umbilicus may lead to a higher rate of postsurgical hernias because quite often a single-port application ends up in an incision of 2–3 cm [17, 18].

New techniques such as robotic cholecystectomy have generated interest and were recently investigated [25, 26]. However,, it seems a valuable aim to investigate further in the concept of reducing access trauma by reducing the size of trocars and also reducing the number of necessary trocars [17–24].

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A new platform for SPS is the Fortimedix Surgical SymphonX™ system with a diameter of only 15 mm [27, 28]. This system allows for the introduction of a camera and of two noncrossing, articulating instruments, which create a comfortable working platform with space to manipulate instruments and tissue, incorporating features comparable to robotic surgery [27, 28]. SymphonX™ carries the ability to perform a laparoscopic procedure such as a cholecystectomy without an additional trocar [29]. Clinical studies show promising results [29].

31.2 The SymphonX™ Platform

The platform was developed in several preclinical tests to evaluate the abilities and learn about shortcomings early [27–29]. The system has been CE-mark-approved and has been used in clinical work. Figure 31.1 demonstrates the platform with the system (diameter <15 mm to pass through a 15 mm trocar) and the articulating instruments. On each side of the introducer, lateral sliding arms are located to provide positional support for the articulating instruments.

Several instruments are accessible via four lumens through the introducer. There are two lateral lumens (channels) for working devices (Fig. 31.2) and one superior lumen for a 5 mm laparoscopic camera, which can be moved in and out according to the necessities.

In addition, there is another inferior lumen in the introducer for an additional 3 mm instrument such as a suction/irrigation device or a small grasper. There are a number of different instruments available for these working channels: a cautery-hook for dissection, curved dissectors, different graspers, a clip-applier, scissors, and a suction/irrigation device. The articulating instruments have especially configurated articulating segments and rigid segments, which allow for stabilization and triangulation incorporating

Fig. 31.2 The introducer provides four different channels. There are two lateral lumens (channels) for working devices and one superior lumen for a 5 mm laparoscopic camera, which can be moved in and out according to the procedure

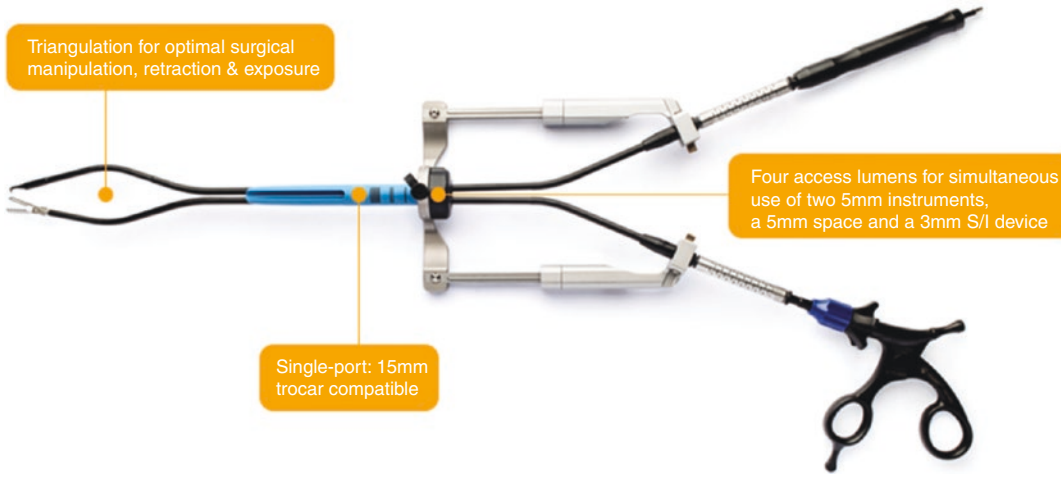

Fig. 31.1 SymphonX™ platform for single-site surgery with articulating instruments and single trocar with a diameter of 15 mm

robotic features without proximal instrument crossing or collision. Each device is able of 360-degree rotation as well as lateral, anterior/posterior, and superior/inferior maneuverability. These manipulations can be performed in the usual laparoscopic "paradigm" without instrument crossing, facilitating the learning process and the technical applicability.

31.3 The Operative Technique

The procedure is started with the standardized preoperative preparations as established in the guidelines of MAS. The patient is positioned in either a supine of beach-chair position. All steps for the preparation of a safe laparoscopic cholecystectomy are followed. A capnoperitoneum is established and then followed by the introduction of the 15 mm trocar, which is needed for the introducer. Care is taken to place the trocar at a distance of about 12–14 cm from the target organ, the gall bladder. After the trocar is safely placed, the introducer is inserted in the trocar and the laparoscope is introduced in the abdominal cavity, followed by a checkup view of the abdomen and also of the right hepatic region as well as the Calot's triangle. The latter can be best inspected after a string-suture is placed through the abdominal wall around the Teres hepatic ligament to pull up the right liver lobe. This exposure allows for a safe dissection of the target organ.

Then, the gallbladder can be retracted and the Calot's triangle can be exposed to start a safe dissection of the important structures. The cystic duct, the cystic artery, and the lateral aspect of the common bile duct are identified. Then the cystic duct and artery are dissected and after a "critical view" can be closed by clips and divided. This is followed by the dissection of the gall bladder in the liver bed. The specimen can be removed with a grasper via the trocar or the trocar incision. In a pilot study, most cases could be performed without any additional trocars for assisting [29]. The mean operative time in this study was 107 min [29].

31.4 Discussion and Comment

Single-port surgery (SPS) became popular several years ago because of the potential of reducing access trauma [13–17]. However, the success of this concept was limited by the cumbersome technique of crossing instruments at the trocar as well as instrument collision [14, 22, 23]. The latter may have led to an increased complication rate, especially common bile duct lesions in single-port cholecystectomies [22, 23]. Furthermore, the necessity in some cases of creating an incision at the umbilicus of 2–3 cm to introduce large single-port systems led to an increased rate of late hernias at the incision site [22, 23]. Current comparisons and reviews report on significant differences in results after classic multiport laparoscopic cholecystectomy versus single-port cholecystectomy [19–24, 30]. Increased rate of adverse events, higher risk of trocar hernias, higher rate of seromas and contusion around the port site, increased risk of bile leaks, and bile duct lesions are reported [19–24, 30]. A word of caution was recently published after a detailed analysis, despite a better cosmetic result [30–34].

Safety can also be added by careful dissection of Calot''s triangle using the "critical view" without exceptions, and demonstrating the anatomy by using a Indocyanine Green (ICG) cholangiography in all cases, which presents the individual anatomy very nicely [29, 35].

Furthermore, the improved handling technique of the "single-port" concept by avoiding crossing and colliding instruments with the ability of allowing for exact and detailed manipulations at the tissue level by articulating instruments has established a safety level also in SPS, using this platform [29]. The system has also been used in patients with inguinal hernias with clinical success [29].

There are limitations regarding the SPS concept. In some cases, more traction or countertraction is needed from different directions in order to expose a structure and/or continue in a safe way the operation. Then, an additional trocar is needed, as was necessary in our study in some

cases [29]. The advantage of articulating instruments to perform precise maneuvers at the tissue level may be at the same time disadvantageous when these articulating shafts are too flexible compared to classic laparoscopic instruments for dissection or grasping. This may be of importance in obese patients. Thus, we do not recommend the application of this system in patients with a BMI >40.

In the future, possible indications for this platform in SPS could be cholecystectomy, inguinal hernia surgery, tubal ligations, benign foregut surgery, and assisting in endoluminal procedures.

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32 Intraoperative Imaging for Procedures of the Gastrointestinal Tract

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32.1 Basics of Intraoperative Imaging in Surgery of the Gastrointestinal Tract and the Abdomen

Hitherto, surgery of the gastrointestinal (GI) tract is performed under indirect vision via endoscopic or laparoscopic imaging systems. In comparison to open surgery, the field of view is restricted, and the surgeon loses haptic feedback to a large extent. Although intraoperative imaging could assist the surgeon by showing additional information, the main standard imaging modalities used in the daily clinical practice remain X-ray imaging, for example, intraoperative cholangiography, transcutaneous sonography, and endosonography. Intraoperative, endoscopic and laparoscopic sonography are used as guidance tools during resection of tumors of the pancreas and GI tract [17, 19] as well as drainage and injection procedures using fine needles [37].

Further imaging methods have been developed to overcome the limitations of minimally invasive procedures (Table 32.1 and Fig. 32.1). Although these modalities are not established in clinical routine practice, some of them such as near-infrared (NIR) fluorescence, laser speckle contrast imaging (LSCI), and narrowband imaging (NBI) have been adopted by surgeons and have been realized as commercial medical

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Table 32.1 Features of different nonstandard intraoperative imaging techniques evaluated in gastrointestinal surgery

	Optical imaging						Hybrid imaging	Thermal imaging
	Fluorescence	LSCI	NBI	OCT	Raman	HSI	PA	IRT
Spatial resolution	Sub-millimeter	Sub-millimeter	Sub-millimeter	Micrometer	Micrometer	Sub-millimeter	Micrometer	Sub-millimeter
Penetration depth	1–2 mm	1–2 mm	1–2 mm	1–2 mm	<1 mm	<5 mm	up to a few cm	<1 mm
Contrast agent	e.g. ICG	None	None	None	None	None	None	None
External tissue stimulation	Optical waves (NIR range)	Optical waves (NIR range)	Optical waves (blue, green and red ranges)	Optical waves (NIR range)	Optical waves (depending on the application)	Optical waves (visual and NIR range)	Optical waves	None
Contact during acquisition	No	No	No	No	No	No	Yes	No
Scanned area	Several cm^2	Several cm^2	A few cm^2	A few mm^2	A few mm^2	Several cm^2	Several cm^2	Several cm^2

several = area till 10 cm x 10 cm
few = area approximatively of 1–2cm x 1–2 cm
Difficult to estimate because depends on the technology and device

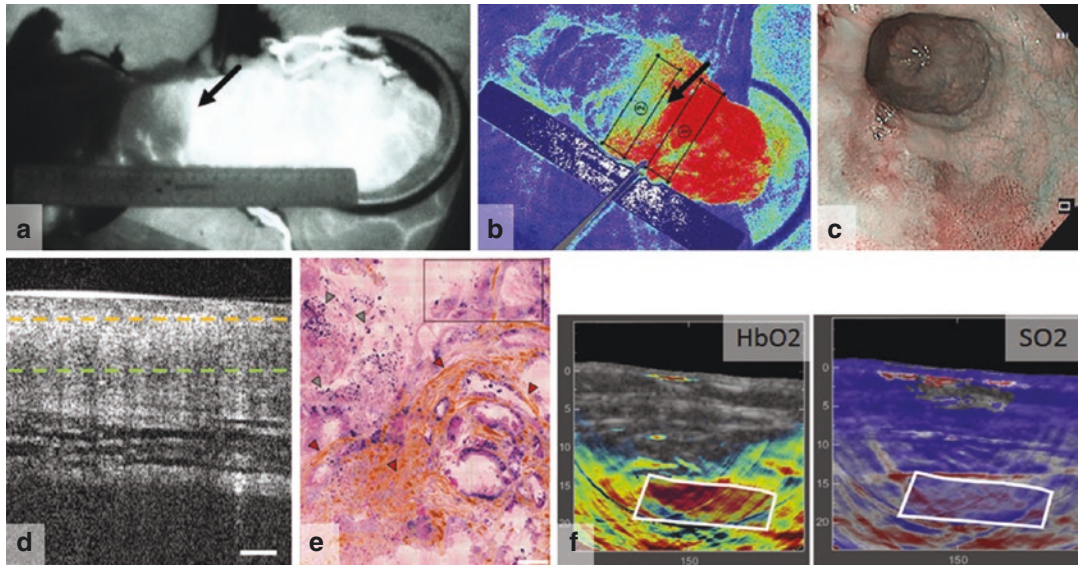

Fig. 32.1 Examples of intraoperative imaging used for diagnosis and therapy of the GI tract. (**a**) and (**b**) transection margins (black arrow) of the in vivo bowel in ICG fluorescence (own image) and LSCI [29]. (**c**) NBI image of cancer of the in vivo esophagus [6]. (**d**) Cross-sectional endoscopic OCT image from in vivo colon polyp (scale white bar is 100 μm) [32]. (**e**) Stimulated Raman histology image of freshly resected colon adenocarcinoma (scale white bar is 100 μm) [43]. (**f**) Tissue hemoglobin (HbO_2) and oxygen saturation (SO_2) parameter images of a patient with active Crohn's disease and computed based on multispectral photoacoustic (PA) imaging [51]

devices [45]. The principle of NIR fluorescence consists of injecting an exogenous dye, for example, indocyanine green (ICG), exciting the molecules of the dye using narrow-band light, and recording the fluorescence signal emitted. This technique is mainly used to estimate tissue perfusion and is still under evaluation to reduce postoperative complications due to anastomotic leak during colorectal and esophageal tumor resection surgery [1, 10, 14, 24]. Diana et al. presented a tool, called fluorescence-based enhanced reality (FLER), to quantify and visualize perfusion information extracted from ICG fluorescence. It consists of averaging the fluorescence signals measured within a limited time window and in providing dynamic perfusion cartographies shown to the surgeon [15]. The main drawback of fluorescence imaging is the injection of exogenous dyes that can cause complications such as allergic reactions. LSCI has been evaluated as alternative noninvasive modality for the visualization of intestinal blood perfusion [29]. This technique measures in real time the light backscattered by the moving red cells in blood under excitation with NIR laser. It is sensitive to motion artifacts that compromise the detection of the blood-derived signal [20]. NBI is a further well-accepted modality in the field of gastrointestinal diagnostic and laryngeal surgery. It uses a narrow range of green, blue, and red wavelengths to enhance the contrast of vascular structures and mucosal patterns. This method is used to distinguish between benign and malignant lesions and to identify tumor margins in esophagus, stomach, and colon cancers [2, 6]. Training is necessary to objectively interpret the images and reduce the interobserver variability.

More recently introduced imaging techniques such as optical coherence tomography (OCT), Raman spectroscopy imaging, photoacoustic (PA) imaging, and infrared thermography (IRT) have been shown to visualize certain aspects of cells and tissue. The principle of OCT consists of stimulating tissue with a light source at a given wavelength, typically in the NIR range, and in measuring the scattered and reflected light coming back to the camera. It provides 2D cross-sectional and 3D images with pixel resolution in the micrometer scale. Small probes compatible with endoscopic systems have been developed.

Spatial scanning mechanisms enable the acquisition of 3D image data [50]. Applications are the diagnosis of esophageal adenocarcinoma, colorectal cancers, inflammatory bowel diseases, visualization of bile duct structures, and research on pathologies of the small intestine such as Crohn's disease [32, 42, 50]. Raman spectroscopy is a spectroscopic method used in chemistry to identify molecules. This technique can be integrated with optical fibers. The assembly of several fibers enables the measurement of small regions of interest, therefore the designation of imaging. Medical application of Raman imaging is, for example, the visualization of single cells and small sections of tissue samples. It has been evaluated for the detection of colon and pancreas cancers on human surgical specimens [43]. A unique development demonstrated the feasibility of magnetic resonance imaging (MRI) guided Raman detection of tissues via a biopsy cannula [3]. Relatively large devices, prolonged acquisition time, and scanned areas limited to a few square millimeters represent the main limitations of OCT and Raman spectroscopy imaging. Photoacoustic (PA) imaging is a new hybrid imaging method that combines optical with US imaging and takes advantage of both modalities [53]. The optical component provides images with high resolution, up to several micrometers, while the ultraound component enables to examine tissue depth, up to several centimeters. The principle consists of exciting endogenous chromophores of tissue, such as hemoglobin, melanin, lipid, and water, or of exogenous dyes by pulsed laser light. Light is absorbed by tissue to a certain extent and converted into heat and pressure. This pressure propagates as broadband acoustic signal, which can be detected by the US probes. PA is well suited for imaging of soft tissue and more specifically for the visualization of the microvascular structures located a couple of centimeters under the skin [23]. Application to the transabdominal monitoring of colon inflammation in Crohn's disease has been reported in [4, 51]. The combination of PA with fiber-optic probes enables minimally invasive applications such as for the diagnosis of early-stage tumors of the GI tract [54]. This study showed that PA enables to measure changes of vascular structures and blood oxygenation parameters correlated with tumors. However, the use of high-energy laser is necessary to visualize tissue depth in centimeter range, which can lead to tissue damage. IRT is a thermal imaging method that passively records the infrared (IR) radiation emitted by any body with a temperature larger than 0 K. The radiation is proportional to the temperature of the body. IR cameras detect the radiation and convert the signal into temperature values. Since tissue temperature depends on its perfusion state, IRT has been evaluated on animal models to monitor tissue perfusion during anastomosis procedures [9, 41]. This method is difficult to apply for endoscopic applications since temperature variations between tissues are not observed in the closed abdominal area.

Multispectral and hyperspectral imaging (MSI/HSI) are optical imaging techniques that represent a much larger variety of tissue characteristics compared to the above-mentioned techniques. They have been introduced in 2010 [33]. The techniques are noninvasive and the acquisition of data is performed in a contactless fashion. Using commercial mobile systems, the data are analyzed and visualized on imaging monitors during surgery [12]. Therefore, MSI/HSI represent interesting tools to support the surgeon in the operating room. The Institute for Computer Assisted Surgery (ICCAS) at the University of Leipzig and the Department of Visceral, Transplant, Thoracic and Vascular Surgery at the University Hospital of Leipzig started to evaluate this modality in "in vitro," "ex vivo," and "in vivo" clinical pilot studies. Technical developments have been undertaken with the objectives to support the surgeons in the interpretation of the data and facilitate the adaptation of MSI/HSI devices to the surgical setup and techniques. This chapter aims at presenting the international state of the art in the field of MSI/HSI and describing the applications during surgery of the GI tract. For additional information about the applications in other medical fields, we recommend the recent review papers of Clancy et al. and Ortega et al. [12, 40].

32.2 State of the Art of MSI and HSI Technologies

32.2.1 Physical Principles

MSI and HSI are noninvasive optical imaging methods that combine the principles of absorption spectroscopy with digital imaging. A region of interest is illuminated with specific lights emitting usually in the visual and NIR range identified as the therapeutic window. The light that is reflected by the tissue is recorded by a camera and analyzed by sensors or spectrometers. When light penetrates the surface of tissue, it is absorbed, scattered, and transmitted according to the specific chemical composition of the tissue. Therefore, the tissue–light interaction generates a defined spectral signature of tissue allowing to decipher the tissue composition. The spectral data provide much more information than the human eye or regular visual cameras.

MSI and HSI devices generate three-dimensional (3D) data called hypercubes. They consist of an x- and y-dimension that represent the spatial coordinates while the third axis corresponds to the spectral dimension. As a result, each pixel of the recorded area is associated with a reflectance spectrum representing the quantity of reflected light measured according to wavelength. MSI and HSI use the same physical principles but differ in the number of spectral bands acquired by the systems. MSI refers to systems acquiring a limited number of bands, usually less than 20, while HSI systems can record up to several hundreds of bands. MSI and HSI are listed under the term of HSI in the following for simplification purposes.

32.2.2 HSI/MSI Systems Technology and Commercial Systems

The different HSI technologies can be divided into three categories: *spatial scanning systems*, *spectral scanning systems*, and *snapshot systems*. An excellent comprehensive description of the different systems is provided in [18]. *Spatial scanning systems* record one spatial point (whisk-broom system) or one line (push-broom system) simultaneously. The scanning of an area of interest is performed by manually or mechanically moving the device or object. Mechanical scanning requires the use of motors, which increases the size of the overall system and adds complexity. Spatial scanning data acquisition requires several seconds and provides data with high spectral resolution. On the other hand, *spectral scanning systems* perform the acquisition of a region of interest for only one wavelength. Mechanical or electronic systems enable to switch between the different spectral bands. The spectral resolution of these systems is limited but usually faster data acquisition is performed than for spatial scanning systems. Misalignments between the spatial images corresponding to different spectral bands can occur if the tissue or camera moves. Moreover, the integration of spectral scanning systems with medical endoscopes is easier than with spatial scanning systems. Finally, *snapshot systems* perform the simultaneous acquisition of a region of interest at several spectral bands in real-time. However, the spatial and spectral resolutions are currently limited. Commercial HSI systems are marketed by different companies, and a few of them are approved for clinical use [12].

In practice, the choice of technology depends highly on the medical application. While spectral scanning systems are compatible with minimally invasive surgical interventions, spatial scanning systems are mostly used during open surgery. Both systems are only suitable for the identification of motionless structures and tissue because of scanning time. Spatial scanning systems are useful for preliminary studies, when spectral features of tissue are still under investigation, because of the high spectral resolution they provide.

32.2.3 Endoscopic Systems

Since minimally invasive surgery is mostly performed for operations of the GI tract, laparoscopic HSI systems are under development. We have identified 12 endoscopic HSI systems

developed in the research field [28]. Most of them are based on spectral or spatial scanning. The spectral range and number of spectral bands of the systems are very variable. Two systems present a large visual and NIR spectral range (500–1000 nm and above), this feature being necessary for preliminary medical investigations. Only 3 out of the 12 systems provide color videos during spectral data acquisition. This feature is essential during laparoscopic procedures. Our group presented a new HSI system compatible with minimally invasive surgery [28]. A miniaturized push-broom system embedded in a $8 \times 6 \times 6$ cm^3 sized housing is connected to a commercial rigid laparoscope with 10 mm optics (Fig. 32.2). The HSI system generates spectral data with 640×480 pixels and 100 spectral channels in the range 500–1000 nm with a spectral resolution of 5 nm. The acquisition time for the HSI data is 4.6 s. Color videos are recorded simultaneously and can be augmented with spectral information. This is the first laparoscopic system that provides HSI data with high spatial and spectral resolutions in the visual and NIR spectral range as well as color videos at the same time. The prototype was technically evaluated, and first acquisitions on resected tissue of patients were successfully performed.

32.3 HSI Data Processing and Analysis

HSI correlates reflectance values to the pixels of the image. Spectral data can therefore not be compared to standard 2D or 3D medical image data for which grayscales or colors are attributed to the pixels or voxels. The interpretation of the HSI data is less intuitive for physicians. Therefore, computer-aided artificial intelligence

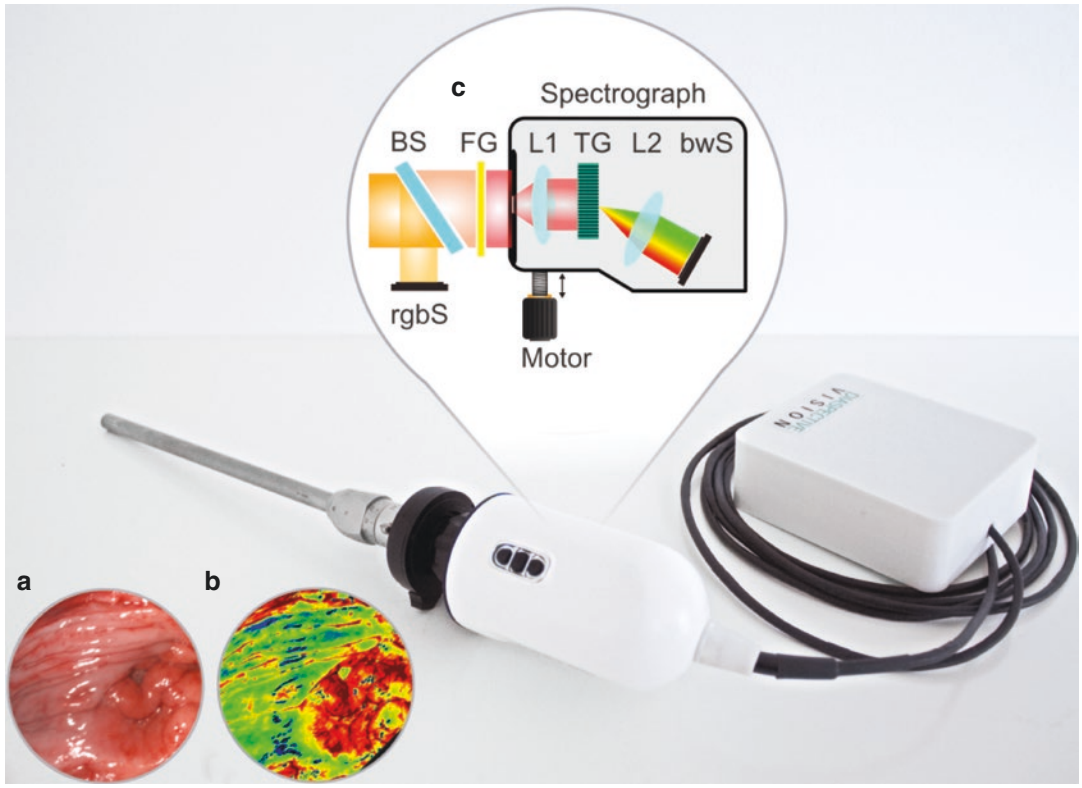

Fig. 32.2 Laparoscopic HSI system developed by Diaspective Vision GmbH, Am Salzhaff, Germany, in collaboration with ICCAS Leipzig University, Germany. The system acquires simultaneously video (**a**) and HSI data with high spatial and spectral resolutions (**b**)

tools are being developed to support the analysis of the HSI data. Four different approaches are described in the following.

32.3.1 Preprocessing of the HSI Data

Preprocessing is a preliminary step to remove noise and artifacts as to normalize and to simplify the spectral data [33]. A common method to smoothen the spectra is the Savitzky–Golay filter. For the comparison of HSI data of different patients and acquired with different systems, spectra are normalized using, for example, the standard normal variate (SNV) method. Also, the calculation of the absorbance based on the reflectance values is often performed. The first and second derivatives of the spectra can be relevant for the computation of physiological parameters (see Sect. 32.3.3). Finally, motion correction can be performed if tissue or camera systems moved during the acquisition. Approaches based on cross-correlation and optical flow are the most common [31]. The removal of areas of the image that do not correspond to human tissue such as gauze, surgical instruments, and specular reflections is performed preliminary to classification and segmentation tasks (see Sect. 32.3.5). For this purpose, basic methods using threshold reflectance values showed to be effective. Processing of the HSI data is time-consuming since it depends on data size. For example, the training of machine learning classification algorithms can take several hours also with a limited number of patient data. Besides the increasing of computer power and the optimization of algorithms, the reduction of the spectral channels using, for example, a principal component analysis (PCA) will shorten the process significantly.

32.3.2 Contrast Enhancement

A first approach to present the HSI data to the surgeon is the selection of appropriate wavelengths that enhance given anatomical structures as it is performed in NBI. For example, Nouri et al. developed a method combining the best three spectral bands to enhance the image contrast of the ureter and blood vessels [38].

32.3.3 Computation of Physiological Spectral Parameters

A second approach determines physiological parameters based on the spectral data. The parameter values are represented in the form of false-color maps. The generation of blood perfusion maps of the skin using RGB cameras is the most common [30, 31]. Such MSI systems have the advantage to provide real-time information video but focus mainly on tissue perfusion measurements. Further parameters related to tissue oxygenation, near-infrared (NIR) perfusion, tissue hemoglobin, and water content computed based on HSI data are described in [22] (Fig. 32.3). The visualization of these maps during operations of the GI tract provides relevant information to surgeons about tissue and organ perfusion as well as edema (see Sect. 32.4).

32.3.4 Augmented Reality-Based Approaches

One application of augmented reality consists of augmenting color videos with spectral information. Barberio et al. developed the guidance tool HYPerspectral Enhanced Reality (HYPER), which performs the overlay of perfusion maps obtained using an open HSI system with videos recorded by an HD camera [7]. An initial calibration process is necessary to align both cameras. The measured alignment error is 1.6 mm. This tool works for fixed acquisition plans only. The further development of this approach to HSI endoscopic systems whose acquisition time of the HSI data requires several seconds would be especially relevant. However, since the camera is continuously moving, fast elastic registration processes have to be used to correctly align the static spectral data with the moving videos.

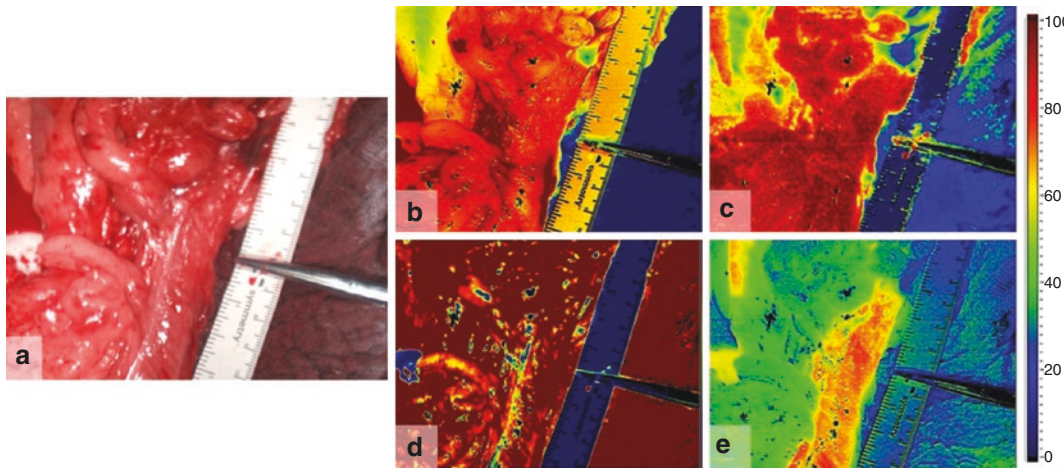

Fig. 32.3 Examples of spectral parameters computed by the commercial TIVITA® Tissue System (Diaspective Vision GmbH, Am Salzhaff, Germany): NIR perfusion (**b**), oxygenation (**c**), tissue hemoglobin (**d**), and tissue water (**e**). The RGB image showing the surgical area (here the bowel during colorectal surgery) is depicted in (**a**)

32.3.5 Automatic Classification Methods

The last kind of approaches reported here are tissue classification methods. They aim at automatically identifying tissues and structures from the hypercubes using methods from artificial intelligence. Visualization methods enable the enhancement of the extracted structures in color images. Supervised classifiers, also called machine learning methods, are the most popular techniques to operate on spectral data. In such approaches, the prediction algorithm is trained based on datasets of manually annotated HSI data, that is, spectral data whose tissue content is known. Consequently, the trained classifier model is then able to automatically label tissue in non-annotated HSI data. This approach is well adapted to the field of HSI because computer-run algorithms are better and faster than humans in identifying specific features within the large spectral data. The identification of risk structures and tumors represent the main surgical applications [12, 18, 39] (see Sect. 32.4). Standard machine learning methods such as random forest (RF), logistic regression (LR), support vector machine (SVM), k-nearest neighbors (kNN), and multilayer perceptron (MLP) have been mostly evaluated [33, 39]. Deep learning (DL) approaches are powerful tools that were, however, little evaluated on HSI data yet. One reason is the limited number of HSI patient data reported in the studies. Some applications of automatic tissue classification are described in more detail in Sects. 32.4.2 and 32.4.3.

Limitations to the performance of the supervised classifiers are the errors in the annotated data, the complex information included in the spectral data, and possible spectral similarities between different kinds of tissue. Firstly, incorrectly annotated HSI data lead to a lower quality of the training dataset and therefore to lower performance of the classifier models. Data annotation is performed by clinicians usually retrospectively to the operation. Automatic computer-assisted methods, for example, based on statistical methods or involving spectral measures such as the spectral angle mapper, can identify incorrect annotations and remove spectral outliers in the training datasets. Secondly, the large information included in the spectral data can reduce the performance of the classifiers. Methods such as the PCA enable to extract from the wavelength bands the most relevant ones to discriminate different tissues. Additionally, the reduction of the number of bands enables to accelerate the computing time. Thirdly, the inter-

and intra-patient variability in tissue composition leads to large variances of spectral features. Therefore, the automatic discrimination among different tissue classes is complex. According to our experience, the performance of supervised classifiers increases rapidly with larger training datasets. Since the number of HSI data of operated patients is limited, approaches to augment the data and to generate synthetic data should be investigated.

32.4 State of the Art of HSI Preclinical and Clinical Applications

Medical applications of HSI cover a large spectrum from the diagnosis to the therapy of diseases [33]. In the surgical field, Shapey et al. identified four main applications: the detection of residual tumor tissue, the classification of critical anatomical structures, the monitoring of tissue oxygenation, and the visualization of target structures under blood [48]. In gastrointestinal surgery, HSI was mainly evaluated during abdominal, colorectal, biliary, intestinal, and gastric surgeries according to Ortega et al. [39]. Most of the reported studies is performed on animal models or ex vivo human tissues. The work developed at ICCAS, University of Leipzig, contains tissue perfusion estimation, tissue characterization and classification, and tumor identification of clinical GI tract data. They are presented in the following and compared to the state of the art of international research.

32.4.1 Estimation of Tissue Perfusion

Evaluation of tissue perfusion represents a large field of medical HSI applications. One reason is that hemoglobin (Hb) is the major contributor to the absorption of light in tissue. The absorbance peak of deoxygenated Hb and the double absorbance peaks of oxygenated Hb (respectively 560, 540, and 580 nm) are in the visual spectral range that is detectable with common sensors. Medical applications are various, for example, the assessment of skin microcirculation for patients in intensive care [16], the monitoring of human wounds [21], and the diagnosis of circulatory diseases [11, 33].

Our team investigated different applications in the field of liver and gastrointestinal surgery. HSI was successfully evaluated on one patient to accurately identify the liver resection plane during hemihepatectomy [49]. A further application concerns the detection of intestinal perfusion deficits in patients with acute mesenteric ischemia [36] (Fig. 32.4). This study including 11 patients showed that oxygenation and perfusion were statistically significantly lower for low perfused tissue than for viable intestine. Also, necrotic tissue was clearly characterized by a local peak at 630 nm of the absorbance spectra. Moreover, Köhler et al. evaluated HSI to demonstrate the benefit of ischemic conditioning effects to enhance the perfusion of the gastric conduit during esophagectomy [27]. The results obtained on the HSI data of 22 patients showed significantly higher tissue oxygenation for the patient group with ischemic conditioning. Finally, one of the

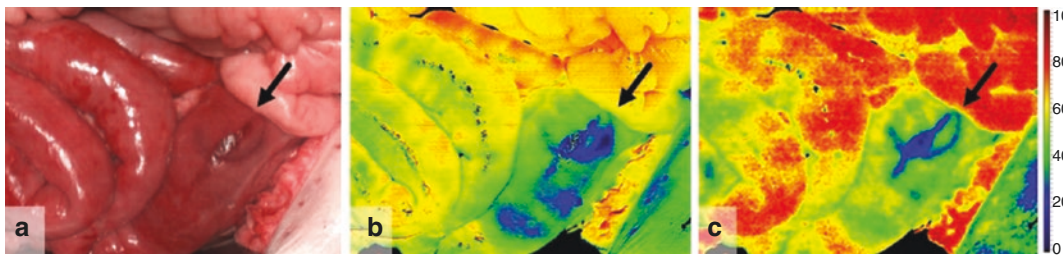

Fig. 32.4 Identification of intestinal perfusion deficits in acute mesenteric ischemia of patient: poor perfused tissue is visible in dark red in the RGB image (**a**) and is represented with low NIR perfusion (**b**) and oxygenation (**c**) values in the corresponding spectral parameter maps

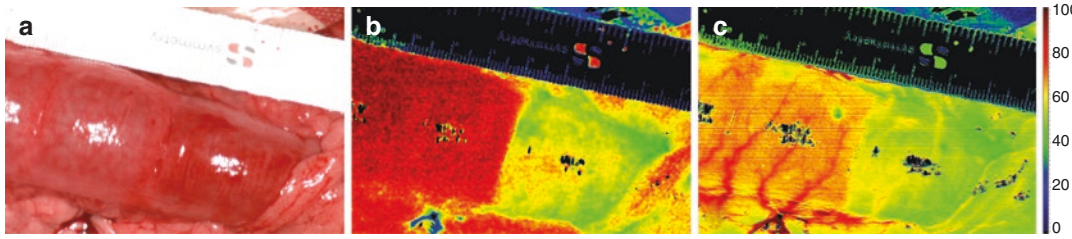

Fig. 32.5 Determination of the transection margins during colorectal resection (**a**): the boundary between the prepared (right) and normally vascularized (left) bowel is clearly visible in the oxygenation (**b**) and NIR perfusion (**c**) maps

most promising applications is the reduction of postoperative complications due to anastomosis leak. Low tissue perfusion is one of the main reasons for anastomosis insufficiency. Therefore, Jansen-Winkeln et al. evaluated HSI for the precise localization of the transection margin plane during colorectal resection [26]. The boundary between well and poorly perfused bowel was accurately identified in 20 out of 24 patients who were recruited in this pilot study (Fig. 32.5). Moreover, the results showed that a distance of up to 13 mm could be reached between the margins estimated visually on the tissue by the surgeon and based on the HSI data. Also, the evaluation of new techniques requires a comparison with established methods. A recently published study including 32 patients compared ICG fluorescence with HSI [25]. The surgical resection lines could be clearly identified in both modalities for 30 out of 32 patients. Although the boundary was always sharply depicted in the ICG images, it appeared more diffuse in the oxygenation maps of some patients. An objective explanation remains unclear. The results of this study suggest that both modalities could be complementarily used.

32.4.2 Tissue Characterization and Classification

It was already mentioned that the reflectance spectrum of tissue represents a spectral signature that enables the characterization of tissue constituents. Therefore, a promising topic of HSI is the automatic recognition of tissue during surgery based on spectral information. The preliminary task consists of extracting spectrally characteristics of tissues. In the literature, the spectrum of properly analyzed structures and organs remains limited. Schols et al. described the first spectral features of different tissues (fat), structures (blood vessel, muscle, nerve), and organs (bowel, ureter) based on spectral data of ex vivo and in vivo tissues of less than 20 patients [44, 46, 47]. Nouri et al. described the spectra of the ureter and blood vessels [38]. Wisotzky et al. analyzed the similarities and differences between the spectra of various tissues including bone, connective tissue, fat, muscle, nerve, and parathyroid gland [52]. Spectral data were acquired during six surgical interventions. In the same way, our group acquired the HSI data of in vivo tissue of seven patients during surgery of the thyroid and parathyroid glands [8]. The spectra showed that the thyroid is on average better oxygenated than the parathyroid and that the water content is larger for the thyroid. Also, the reflectance spectra of the liver, gall bladder, and bile duct of in vivo tissue of seven patients were analyzed [13]. It showed that the hemoglobin highly contributed to the spectra of the liver. The presence of bile was observable in the spectra of the gall bladder and bile duct, as well as collagen and elastin in the spectra of the bile duct.

These preliminary studies conclude that tissues clearly show different spectral features. This signature can be theoretically used to automatically identify anatomical structures that are difficult to discriminate intraoperatively by the human eye and that need to be preserved during surgery. This can be achieved using classification methods, as described in Sect. 32.3.5. Examples of applications performed by our group are (i) the automatic identification of the parathyroid gland,

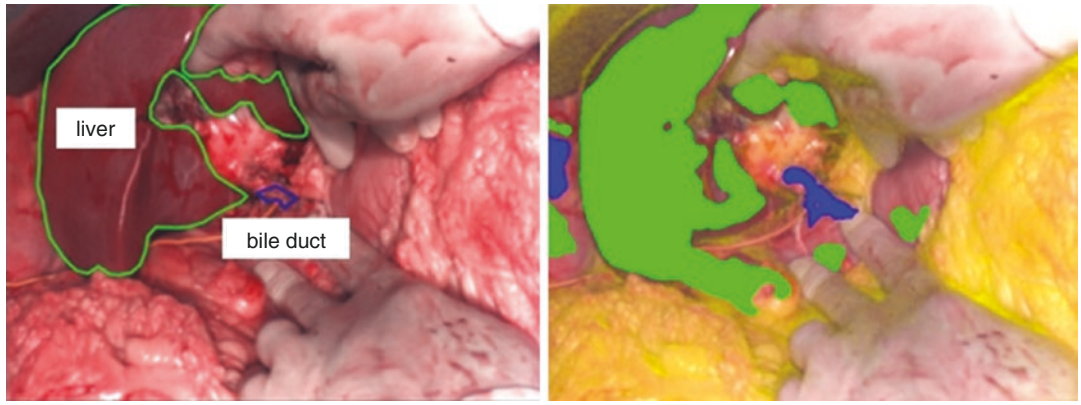

Fig. 32.6 Automatic identification of the bile duct (in human). Left: manual annotations of the contours of the liver (green) and the bile duct (blue). Right: the pixels of the image automatically labeled as liver and bile duct are respectively represented in green and blue.

(ii) the recurrent laryngeal nerve, and (iii) the bile duct using different standard machine learning methods [35]. Figure 32.6 shows preliminary results obtained using in vivo HSI data acquired during liver transplantation. The adaptation of such tools to the detection of blood vessels and nerves during gastrointestinal surgery could reduce possible tissue damages.

32.4.3 Tumor Identification

The identification of a tumor-bearing segment of the GI tract is a crucial step for the oncologically appropriate resection. In particular, it is necessary to accurately identify cancer tissue during the diagnostic phase (e.g., flexible endoscopy) or surgical resection to be sure that no tumor is left behind. HSI is currently being evaluated for this purpose including the development of an optical probe to perform in vivo analysis of malignant lesions. Applications for breast, head and neck, brain, and gastrointestinal cancers based on ex vivo and in vivo animal and human tissues are reported in the review of Halicek et al. [18]. In the field of gastrointestinal surgery, studies involving human tissue have been conducted using stained histological slides and resected tissue. The combination of HSI with machine learning algorithms is mostly performed for automatic tumor identification.

Histological Slides Ortega et al. published recently a review paper about the analysis of histological slides of cancer tissue using HSI based on the examination of 192 scientific articles [40]. Eleven studies concerned colon cancers (carcinoma and metastasis) and one pancreatic cancer. Gastrointestinal cancers remain therefore a limited application field. The paper concludes that HSI and classification algorithms lead to a more robust diagnosis of cancers. Our group performed a study on 56 specimens with Barrett's esophagus. The slides were stained with hematoxylin and eosin (H&E). An HSI camera was coupled with the microscope to acquire HSI microscopic data. Tumor identification was performed using different machine learning models. The best results to differentiate blank, stroma, squamous epithelium, and esophageal adenocarcinoma were obtained with a multilayer perceptron model with an overall F1 score and sensitivity of 90%. These preliminary results showed that the differentiation between stroma and squamous epithelium remains complex since the absorbance spectra look similar. Investigation performed on stained tissue mainly reveals the dyes used. Therefore, the quality of the results depends on different factors linked with staining techniques such as dye concentration. The examination of unstained specimens is a promising topic as pointed out by Ortega et al. [40]. Although studies on histological tissue samples represent a

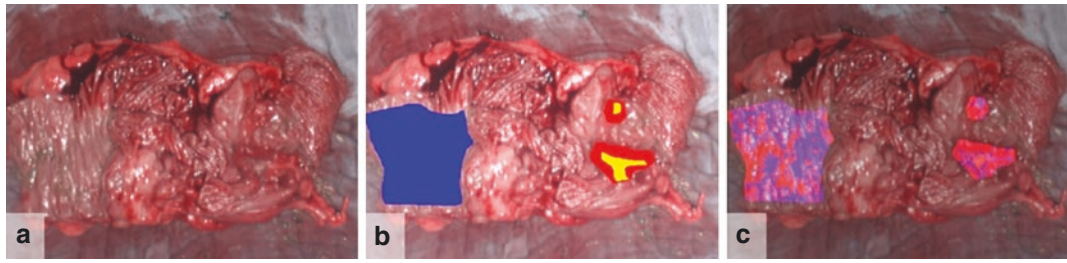

Fig. 32.7 Automatic classification of human colon tumor tissue. (**a**) Color image of the interior wall of the colon. (**b**) Manual annotations of healthy tissue (blue), tumor (yellow), and tumor margins (red). (**c**) Automatic labeling of the pixels of the annotated areas in (**b**) as healthy tissue (blue) and tumor (red).

preliminary step in the evaluation of HSI for the identification of tumors, they are not intended to directly support the surgeon during oncological surgeries.

Resected Tissue Resected tissue represents a good model if the acquisition with the imaging device is performed directly after resection. Also, open HSI systems can be used. The number of studies performed with ex vivo tissue of the GI tract is limited. Baltussen et al. [5] acquired HSI data of tissue samples of 32 patients using a laparoscopic HSI system including two cameras to cover the spectrum range between 400 and 1700 nm. Automatic classification of fat, healthy colorectal wall, and tumor tissue was performed using a quadratic classifier and linear support vector machines (SVM). An accuracy of 0.88 to distinguish the three tissue types was obtained on the test data. We focused on the detection of tumors of the esophagus combining extraluminal HSI acquisition with automatic classification approaches [34]. The results obtained on 11 fresh resected tissues showed that the SVM model provided the best performance with 63% sensitivity and 69% specificity using a leave-one patient-out cross-validation. The main limitation of this study was the performance of the extraluminal acquisition of tissue using an open HSI system. Since esophageal tumors are located in the internal part of the conduit and since the maximum penetration depth of HSI is 6 mm (in the NIR range), better results are expected if intraluminal acquisitions are performed. Preliminary results of tumor classification obtained on HSI data of the interior wall of the colon are depicted in Fig. 32.7.

32.5 Discussion and Conclusion

HSI is a noninvasive optical imaging method that shows very promising results in medicine in general. Moreover, since the acquisition is performed contactless and commercial systems are mobile, compact, and user-friendly, the technique is suitable for the operating room. Therefore, HSI is an emerging modality for intraoperative use, especially in surgery of the GI tract. The field of surgical applications is vastly reflected by the increasing number of new articles published. The main applications that have been reported in this chapter concern the evaluation of tissue perfusion, tissue classification, and tumor identification. At the University Hospital of Leipzig, HSI is routinely used to estimate perfusion of tissue at the anastomosis position during colorectal and esophagus resections and perfusion of the bowel during acute mesenteric ischemia. Automatic tissue classification and tumor identification are under development. Our group evaluated standard machine learning methods to discriminate the parathyroid gland and the bile duct from surrounding tissue as well as to identify tumor tissue. Classification was performed on spectral data of histological slides, resected tissues, and in vivo tissue of patients. Preliminary results performed under laboratory conditions are very promising, but the tools have not been translated to the operating room yet. Therefore, clinical

studies and technical developments are still needed to further evaluate and establish HSI in the medical and surgical setups. Future research directions are suggested in the following.

Firstly, the hardware of HSI devices requires further technical development. Optimization is often a trade-off between spatial and spectral resolutions of the hypercubes, on the one hand, and time of acquisition, on the other hand. Therefore, hardware optimizations are realized regarding specific medical applications, for example, the evaluation of tissue perfusion. Moreover, gastrointestinal operations are mostly performed as minimally invasive procedures. Few laparoscopic and endoscopic HSI systems are under development in the research field. We presented a prototype of a laparoscopic HSI system providing simultaneously HSI data of high spatial and spectral resolutions and color videos Fig.32.2. The integration of such endoscopic HSI systems with medical robotic systems is under development. A few commercial systems are certified for medical use so far. Optimization of the HSI devices, especially the development of endoscopic systems, and their certification for medical use is a prerequisite to facilitate new clinical studies.

Research on the development of tools to support the surgeon in the interpretation of the HSI data is an important topic. Limited HSI data are already available [12], hence we are working on an HSI/MSI atlas. Evaluation of standard machine learning methods for HSI analysis showed promising results, but the tools are currently not robust enough to be used during patient operations. The main limitation is the intra- and inter-individual variabilities in tissue composition, which makes its accurate discrimination difficult. Although deep learning approaches achieved impressive results on large radiological datasets for disease diagnosis purposes, only a few have yet been evaluated for HSI data. The amount of imaging data in the surgical field is in general limited, which represents a limitation to the performance of such methods. Therefore, the investigation of approaches to augment the HSI data and to generate new synthetic HSI data is an important task to increase the datasets and to further evaluate the newest techniques of artificial intelligence. HSI is an optical imaging technique that provides information on tissue surface (less than six millimeters). The combination of HSI with another noninvasive imaging method such as US and photoacoustic could be relevant.

In conclusion, HSI is a promising imaging modality to be used during gastrointestinal surgery. It is noninvasive, contactless, and user-friendly. The spectral data provide information valuable for various applications. Finally, there is a need to carry out larger clinical studies for the acquisition of large datasets of spectral data for various surgical applications. The comparison of HSI with standard imaging methods has to be performed to demonstrate evidence. Also, the open-access availability of these HSI data will benefit the clinical and technical research as well as the industry to promote further developments of this imaging modality.

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33 Fluorescence-Guided Surgery of the Biliary Tree Utilizing Indocyanine Green (ICG)

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33.1 Introduction

Laparoscopic cholecystectomy is one of the most commonly performed operations in the United States, with over 750,000 cases performed annually [1]. Since the introduction of LC, decades of research demonstrates safety and efficacy making it the standard of care for benign pathology of the gallbladder. Demonstrated benefits include improved cosmetic outcome, shorter length of stay (LOS), earlier return to work, and decreased postoperative pain and hernia [2–4]. Despite advances in laparoscopic techniques, equipment, and surgeon experience, iatrogenic injury to the common bile duct (CBDI) still occurs at a rate of 0.08% to 2.3%, while conversion to open surgery occurs at a rate between 3% and 15% [5–13]. While conversion to open is not a complication of surgery, it significantly increases morbidity and mortality, risk of surgical site infection, pulmonary complications, and LOS and is associated with substantial costs to the patient and the healthcare system [14, 15].

CBDI has a negative impact on overall survival and quality of life, even 10 years after the event [16]. In response to increasing complication rates, Strasberg et al. introduced the critical view of safety (CVS) in 1995, as a preventative measure to decrease the risk of injury to extrahepatic bile ducts [17]. Literature continues to indicate the primary cause of CBDI is an error in visual perception of the anatomy in 71–97% of cases. Factors increasing the potential for distorted anatomy include obesity, past or ongoing inflammation, variant ductal anatomy, and limited surgical experience [18, 19]. The use of intraoperative cholangiography (IOC) has been recommended to help prevent misinterpretation of biliary anatomy, though its routine use is debated [20–22]. The reported incidence of CBDI during LC ranges from 0.03% to 2.6%, with significant heterogeneity across studies [2, 18, 23]. While the initial increase in rate of CBDI was attributed to the learning curve with the laparoscopic approach, CBDI continues to occur at a nonzero rate despite improved quality of equipment and increased surgeon experience with the technique [17, 18].

In the past 7–8 years, an alternative imaging modality has been employed allowing for fluorescence cholangiography. Indocyanine green (ICG) dye allows for fluorescent imaging of the extrahepatic biliary tree in real time during laparoscopic cholecystectomy, providing an

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innovative surgical adjunct to be used with "critical view of safety" [24]. Indocyanine green dye (ICG) is a water-soluble dye with spectral absorption at 800 nm. When injected intravenously, ICG binds plasma proteins before being rapidly metabolized by hepatocytes and excreted exclusively into the bile; protein-bound ICG fluoresces green when illuminated with near-infrared (NIR) light [21, 24]. Dynamic, real-time NIR light is applied via a specialized light source and cable through a standard laparoscopic scope; device toggles allow for surgeon-controlled switching between white light and NIR light during surgery. Through constant reassessment of the anatomy with NIR imaging, surgeons may continuously identify the position of critical biliary structures; biliary structures are often identifiable prior to dissection of peritoneal layer of the gallbladder. FC offers the potential detailed anatomical mapping of extrahepatic biliary structures, and may be a useful adjunct to the CVS. The technology incorporates smoothly into the operation without increased need for staffing or additional supplies in the operative theater, beyond the addition of a NIR-capable laparoscope. In contrast, IOC can be time consuming and involves exposure of the patient and ancillary staff to radiation, with associated increases in cost. A 2014 study reported that the mean cost of surgery generated by IOC (US $778.43) was greater than the cost with FC ($14.10) [22]. With a growing body of literature, some surgeons have advocated for FC to become the standard of care in laparoscopic cholecystectomy.

33.2 Indications for Use and Adverse Reactions

ICG is currently used for all laparoscopic cholecystectomies in our group, regardless of diagnosis or emergent/elective classification. The technology is now our standard of care in the Minimally Invasive Surgery division since it is was first used at UCSD for cholecystectomy in 2013. Other members of our surgery department utilize ICG on a selective basis, and it is often not used acutely by our emergency general surgery (EGS) service at the county hospital.

No absolute contraindications exist for the administration of ICG dye, and risk of an adverse event with ICG is low. Anaphylactic reaction is reported at a rate of less than 0.05%, with a 0.34% overall incidence of mild adverse reaction (i.e., urticaria, rash) [25]. Our group avoids the use of ICG dye in patients with a history of anaphylactic reaction to shellfish or iodine out of an abundance of caution. Existing evidence supports the safety of ICG use during pregnancy; however, the drug is classified by the Food and Drug Administration as pregnancy category C indicating fetal harm is unknown. No literature attributing mortality from an anaphylactic reaction to administration of ICG is published. As a surrogate marker, the mortality rate following adverse reaction to iodine contrast agents is 0.51% [26]. Anecdotally, we have not experienced any severe adverse reactions with the use of ICG at our prescribed dose.

33.3 Surgical Technique

An Indocyanine Green for Injection, USP (HUB Pharmaceuticals, LLC, Rancho Cucamonga, CA) 25 mg vial is reconstituted using 10 ml of sterile water. 7.5 mg ICG (3 ml of a 25 mg/10 ml solution) is administered intravenously in the preoperative holding area at least 45 minutes prior to surgery. While this is protocol at our institution, there are reports of wide variability of dose and timing of dose delivery among other institutions [27].

Laparoscopic cholecystectomy is then performed in standard fashion as well described in the past decades. Fluorescence cholangiography is performed using either a 5 mm or 10 mm laparoscope with the Stryker 1588 or 1688 AIM camera platforms. Our current equipment is capable of switching from bright light to fluorescent mode without changing the camera or light cord via a button on the camera head.

FC is performed throughout the course of the procedure, in particular at the following time points: prior to peritoneal dissection (Fig. 33.1), during the course of skeletonizing the cystic duct (Fig. 33.2), prior to clipping the cystic duct/critical view of safety (Fig. 33.3), post-

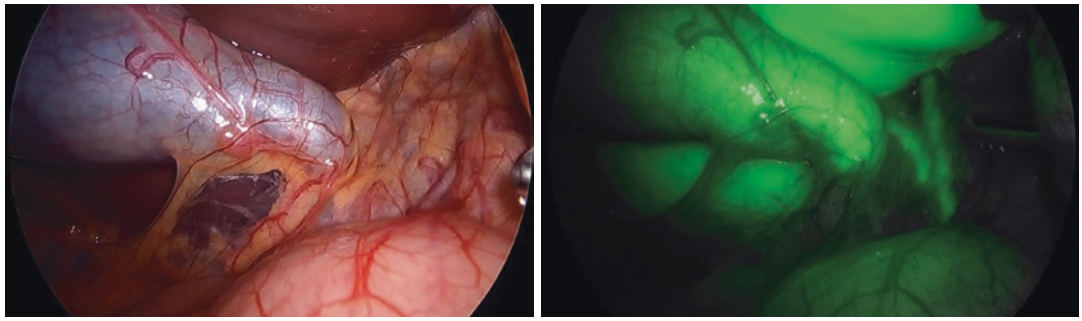

Fig. 33.1 White light (left) vs. ICG (right) of extrahepatic biliary anatomy prior to peritoneal dissection

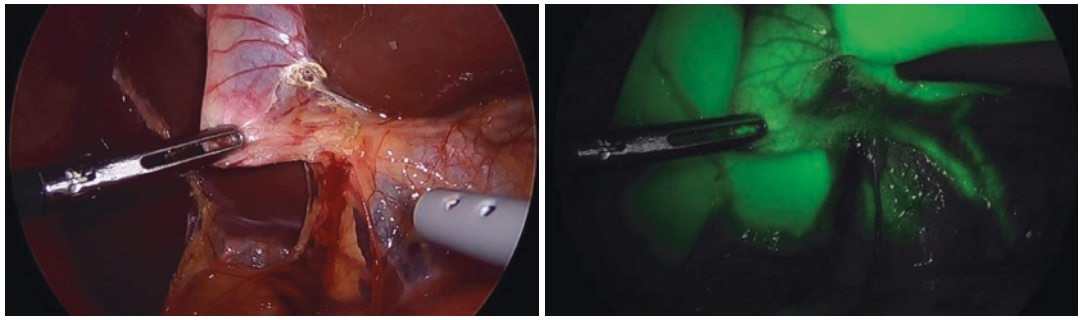

Fig. 33.2 WL (left) vs. ICG (right) of biliary anatomy during cystic duct dissection

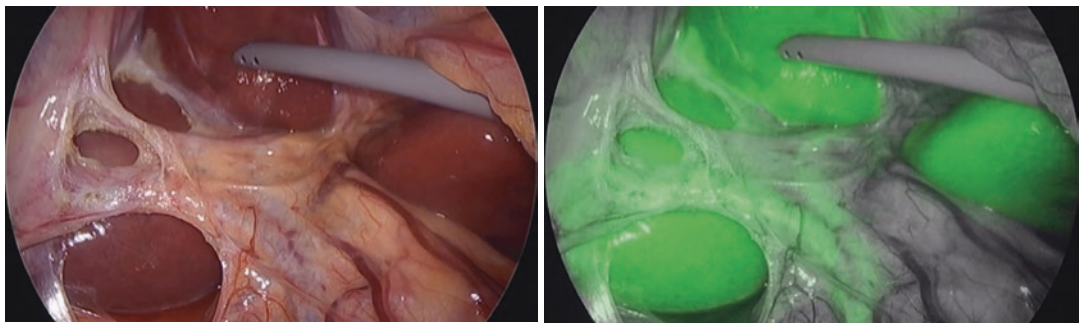

Fig. 33.3 WL (left) vs. ICG (right) of critical view of safety

cystic duct transection (Fig. 33.4), and immediately after removal of the gallbladder but prior to closure.

33.4 Outcomes Data on ICG Use in Cholecystectomy

The global experience with FC continues to expand with surgical outcomes and overall benefit being actively studied. We performed a literature review of studies published through 2019 and identified 34 studies detailing experience with FC for either laparoscopic ($n = 31$) or robotic-assisted laparoscopic cholecystectomy ($n = 3$) with a pooled total of 2443 patients (Table 33.1). There were no reported instances of CBDI in the literature. Despite the potential for FC to decrease the rate of CBDI, this finding was likely related to the small sample size as thousands of patients would be needed to identify subtle differences in CBDI for LC vs. FC. Strasberg et al. highlighted these challenges, stating that a randomized trial for differ-

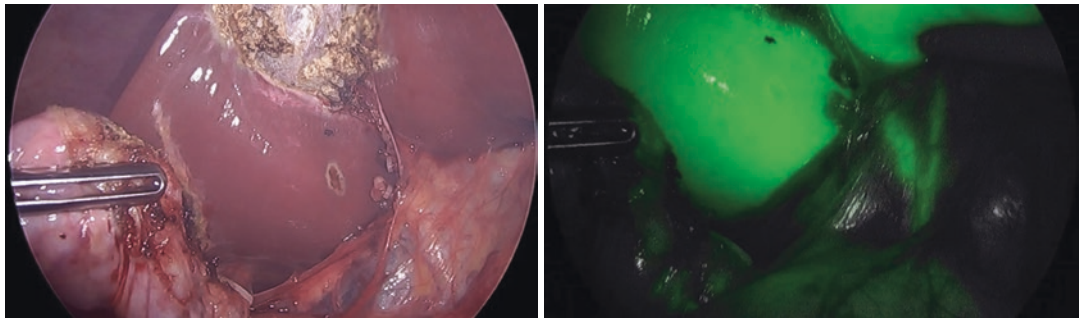

Fig. 33.4 WL (left) vs. ICG (right) after cystic duct transection showing patency of common hepatic duct

Table 33.1 Studies reporting experience with fluorescent cholangiography during laparoscopic cholecystectomy (excluding robotic-assisted series)

First author (year)	Total patients	Bile duct injuries	Adverse reactions	Convert to open
Ishizawa (2010) [21]	52	0	0	
Tagaya (2010) [28]	7	0	0	
Ishizawa (2011) [29]	7	0	0	
Schols (2013) [30]	15	0	0	
Schols (2013) [30]	30	0	0	1
Tagaya (2013) [31]	15	0	0	
Dip (2014) [22]	43	0	0	
Boni (2015) [32]	52	0	0	
Dip (2015) [33]	45	0	0	
Kono (2015) [34]	108			
Osayi (2015) [35]	82	0	0	
van Dam (2015) [36]	37	0	0	
Dip (2016)	70	0	0	0
Igami (2016) [37]	21	0	0	
Tagaya (2016)	25	0	0	0
Zroback (2016) [38]	12	0	0	
Ankersmit (2017) [39]	18	0	0	
Koirala (2017) [40]	12	0	0	
Hiwatashi (2018) [41]	65		0	7
Pesce (2018) [42]	50	0	0	4
Tsutsui (2018) [43]	72		0	2
Ambe (2019) [44]	29	0	0	0
Calabro (2019) [45]	29	0	0	
Dip (2019) [46]	318	0	0	1
Bleszynski (2019) [47]	108	0	0	0
Quaresima (2019) [48]	44	0	0	0
Pesce (2019) [49]	26	0	0	0
Agnus (2019) [27]	314	0	1 (rash)	
Yoshiya (2019) [50]	39	0	0	1
Keeratibharat (2019) [51]	20	0	0	0
Esposito (2019) [52]	15	0	0	0
Total	*1780*	*0*	*1*	*16/911*

ences in CBDI would be exceedingly challenging to perform with this low rate, and would require approximately 4500 patients per arm [53]. Reported rates of CBDI in laparoscopic cholecystectomy alone range from 0.08% to 1.5% [6–8].

A systematic review of FC performed by Vlek et al. reported a rate of conversion to open of 0.5% (1/197 patients) [54]. In our review of the literature, the pooled rate of conversion among studies reporting this outcome was 1.76% (Table 33.1). By comparison, reported rates of conversion to open in LC range from 5% to 10% [55, 56].

Another outcomes measure reported in literature is operative time for LC versus FC. In six studies were operative time is reported, an average of 15-minute OR time reduction was seen in FC compared to LC (Table 33.2).

33.5 Experience at University of California, San Diego

As FC has been standard of care in our division since 2013 but selectively used by other faculty, we have recently reviewed LC and FC across our institution. A total of 1389 patients were identified from 2013 to 2019 who underwent laparoscopic cholecystectomy. 989 (71.2%) patients underwent standard bright light LC; 400 (28.8%) patients underwent FC. Mean age was 47.4 years (range 15–94) in the LC group and 51.5 years (range 18–86) in the FC group ($p < 0.0001$). 68.6% versus 72.5% of patients were female in the LC versus FC groups, respectively ($p = 0.1757$). Average BMI in the LC group was 29.85 kg/m^2, while average BMI in the LC group was 28.41 kg/m^2 ($p = 0.002$). Patients presented with a variety of indications for cholecystectomy: 38.8% with biliary colic, 31.5% with acute or chronic cholecystitis, and 14.4% with gallstone pancreatitis. Other diagnoses included gallbladder polyps, choledocholithiasis, cholangitis, biliary dyskinesia, adenomyomatosis, and other benign biliary disease.

FC had a significant mean operative time reduction of 26.5 minutes compared to LC (Table 33.3). This relationship held true for obese patients (BMI > 30). OR time reduction was also noted to be significant in inflamed versus non-inflamed subgroups comparing FC versus LC (Table 33.3). FC had an overall conversion to open at a rate of 1.5%, while LC converted at a rate of 8.5% ($p < 0.0001$). Conversion to open in inflamed subgroups was 2.9% FC versus 16.7% LC ($p < 0.001$) (Table 33.3); in non-inflamed subgroup, conversion was 0.76% FC versus 4.6% LC ($p < 0.001$).

After controlling for clinically relevant predictors via multivariable logistic regression, FC was associated with a 78.8% odds reduction for conversion to an open procedure ($p = 0.001$, OR = 0.212, Table 33.4). Subgroup analysis of only patients with inflamed gallbladder pathology also showed an 84.5% odds reduction in conversion with FC ($p = 0.002$, OR = 0.155,

Table 33.2 Comparison of operative duration between fluorescent cholangiography and standard laparoscopy

First author (year)	Number of patients (n)	Operative duration (FC)	Operative duration (LC)	Difference in duration	Total decreased minutes with FC
Ambe (2019) [44]	29	53	54	−1	−29
Calabro (2019) [45]	29			−16	−464
Bleszynski (2019) [47]	108	70	80	−10	−1080
Quaresima (2019) [48]	44	86.9	118	−31.1	−1368.4
Yoshiya (2019) [50]	39	129	150	−21	−819
Esposito (2019) [52]	15	52	69	−17	−255
Total	264			−96.1	−4015.4
Mean difference in operative duration			*−15.21*		

Table 33.3 Patient outcomes stratified by inflamed vs. non-inflamed gallbladder process

Inflamed				
	ICG (n = 137)	Non-ICG (n = 318)	p-value	95% CI
Operative time	83.6	117.2	<0.0001	24.09–43.05
Operative time, BMI ≥ 30	90.38	122.0	0.0006	13.76–49.53
Conversion to open	4 (2.92%)	53 (16.67%)	<0.0001	–
Conversion to open BMI ≥ 30	2 (4.88%)	18 (12.68%)	0.2542	–
EBL	19.99	47.37	0.0029	9.437–45.34
Drain placement	12 (8.76%)	72 (22.64%)	0.0003	–
LOS (days)	0.8686	2.283	<0.0001	0.8773–1.952
Non-inflamed				
	ICG (n = 263)	Non-ICG (n = 671)	p-value	95% CI
Operative time	66.61	90.26	<0.0001	17.46–29.85
Operative time, BMI ≥ 30	68.45	96.29	<0.0001	16.41–39.27
Conversion to open	2 (0.76%)	31 (4.62%)	0.0025	–
Conversion to open BMI ≥ 30	0	14 (4.86%)	0.0464	–
EBL	13.29	17.64	0.0473	0.05178–8.653
Drain placement	6 (2.28%)	37 (5.51%)	0.0366	–
LOS (days)	0.5894	1.183	<0.0001	0.3440–0.8439

Table 33.4 Univariable and multivariable logistic regression analysis – conversion to open

	Univariable			Multivariable		
	p-value	OR	95% CI	p-value	OR	95% CI
Age	<0.001	1.032	1.019–1.046	0.055	–	–
Sex	*<0.001*	*0.248*	*0.159–0.385*	*<0.001*	*0.308*	*0.195–0.488*
BMI ≥ 30	0.614	–	–	–	–	–
CCI 0	<0.001	Ref	–	0.447	Ref	–
CCI 1	0.084	–	–	0.644	–	–
CCI 2	0.001	3.098	1.548–6.2	0.125	–	–
CCI ≥ 3	<0.001	3.709	2.079–6.619	0.260	–	–
Nonelective	0.038	1.579	1.027–2.427	0.191	–	–
Fellow	0.001	0.421	0.248–0.714	0.540	–	–
Resident	0.046	7.503	1.035–54.420	0.112	–	–
2013–2015	0.019	Ref	–	0.168	Ref	–
2016–2017	0.287	–	–	0.332	–	–
2018–2019	0.005	0.411	0.225–0.752	0.060	–	–
ICG	*<0.001*	*0.164*	*0.071–0.379*	*0.001*	*0.212*	*0.086–0.526*
Years in practice	0.695	–	–			
Location (HC vs. LJ)	0.353	–	–			

CCI Charlson comorbidity index, *HC* Hillcrest, *LJ* La Jolla

Table 33.4) in multivariable analysis. Decreased conversion to open rates is what likely led to the findings of decrease length of stay for FC versus LC (Table 33.3).

One CBDI occurred in the LC group (0.1%); zero in the FC group. No statistical significance was seen in the rate of CBDI injury between groups, but we note a small sample size as a limiting factor. In total, 11 patients presented with postoperative biloma or bile leak, 9 (0.91%) in the LC group and 2 (0.5%) in the FC group ($p = 0.74$). Two inpatient mortalities occurred within the LC group. One patient with multiple comorbidities sustained an aspiration event leading to acute hypoxia and cardiovascular collapse on postoperative day 4 from a laparoscopic converted to open cholecystectomy for gallstone pancreatitis. The second mortality occurred as a result of intraop-

erative hemorrhage secondary to severe vasculobiliary injury after attempted fundus-down laparoscopic cholecystectomy in an inflamed gallbladder, with subsequent conversion to open cholecystectomy and cardiac arrest. No differences were observed in 30-day morbidity, mortality, readmissions, or ED visits between groups.

33.6 Technology Adoption and Cost of Use

Despite the widespread use of laparoscopic cholecystectomy, fluorescent cholangiography has not yet become standard of care as an adjunct to the critical view of safety. Currently, data and review of our outcomes has shown support for routine use of FC due to decreased operative time, conversion to open, and LOS regardless of BMI and inflamed pathology. Whether any significant impact is made for reduction in CBDI remains to be seen; however, there are zero reported cases of CBDI in FC in current literature. These outcomes suggest that improved visualization of the biliary tree via ICG provides a GPS-like view of anatomy and can guide targeted, efficient, and safe operative technique in conjunction with the CVS. The incorporation of ICG cholangiography into LC has the potential to provide real-time visualization of the extrahepatic biliary tree prior to commencing dissection within Calot's triangle [21]. Anecdotally, we find the biliary anatomy can be identified in this manner in most patients, although there are certainly cases where further dissection is needed before ICG is useful as an adjunct for visualization.

The cost of technology adoption is often a hurdle in health systems. With regard to capital costs, FC capability requires two different devices for NIR imaging in addition to standard laparoscopic equipment: (1) a specialized fiber-optic cable and (2) a specialized high-definition laparoscope. A standard laparoscopic tower can be used for both FC and LC. Cost of a single dose of ICG ranges from $17 to $130 as determined from wholesale drug price and literature review [22]. Any use of additional instruments and disposable supplies is equivalent to LC.

With reduction in average operative time and length of stay, technology adoption may prove to be cost-efficient [22]. A 2018 cross-sectional, longitudinal analysis of 302 short-term and specialty care hospitals in California reported the mean cost of 1 minute of operating room (OR) time as $37.45 (SD $16.04) in the inpatient setting and $36.14 (SD $19.53) in an ambulatory setting [57]. We gathered price data from the University of California, San Diego (UCSD) Medical Center Business Office on laparoscopic towers, light cables, laparoscopes, and ongoing service agreements with our laparoscopic imaging equipment provider. We estimate an average cost per case (over the lifetime of the equipment, assuming 50 LC per year) for LC of $1163.51 and $740.79 for FC, accounting for case duration. A complete cost analysis is planning to be performed with focus on expenditure for the following events: the index operation, complications of CBDI, conversion to open, and adverse reaction to ICG.

33.7 Other Applications

ICG fluorescence has been reported to be of safe and effective use in pediatric biliary surgery, particularly laparoscopic cholecystectomy [45]. Additionally, there are reports of beneficial use in robotic gallbladder adenocarcinoma resection as well as complex/aberrant anatomy in pancreaticoduodenectomy [58, 59].

33.8 Conclusions and Future Directions

Fluorescence cholangiography provides a noninvasive confirmation of the extrahepatic biliary anatomy during laparoscopic cholecystectomy, reducing operative time, LOS, and rate of conversion to open surgery. ICG has been shown to improve visualization before dissection of Calot's triangle and rapid identification of cystic duct-CHD junction during dissection; improved visualization may be apparent in higher BMI and inflamed surgical fields, resulting in improved

patient safety. While implementation of the CVS has undoubtedly improved the safety of LC, data suggest that routine use of ICG cholangiography may be a logical adjunct to the CVS. Future studies should focus on (1) examining the crucial time points with respect to identification of anatomy; (2) optimal timing and dosage of ICG; (3) the effect of BMI, visceral fat, and inflamed versus non-inflamed disease processes; and (4) rates of CBDI and complications as compared to historical outcomes. While the unit price of ICG is low, capital cost of specialized equipment is needed to perform FC and may vary. Costs may be offset by decreasing OR time and LOS; a complete cost analysis would be beneficial for analyzing the long-term costs of ICG technology adoption in a health system.

Fluorescence cholangiography using ICG provides a real-time adjunct to expedite identification of crucial biliary structures and is gaining reputation for use as standard of care in conjunction with the critical view of safety.

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34 ICG Image-Guided Surgery with the Assessment for Anastomotic Safety

Sonia L. Ramamoorthy and Jared S. Matson

34.1 Introduction/Background

The practice of gastrointestinal anastomosis in humans has existed since the early 1700s, when Ramdohr, surgeon to the Duke of Brunswick, successfully utilized an invagination technique to treat a complete transection of the intestine in a soldier and in the resection of an incarcerated hernia [1, 2]. Anastomosis was highly controversial at the time, however, with many surgeons holding to the belief that injuries to the bowel were best treated by ostomy or by allowing the body to heal without intervention [1]. It was not until 1826 when Antoine Lembert described the importance of serosal apposition that bowel anastomosis became more widespread [3]. In the 200 years since, gastrointestinal anastomosis has become routine in the treatment of conditions ranging from trauma to cancer. While far safer and more successful today than in prior centuries, anastomotic leak remains one of the most feared complications of any anastomotic procedure. Many factors contribute to this complication, from patient-related factors such as nutritional status or diabetes to procedural details such as blood loss or location of the anastomosis. One contributor that has been studied recently is the vascular supply to the anastomosis. As technology has evolved, our ability to see and measure blood flow intraoperatively has improved, particularly with near-infrared imaging and fluorophores such as indocyanine green dye. In this chapter, we will explore the history of gastrointestinal anastomosis, consequences of anastomotic leak, and techniques for ensuring anastomotic integrity including fluorescence angiography with indocyanine green.

34.1.1 History of GI Anastomosis

Ramdohr's technique from 1730 included inserting one end of the severed bowel into the other and securing with a single suture that was then brought out of the abdomen to secure the bowel to the abdominal wall and allow for future removal of the suture [1]. Modifications of this technique over the next century continued to be minimally effective owing largely to the practice of approximating the mucosa to the serosa [1]. After Lembert's description of serosal apposition, the next major development affecting the success of bowel anastomosis was Sir Joseph Lister's introduction of aseptic silk suture and the application of the concept of aseptic surgery to

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intestinal wounds in the 1860s [1]. Other major innovations and breakthroughs over the next 150 years include improved understanding of wound healing, the development of surgical stapling devices, the advent of endoscopy and laparoscopic surgery, and the debut of the surgical robot [4]. The foundational tenets have remained since those early times, though, of minimizing tension, aseptic technique, and approximation of appropriate layers of tissue.

In the modern era, emphasis has shifted from surgical innovation to the practice of evidence-based medicine and the analysis and application of large amounts of data. Anastomotic leak is perhaps the most feared complication following gastrointestinal surgery and has thus been studied extensively. One of the difficulties in studying anastomotic leak, however, is heterogeneity in the definition of anastomotic leak. In 2001, Bruce et al. published a systematic review examining definitions of anastomotic leak in the literature and found 13 different definitions of upper gastrointestinal leak and 29 different definitions of lower gastrointestinal leak, and that a 1991 proposal for a standard definition by the UK Surgical Infection Study Group ("the leak of luminal contents from a surgical join between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple-organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localized area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a subclinical leak") was not adopted in any other studies [5, 6]. In 2010, the International Study Group of Rectal Cancer proposed an alternative definition, "a defect of the intestinal wall at the anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments," which was the foundation for the International Multispecialty Anastomotic Leak Global Improvement Exchange definition [7, 8]. Unfortunately, this definition has also rarely been used in the published literature. This prompted Daniel et al. to attempt to find a consensus definition using the Delphi method, but only 7/15 (47%) of scenarios achieved consensus [9]. While this underlines one of the ongoing difficulties in understanding gastrointestinal anastomosis and anastomotic leak, it does not invalidate much of what has been shown.

There have been many studies that have identified and investigated various factors that are associated with and may be predictive of anastomotic leak. This has obvious clinical implications, as determining which factors are associated with anastomotic leak may allow for improved preoperative risk assessment and counseling, potential correction of modifiable risk factors, or alterations in the surgical plan (such as making use of a protective stoma in a higher-risk anastomosis). There are a number of ways of classifying these risk factors, including patient-related versus procedure-related and modifiable versus nonmodifiable. Patient-related factors include prior radiotherapy, higher American Society of Anesthesiologists (ASA) score (>2), renal disease, obesity, diabetes, steroid treatment, preoperative leukocytosis, anemia, malnutrition, male sex, smoking, excess alcohol use, chemotherapy, prior abdominal surgery, anticoagulant use, and nonsteroidal anti-inflammatory (NSAID) use [8, 10–34]. Of these, NSAID use, anticoagulant use, excess alcohol intake, smoking, malnutrition, anemia, steroid treatment, and obesity could be considered modifiable. Procedure-related factors are need for blood transfusion/significant blood loss, duration of the operation, type of procedure/anastomosis (especially low rectal anastomosis), conduit used (for esophageal procedures), emergency operation, contamination of the operative field, intraoperative complications, and surgeon experience [8, 10, 12, 14–16, 19, 22, 23, 25, 26, 31, 33–38]. In this group, intraoperative complications, contamination, conduit used, duration of the operation, and blood loss/transfusion may be considered modifiable. Because of heterogeneity in definitions of anastomotic leak, there is debate about the significance of some of these risk factors. Those that are most agreed upon include male sex and low anastomosis for pelvic surgery, ASA class >2, smoking, immunosuppression, malnutrition, type of procedure, duration of sur-

Table 34.1 Risk factors for anastomotic leak

Risk factor type	*Potentially modifiable*	*Nonmodifiable*
Patient-related factors	*NSAID use* *Anticoagulant use* *Excess alcohol intake* *Smoking* *Malnutrition* *Anemia* *Steroid treatment* *Obesity*	*Prior radiation* *ASA class* *Renal disease* *Diabetes* *Leukocytosis* *Male sex* *Chemotherapy* *Prior abdominal surgery*
Procedure-related factors	*Intraoperative complications* *Contamination* *Conduit* *Duration of surgery* *Blood loss* *Perioperative transfusion*	*Type of procedure/anastomosis* *Emergency operation* *Surgeon experience*

gery, conduit used, emergency surgery, and blood loss/transfusion (Table 34.1).

34.1.2 Consequences of Anastomotic Failure/Leak

These many studies investigating possible risk factors for leak are driven by the potentially severe consequences of this complication. Of most importance, mortality is increased in patients experiencing anastomotic leak, with some studies showing rates above 20% [10, 23, 26, 39–41]. Additionally, in colorectal cancer cases, anastomotic leak is associated with increased local and distant recurrence as well as cancer-specific and all-cause long-term mortality [40–43]. Anastomotic leak is also associated with increased hospital length of stay (Frasson et al. found a median 23 days versus 7 days) and increased expense, with costs estimated at $95,550 versus $26,420 (USD) for standard inpatient costs [10, 23, 44]. Finally, patients who experience an anastomotic leak have lower quality of life and satisfaction with their quality of care and surgeon [45].

Morbidity related to anastomotic leak (and leak rates) varies depending on the operation performed and the type of anastomosis that is made. For esophagectomy, leak rates vary from 1.6% to 53%, and the leak rate is significantly higher for cervical compared to thoracic anastomosis (a meta-analysis by Biere et al. showed an odds ratio [OR] of 3.43) [46, 47]. It is still considered a viable option, however, given the higher morbidity associated with an intrathoracic leak, which may lead to severe infectious complications such as mediastinitis, empyema, or pneumonia. Colorectal leak rates similarly depend on location and type of anastomosis, with low pelvic (distal colorectal, coloanal, or ileoanal) rates between 1% and 20%, colo-colonic rates between 0% and 4%, and ileocolic rates between 0.02% and 7% [40, 48]. Outside of low pelvic anastomoses, several studies have shown highest leak rates for colo-colonic anastomosis, such as may be performed for a transverse colectomy, or segmental left colectomy [40, 49]. The risk associated with ileocolic anastomosis compared to other anastomoses is less well-established, with some recent studies showing higher leak rates than high colorectal anastomoses and others showing no difference or even lower leak rates [16, 31, 40, 49]. The sequelae depend largely on the severity of the leak, with more severe leaks often requiring takedown of the anastomosis and permanent stoma [39].

34.1.3 Techniques for Ensuring Anastomotic Integrity and Avoiding Leak

Considering the numerous potential adverse effects of anastomotic leak and the number of nonmodifiable risk factors that are associated with leak, much thought has been devoted to possible

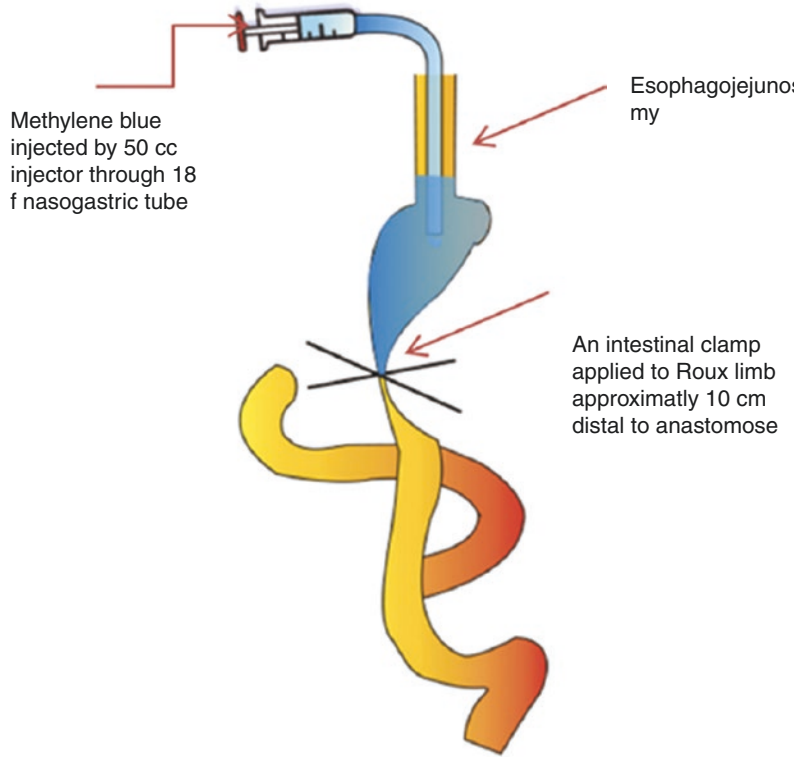

Fig. 34.1 Schematic representation of technical method of methylene blue test [56]

techniques for intraoperative assessment of the anastomosis and avoidance of breakdown. It is natural for surgeons to rely on their experience and intuition in assessing an anastomosis. One of the longest-standing practices for evaluating an anastomosis and/or evaluating the bowel prior to dividing or creating an anastomosis is visual inspection and palpation. This includes ensuring adequate perfusion by dividing the bowel where it does not appear dusky, by palpating for a pulse in the mesentery, and by watching for sufficient bleeding from the cut edge. It also includes searching the anastomosis for any visible or palpable defects, assessing the tension on the anastomosis, and ensuring the integrity of the doughnuts left from circular staple fires. Unfortunately, surgeons' impression of the risk of anastomotic leak has been shown to be unreliable [50].

Another method that has been studied is the air leak test (ALT). In this technique for colorectal surgery, the newly created anastomosis is submerged under irrigation fluid, the proximal bowel is occluded, and the distal bowel is insufflated by endoscope. For a foregut procedure, the bowel distal to the anastomosis would be occluded and proximal bowel insufflated. Lack of an airtight anastomosis is proven by escape of insufflation into the irrigant appearing as bubbles. This allows for immediate revision or repair by oversewing the area of leak and additional protection in colorectal surgery by proximal diversion if that was not previously planned. In some studies, positive ALT in colorectal anastomosis (indicating air leak was present) has been associated with higher rates of clinical leak despite repair than an initially negative test [51, 52]. Allaix et al. found no clinical leaks in patients who had repair of an anastomosis following a positive ALT, though, and multivariate analysis showed ALT was independently associated with reduced rates of clinical leak [53]. Repair of air leak in esophagojejunostomy has also been shown to be effective at preventing future clinical leaks, though some patients with negative leak tests will go on to develop anastomotic leak [54].

Testing the anastomosis by distention of the lumen with dilute methylene blue dye rather than air has also been utilized (Figs. 34.1 and 34.2). Studies of both colonic and esophagojejunal

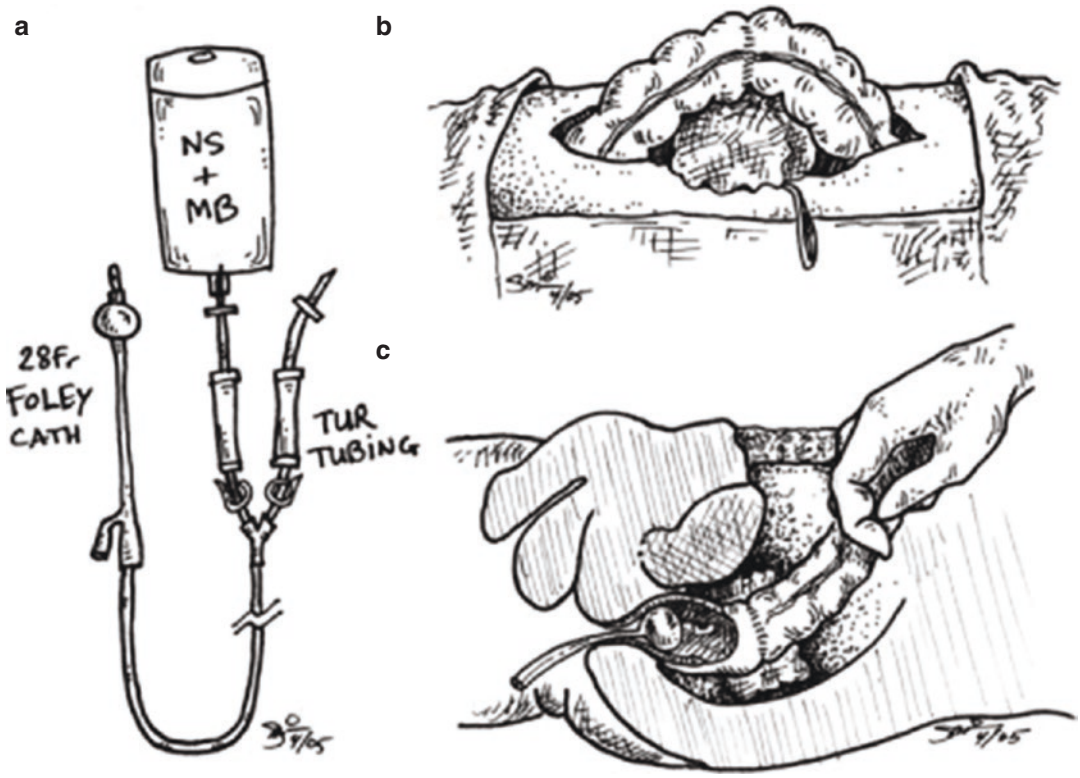

Fig. 34.2 MBE apparatus and method. (**a**). Apparatus for methylene blue enema. (**b**). Anastomosis with gauze pads beneath: (**c**). Cross-sectional view (pelvis) [55]

anastomoses have shown no clinical leaks following repair of anastomoses with a positive methylene blue dye test, though patients with negative tests may still develop leak [55, 56].

Finally, intraoperative endoscopy is another common procedure for anastomotic evaluation. It has the potential to identify leak, bleeding, a narrow or nonpatent anastomosis, or poor perfusion. Its efficacy in preventing postoperative anastomotic leak or bleeding is unclear, however [57–59].

One frustration for surgeons is the persistence of postoperative anastomotic leak even when intraoperative testing is negative. It has been hypothesized that this may be due to inadequate perfusion to the anastomosis to allow healing, with subsequent breakdown [60, 61]. This highlights the importance of ensuring a good blood supply while creating the anastomosis. While there are several possible ways to do this, one that has had encouraging early results is fluorescence angiography with indocyanine green dye (ICG).

34.2 Indocyanine Green in Perfusion Assessment

ICG is a sterile, water-soluble, essentially nontoxic medical dye that may be injected intravenously. It was first studied in humans in the 1950s and 1960s, where it was used to determine cardiac output and blood flow to the liver [62]. In ensuing decades, it was studied extensively in ophthalmic imaging, where its safety was confirmed [63, 64]. At the turn of the century, its use remained largely limited to ophthalmologic applications and determination of hepatic function. As digital imaging resolution improved, it saw expanded use. It was approved for neurosurgical applications in the early 2000s and was then adopted in breast, general, and plastic surgery for evaluation of skin-flap viability; in vascular surgery in assessing peripheral vasculature for limb ischemia; in endocrine and head and neck surgery to detect and evaluate perfusion to parathyroid glands; in bariatric and foregut surgery and surgi-

cal oncology in assessing upper gastrointestinal anastomoses or predicting viability; in colorectal surgery in evaluating lower gastrointestinal anastomoses; in gynecologic surgery in imaging vaginal cuff perfusion; in various surgical subspecialties in lymphatic imaging; in general and hepatobiliary surgery in visualizing biliary system anatomy; and in cardiac surgery for intraoperative coronary artery bypass graft assessment [61, 65–80].

34.2.1 Background and Properties of ICG

ICG is a tricarbocyanine compound that may be reconstituted in aqueous solution for intravascular injection. It is relatively unstable in solution (it will degrade within approximately 10 hours) and sensitive to light, so it must be kept in crystal form with minimal exposure to light until it is ready for use. It circulates bound to plasma proteins (primarily albumin) with minimal leakage into the interstitium. It is cleared by the liver and excreted into bile with a half-life of approximately 3–4 minutes [81, 82]. This allows for multiple injections during a single procedure, with a second injection feasible within 15 minutes [81]. Standard doses are typically less than 2 mg/kg, and several studies have shown that a dose of 2.5 mg may be effective [75, 83, 84]. This is far less than the estimated LD_{50} of 50–80 mg/kg [81]. The primary exception to its excellent safety profile is in patients with an allergy to iodine. It is thought that there may be cross-reactivity with the iodide component of ICG that could lead to hypotension or even anaphylactic shock [85].

ICG absorbs near-infrared (NIR) light with a peak absorption at approximately 800 nm and emits a fluorescent signal at 832 nm that may be detected by various imaging modalities but is outside the spectrum of visible light. This is actually advantageous in its surgical application, as the near-infrared light that must be used to provoke fluorescence probes several millimeters deeper into tissues than white light [81]. There are currently a number of commercially available systems that may be utilized for NIR fluorescent imaging with ICG. These include Firefly® Fluorescent Imaging for the Da Vinci surgical robot (Intuitive Surgical, Inc., Sunnyvale, CA) and PINPOINT® endoscopic fluorescence imaging, Spy Elite®, and SPY Portable Handheld Imager (SPY-PHI)® for open surgery (Stryker, Kalamazoo, MI), among others.

34.2.2 Current Uses of Indocyanine Green in Perfusion Assessment

Many surgical fields have taken advantage of these properties of ICG for a variety of applications. A number of these are related specifically to the evaluation of blood flow or organ perfusion.

In neurosurgery, vascular surgery, and cardiac surgery, ICG angiography can be used to visualize vessels and identify potential anomalies, such as primary non-patency, aberrant anatomy, occlusions, or arteriovenous malformations [66]. In some cases, though, ICG angiography may not be as effective as other options. Because of the limited tissue penetration of near-infrared light and fluorescent signal, some important abnormalities might result in inadequate visualization of the vessels/blood flow. This could include severe atherosclerotic disease or an aneurysm sac filled with clot. Additionally, it may be used to assess perfusion in cases of peripheral arterial disease (PAD), critical limb ischemia (CLI), amputation, or trauma [65, 86–89]. This can predict the adequacy of treatment for PAD or CLI, determine the appropriate level for amputation and likelihood of healing, and guide treatment decisions in trauma.

This ability of ICG angiography to assess perfusion has found particular value in gastrointestinal surgery. Because adequate blood supply is essential to healing an initially watertight anastomosis and preventing breakdown and leak, various techniques have been employed by surgeons to attempt to ensure that there is sufficient blood flow to the area. These have included subjective and potentially unreliable indicators such as bowel wall color, bleeding at the cut edge of the

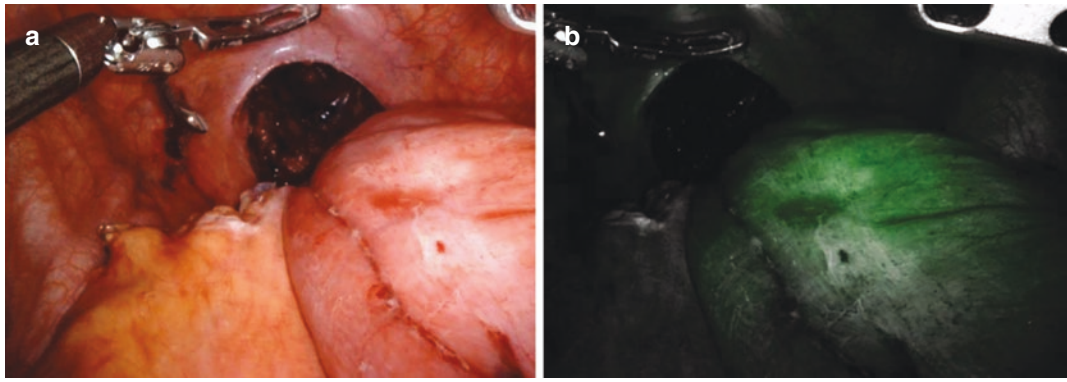

Fig. 34.3 Visualization of a J-pouch prior to anal anastomosis under white light (**a**) and near-infrared light with after injection of ICG (**b**)

bowel, the presence of detectable Doppler signals in the mesentery, and palpable pulses at vessels such as the marginal artery for distal colon/rectal resection or in the right gastroepiploic artery for esophagectomy [60, 90]. Some drawbacks are that these techniques may poorly reflect the microperfusion at the level of the anastomosis, might not reflect the perfusion from both the distal and proximal sides of the anastomosis, or might not be available with minimally invasive surgical technique. ICG angiography is quick, safe, and intuitive and may better represent the true perfusion to the anastomosis (Fig. 34.3).

34.2.2.1 Colorectal Surgery

ICG angiography has been studied in colorectal surgery since at least 2010, when Kudszus et al. published their retrospective study demonstrating an association between the use of ICG angiography and reduced leak rates and hospital length of stay [91]. Since that time, dozens of studies have been performed (Table 34.2), many of limited quality and often with conflicting results [60, 61, 70, 72, 91–121]. There are several studies of note, however, including recent randomized controlled trials.

PILLAR II

The Perfusion Assessment in Laparoscopic Left-sided/Anterior Resection (PILLAR II) study by Jafari et al. is one of the landmark studies on ICG angiography in colorectal surgery [70]. It was the first moderate-sized prospective, multicenter study on the topic, with 139 patients included. They included patients 18 or older undergoing laparoscopic or robot-assisted left colectomy or anterior resection with planned anastomosis 5–15 cm from the anal verge. They used the PINPOINT endoscopic fluorescence imaging system to assess perfusion just prior to bowel transection and transanally after the anastomosis was performed.

Their results showed successful fluorescence imaging in 98.6% of patients leading to an alteration in surgical plan/care in 7.9% of patients. This was primarily a change in planned transection line (6.5%) of patients, though transanal assessment necessitated takedown and revision of the anastomosis in one patient. There was also one patient in whom transanal fluorescence imaging confirmed adequate perfusion to the anastomosis after concerns arose under traditional methods of assessment. Notably, none of the patients who experienced a change in surgical plan developed anastomotic leak. Overall, two patients developed leak (1.4%) and both resolved with conservative treatment. This is far lower than previously reported leak rates.

There are some limitations to the study. There was a lack of standardization across institutions in operative technique and perioperative care. The "standard of care" or "traditional" assessment of the anastomosis was also not standardized. There was also no control group with whom to compare outcomes, so the low leak rate may be more reflective of surgeon experience and skill at

Table 34.2 Studied uses of ICG angiography in colorectal and foregut surgery with literature support

Field of surgery	Potential uses for ICG angiography	Supporting studies
Colon and rectal surgery	Changing resection margin/ transection site	Observational feasibility [70, 72, 93, 96, 100, 105, 111], retrospective case series [94, 109, 121], retrospective cohort [61, 98, 104, 113, 119], retrospective matched-pairs [91, 116], prospective cohort [95, 110, 130], prospective multicenter cohort with mixed historical/concomitant controls [101], meta-analysis [122, 124, 126], randomized controlled trial [117, 118]
	Revising anastomosis	Observational feasibility [70, 106], retrospective cohort [119], prospective multicenter cohort with mixed historical/concomitant controls [101], meta-analysis [126]
	Determining need for protective ostomy	Observational feasibility [92, 93, 105, 108], meta-analysis [126]
	Predicting anastomotic leak	Observational feasibility [102, 106, 114, 115], retrospective case series [120]
	Reducing anastomotic leak rates	Randomized controlled trial [117], retrospective cohort [61, 98, 104, 119], retrospective matched-pairs [91, 116], prospective cohort [95], prospective multicenter cohort with mixed historical/concomitant controls [101], meta-analysis [122–126]
Foregut surgery	Changing resection margin	Observational feasibility [131–133], meta-analysis [127, 128]
	Revising anastomosis	Case series [134]
	Predicting anastomotic leak	Observational feasibility [90, 135], retrospective cohort [136], meta-analysis [129, 137]
	Preventing anastomotic leak	Retrospective cohort [138], meta-analysis [127–129]
	Predicting stricture	Case report [139], observational feasibility [135]

these primarily academic specialty practices. Finally, the intensity of the fluorescent signal was not measured quantitatively leaving the adequacy of perfusion on fluorescent imaging up to surgeon interpretation.

Additional Prospective Studies

Since PILLAR II, several large prospective trials have been published, including two randomized controlled trials. Ris et al. prospectively studied 504 patients undergoing high anterior resection or reversal of Hartmann's or low anterior resection (LAR) with ICG angiography [101]. They found that 5.8% of patients required a change in site of transection after fluorescent imaging (additional resection between 0.5 and 20 cm) with leak rates of 2.4% overall, 2.6% for colorectal anastomosis, and 3% for LAR. These were significantly lower than for similar surgeries performed at the same facilities without fluorescent imaging perfusion assessment (5.8% overall, 6.9% for colorectal anastomosis, and 10.7% for LAR). They also found that five patients for whom a diverting ostomy was planned were able to forego diversion after fluorescent imaging assessment of the completed anastomosis and that this group had no leaks. Morales-Conde et al. prospectively collected data on 192 patients undergoing any colorectal surgery with anastomosis [110]. They separated their patients into groups based on the surgery performed, including right hemicolectomy, left hemicolectomy, anterior resection of the rectum (subdivided into LAR with partial mesorectal excision and ultra-LAR with total mesorectal excision), and segmental resection of the splenic flexure. They found that 18.2% of patients had a change in transection site based on ICG angiography, with rates over 25% in both the anterior resection and left hemicolectomy groups. Two patients had a transection line moved more distally based on fluorescence imaging, which might reduce tension on the anastomosis. Of the patients who had a change in transection line, 8.6% had an anasto-

motic leak. Overall leak rate was 2.6%. Alekseev et al. conducted a randomized controlled trial of patients undergoing sigmoid or rectal resection [117]. They analyzed 377 patients, 187 of whom were randomized to near-infrared fluorescent imaging perfusion assessment and 190 of whom were randomized to standard visual clinical assessment. Patients underwent elective resection of sigmoid or rectal neoplasms with colorectal anastomosis less than 15 cm from the anal verge and were followed for clinical leak up to 30 days postoperatively. If a clinical leak had not been detected, patients received a contrast enema or pelvic CT by 30 days postoperatively. They found that 19.2% of patients had insufficient blood supply to the planned transection site by ICG angiography, with up to 5 cm of additional bowel resected. Overall complication rates and grades were similar between groups. They did find a significantly lower rate of anastomotic leak in the ICG angiography group compared to the non-ICG group (9.1% vs 16.3%, $p = 0.04$). They found that this difference could be almost entirely attributed to asymptomatic low (4–8 cm from anal verge) radiological leaks (14.4% vs 25.7%, $p = 0.04$) and that were no significant differences in either high (8–15 cm from anal verge) anastomotic leaks or symptomatic low anastomotic leaks. De Nardi et al. also performed a randomized controlled trial of patients undergoing laparoscopic left-sided colon or anterior rectal resection with colorectal anastomosis between 2 and 15 cm from the anal verge with ligation of the IMA [118]. They included 240 patients in their analysis, 118 in the ICG angiography group and 122 in the control group. They powered their study to detect a difference in leak rates of 1.5% in the study group and 10% in the control group. They found a rate of changing the transection site of 11% in the ICG group, with additional resection ranging from 2 to 16 cm. They found no significant difference in leak rate between groups (5% in the ICG group and 9% in the control, $p = 0.2$). 16/17 anastomotic leaks were detected clinically, with just one asymptomatic leak found on routine imaging prior to closure of the protective ostomy. One patient in the control group died after developing anastomotic leak. Overall, these and other studies demonstrate that the use of ICG leads to a change in the transection site in a substantial minority of cases, with the potential to avoid malperfusion to the anastomosis, allow for a more distal transection site with less tension, or forego a protective ostomy and the requirement for an additional surgery. There is insufficient evidence at this time to state that it reduces the rate of anastomotic leak, however, despite the recent publication of the first two randomized controlled trials.

Reviews and Meta-Analyses

In addition to original publications, the last several years have seen a number of systematic reviews and meta-analyses published regarding fluorescence angiography and colorectal surgery. The 2018 review by van den Bos et al. focused on ease of use, added case time, complications related to the technique, and costs [122]. Additional outcomes included changes to the operative plan, postoperative complications, and attempts to quantify the fluorescent signal. They included ten studies in their review and found a change in resection margin in 10.8% of cases. Anastomotic leak rate was 3.5% in the ICG angiography group and 7.4% in the traditional assessment group. Only two of the studies attempted to quantify the fluorescent signal. Shen et al. performed a review and meta-analysis the same year focusing on surgeries for colorectal cancer and including a control group [123]. They found four retrospective case-control studies for meta-analysis with a total of 1177 patients. They found a pooled odds ratio for anastomotic leak of 0.27 ($p < 0.001$) with the use of ICG angiography compared to traditional assessment. Blanco-Colino et al. similarly performed a 2018 meta-analysis and included all studies looking at anastomotic leak in colon or rectal resection with anastomosis [124]. They included five studies with 1302 total patients. They found a nonsignificant reduction in leak rate with ICG angiography (OR 0.51, $p = 0.10$). When limiting the analysis to cancer cases, they did find a significant reduction in leak rate (OR 0.34, $p = 0.006$). Rausa et al. performed a systematic review and meta-analysis in 2019 and included articles involving colorectal

surgery with anastomosis and the use of one or more intraoperative anastomotic leak tests [125]. They included 11 studies and 3844 patients in their analysis. They found that the risk of leak was significantly lower in patients undergoing ICG angiography than in the control group (relative risk [RR] 0.44) and was also lower than the groups who had only ALT or intraoperative colonoscopy (IOC), though these did not reach statistical significance. Both the ALT and IOC groups had nonsignificant reductions in the risk of leak compared to control. Finally, Arezzo et al. conducted an individual participant analysis in 2020 from studies comparing ICG angiography to standard practice in assessment of anastomotic perfusion during rectal cancer operations and the influence on anastomotic leak [126]. They found 20 eligible studies including 15 published and 5 ongoing trials. 9 of the 20 authors responded (2 randomized trials and 7 non-randomized studies) and shared their data on a total of 1330 patients. There was a significantly greater rate of redoing the anastomosis in the ICG group compared to controls (2.0% vs 0.2%, $p = 0.011$), and 11.3% of patients required a change in the transection site after fluorescence angiography. There was a statistically significant reduction in odds of anastomotic leak with ICG perfusion assessment (OR 0.341, $p < 0.001$), with a leak rate of 4.2% in the ICG group and 11.3% in the controls. Subgroup analysis showed significantly reduced odds of leak with ICG angiography among male patients, patients older than 65 years, overweight patients (BMI ≥ 25 kg/m^2), and patients with anastomosis $\leq$6 cm from the anal verge. Overall, these studies support the thought that the use of ICG angiography is associated with lower leak rates. There remains insufficient data from randomized controlled trials to claim a causal relationship, but there are a number of studies underway that will help to definitively answer that question. Regardless, the literature to date has shown that ICG angiography may change transection site in up to 25% of cases, allowing some patients to have a more distal transection and less tension on the anastomosis, while others require up to 20 cm of additional bowel removed. It may also allow for more judicious use of diverting ostomies, potentially saving patients the recovery and costs associated with another surgery and the complications associated with an ileostomy.

34.2.2.2 Foregut Surgery

While the field of foregut surgery has seen fewer studies on the use of near-infrared imaging for perfusion assessment than has colorectal surgery, there have been a number of studies published since the late 2000s (Table 34.2). The majority of these have focused on perfusion assessment of the conduit following esophagectomy, though studies have been performed on gastrectomy for gastric cancer, preventing leak in bariatric surgery, and other topics (Fig. 34.4). Optimization of perfusion in esophagectomy is particularly important considering the potentially devastating consequences of leak with an intrathoracic anastomosis and that leak rates in cervical anastomosis are over 50% in some studies (though typically with less severe morbidity) [46].

The literature on ICG angiography in foregut surgery lacks good-quality prospective studies. Additionally, there have been few studies that have included a control group. Three recent meta-analyses do suggest that fluorescence angiography may be able to reduce leak rates in esophagectomy, though [127–129]. Van Daele et al. included 19 studies in their review and analyzed a total of 1192 patients, 758 who had perioperative ICG angiography performed and 434 for whom anastomotic site was determined based on clinical judgment [128]. They found that the surgical plan was

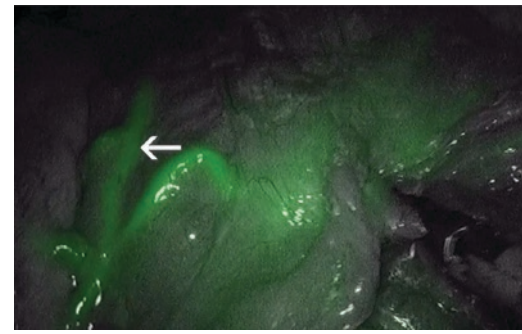

Fig. 34.4 Utilization of ICG fluorescence angiography to identify and preserve the gastroepiploic artery (arrow) while mobilizing the gastric conduit during esophagectomy

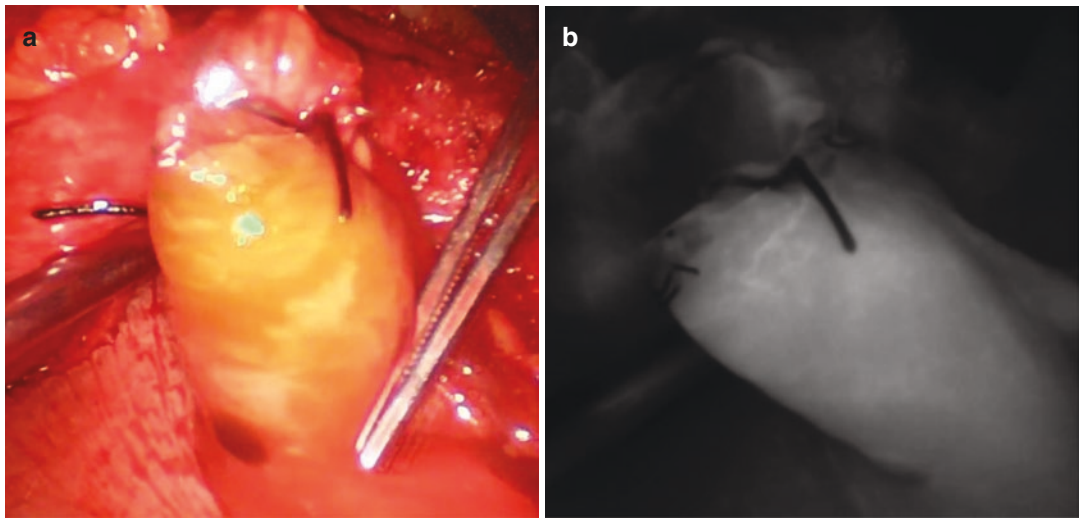

Fig. 34.5 Evaluation of the cervical esophagogastric anastomosis following esophagectomy. While the anastomosis appeared healthy under white light (**a**), ICG fluorescence angiography showed a lack of perfusion at the tip of the gastric conduit (**b**). This was resected and the anastomosis was redone with improved perfusion

altered in 12.4% of the ICG cases, with differing approaches based on study (e.g., additional resection and relocation of the anastomosis if conduit of sufficient length, using an end-to-end instead of end-to-side anastomosis, or creating additional vascular anastomoses) (Fig. 34.5). The leak rate among these patients was 6.5%, similar to the rate of 6.3% in 592 patients deemed to have good perfusion under fluorescence angiography. This was significantly less than the 20.5% leak rate in the non-ICG patients or the 47.8% leak rate in the group that had poor perfusion but no surgical alteration. Slooter et al. found 22 studies that met their criteria of studying ICG fluorescence angiography in esophagectomy [127]. They found a change in management rate of almost 25% among eight studies that included this outcome and a pooled incidence of anastomotic leak/graft necrosis among those patients of 14% compared to 11% overall in the ICG cohort. They also found an overall lower rate of anastomotic leak and graft necrosis in patients evaluated with ICG (OR 0.30). Ladak et al. found 17 studies that met their inclusion criteria [129]. Their meta-analysis included 1067 patients, 631 who received ICG angiography and 436 in the control group. Across all studies, they found a leak rate of 10.8%. In studies that included an intervention for poor perfusion by ICG angiography, the rate was 5.7% compared to 22.9% in the control group. Although each of these studies is limited by the significant heterogeneity and often poor quality of the studies that they included in their analysis, the results do suggest that ICG angiography has the potential to reduce leak rates in esophagectomy. There is just one randomized trial on ClinicalTrials.gov, and additional large prospective studies will be required to determine its optimal use.

34.3 Clinical Implications and Directions for Future Study

34.3.1 The Future of ICG in Perfusion Assessment and Anastomotic Safety

While the broad use of perfusion assessment with ICG at the time of anastomosis has yet to become standard of care, it is considered a best practice by many. There are several challenges to consider when applying this technology. First, access to this promising technology remains a challenge for many. As the data continues to support its routine use for gastroesophageal and intestinal surgery, it will become increasingly necessary to integrate

this feature into all operative imaging systems. Additionally, quantifying perfusion and creating "perfusion metrics" has become an important area for investigation. Perfusion of an end organ can be impacted by several patient-related factors including blood pressure and heart rate, preexisting vascular disease, scarring, injury, and prior surgery. Perfusion metrics must then be correlated with patient outcomes to demonstrate clinical value. Early studies are beginning to show promise in this area of study [106, 114]. Finally, fluorescence angiography with ICG requires intravenous administration at the time of assessment and has a short half-life in the bloodstream before being washed out. For this reason, ICG is often given in repeated doses to visualize perfusion. Repeat subsequent doses can lead to a higher false positive signal of adequate perfusion as the background can build up. The appropriate dosing and time for expected visualization remains an enigma with most surgeons using a similar dose for all patients. The optimal "dose-to-signal" ratio should be validated for surgeons to fully realize the benefit of this information intraoperatively.

The future of perfusion angiography for anastomotic assessment is an exciting area for research and pharma/device development. The initial use of ICG for this purpose has shown great potential for reducing the most serious complication (anastomotic leak) for intestinal surgeons. Future directions for research include developing "perfusion metrics" which will guide surgical decision-making as it relates to patient health outcomes. Newer fluorophores and imaging technology combined with artificial intelligence and machine learning will all play an important role in the interpretation fluorescence angiography in the future, thus making perfusion testing at the time of anastomosis a necessary aspect of optimal surgical care.

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Advanced Endoscopic Imaging Methods

35

Friedrich Foerster and Helmut Neumann

35.1 Introduction

The past three decades have seen a rapid evolution of endoscopic imaging methods. The common goal of new imaging technologies has been to facilitate a more accurate assessment of the visualized tissue in order to better guide diagnosis and therapy. Developments in this field include magnification, dye-based chromoendoscopy (DBCE), and virtual chromoendoscopy (VCE) provided by various imaging systems such as narrowband imaging (NBI), Fujinon intelligent color enhancement (FICE), blue light imaging (BLI), and linked color imaging (LCI). With promising signals from studies on artificial intelligence (AI), it is very likely that the years ahead will bring yet another set of endoscopic imaging methods to maturity.

35.2 Artificial Intelligence

AI, in a medical context also referred to as computer-assisted diagnosis (CAD), enables machines to process information in a manner similar to humans, however, potentially at a much higher efficiency. AI holds the promise to revolutionize endoscopic diagnosis. Therefore, it has received growing attention from the scientific community in recent years [1]. Two key approaches underlying AI are machine learning and deep learning (DL), which can be employed to analyze images (reviewed in [2]). DL involves artificial neural networks (ANNs) aiming to replicate the learning process of the human brain. ANNs are able to process large volumes of high dimensional data, which is useful for endoscopic image recognition [3].

Convolutional neural networks (CNNs) are a particular kind of ANN, in which a feed-forward algorithm is utilized whose connectivity pattern was inspired by the visual cortex [4]. CNNs convolve the image first and then reduce it further in size by max pooling and threshold-based activation (ReLu function). Using this approach, CNNs avoid the risk of overfitting of the model, which makes it an attractive method for endoscopic imaging [3].

The first AI applications for endoscopy (colonoscopy in particular) have received regulatory approval: WavSTAT4 (SpectraScience, San Diego, CA, USA), which uses laser-induced fluorescence spectroscopy, and EndoBrain, which employs endocytoscopy (Olympus, Tokyo, Japan). More recently, CAD EYE (Fujifilm, Tokyo, Japan) has received regulatory approval allowing for both colorectal polyp detection and characterization by just simply pushing a button on the handle of the endoscope. All systems

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described above are capable of differentiating neoplastic from non-neoplastic colorectal polyps (for details, see below) [5, 6].

35.3 AI in Upper Gastrointestinal Endoscopy

To date, mostly retrospective studies have been performed for CAD in upper gastrointestinal (GI) endoscopy [7] with two studies being prospective [8, 9]. One study demonstrated that real-time diagnosis of early gastric cancer is feasible [10]. Most of the available imaging modalities have been evaluated including, recently, volume laser endomicroscopy (VLE) [11]. In a first randomized controlled trial (RCT), CAD-assisted white light endoscopy (WLE; WISENSE) revealed significantly fewer blind spots than conventional gastroscopy (5.86% vs. 22.46%, $P < 0.001$) [12].

35.3.1 Barrett's Neoplasia

For Barrett's neoplasia, the first CAD studies demonstrated diagnostic test performances similar to histopathology. CAD evaluation of a dataset containing 405 endoscopic optical coherence tomography pictures from 13 patients that were paired with histological sections of corresponding biopsies yielded sensitivity, specificity, and accuracy of 82%, 74%, and 83%, respectively [13]. A more recent study with a slightly larger cohort (100 images from 44 patients) demonstrated a similar performance [14]. In a study with images obtained with a fiberoptic high-resolution microendoscope from 230 sites in 58 patients, a fully automated image processing algorithm calculating quantitative image features yielded a sensitivity of 88% and a specificity of 85% in a validation cohort [15]. A recent study of CAD using histograms on VLE images demonstrated a remarkable diagnostic performance with sensitivity 90% and specificity 93%, respectively. However, with only 60 VLE images tested, this warrants further large scale validation [11].

35.3.2 Squamous Cell Cancer (SCC)

One study on the diagnosis of SCC employed tablet-interfaced high-resolution microendoscopy (HRME) and demonstrated an imaging performance comparable to first-generation laptop-interfaced HRME systems, however, at a lower cost. In a post-hoc quantitative analysis, the system identified SCC with a sensitivity and specificity of 95% and 91%, respectively [16]. In another study using NBI, a CAD model was developed to evaluate the feasibility of automated classification of intrapapillary capillary loops (IPCLs) in order to detect SCC [17]. Another recent study demonstrated the ability of CNN to detect esophageal cancer in a test database of 1118 images with a sensitivity of 98% and a negative predictive value (NPV) of 95% after training it with 8428 images [18]. This group also demonstrated that its CNN outperforms experienced endoscopists both in speed and accuracy when predicting the depth of invasion [19]. Also from the same group, the combination of endocytoscopy (ECS) and a CNN-based AI that was based on GoogLeNet and trained using 1141 malignant and 3574 nonmalignant ECS images achieved an overall accuracy of 90.9% in distinguishing healthy and malignant esophageal mucosa [20]. Regarding detection of early SCC and differentiation from inflammation, a retrospectively trained AI network reported an excellent performance with a sensitivity of 97% and a specificity of 94% [21]. A CNN was also capable of detecting SCC in endoscopic videos. However, its positive predictive value (PPV) was fairly low at 42.1% reflecting a higher false-positive rate, which leaves room for future improvement [22].

35.3.3 Gastric Cancer

CAD and its utility for guiding clinical decision-making have also been evaluated in the context of gastric cancer by testing its accuracy regarding diagnosis, the depth of invasion, and the delineation of borders.

A first study using magnifying endoscopy with FICE on 46 images of gastric cancer

produced sensitivity, specificity, and overall accuracy rates of 85%, 87%, and 86%, respectively [23]. The performance was improved in a follow-up study employing BLI [24]. A CNN trained with 13,854 images of gastric cancer correctly diagnosed 71 of 77 gastric malignancies within 47 seconds in a set of 2296 images, resulting in a sensitivity of 92.2%. However, 161 noncancerous lesions were categorized as cancerous, leading to a PPV of only 30.6% [25]. This CNN was evaluated in a pilot study with video images, which demonstrated a sensitivity of 94.1% similar to the study with still images [10]. Another study employing CAD in combination with NBI for magnification trained a support vector machine with 126 images, which was then tested with 61 cancerous and 20 noncancerous images. The system achieved diagnostic accuracy of 96.3% with sensitivity of 96.7% and specificity of 95% at a rate of 0.41 ± 0.01 seconds per image. However, its performance was limited when delineating the borders of lesions (accuracy of 73.8%, sensitivity of 65.5%, and specificity of 80.8%) [26].

Regarding the AI-based evaluation of the invasion depth in early gastric cancer, a CNN-CAD system was trained with 790 images and then tested with 203 images. The reported sensitivity and specificity were 76.47% and 95.56%, respectively, with an overall accuracy of 89.16%. Of note, the CNN-CAD system achieved significantly higher accuracy (by 17.25%) and specificity (by 32.21%) in comparison to human endoscopists [27].

Finally, an image retrieval framework for the retargeting of optical biopsies in the setting of serial examinations was developed using 13 in vivo gastrointestinal videos from six patients, which outperformed conventional retargeting approaches [28].

35.3.4 *Helicobacter pylori*

So far, all studies evaluating CAD for the diagnosis of *Helicobacter pylori* infection have involved DL. In this context, AI has the potential to improve diagnostic performance by eliminating the false-positive rate due to conventional sampling error.

An early study using a refined feature selection with neural network (RFSNN) technique based on images from 30 patients yielded a sensitivity of 85.4% and a specificity of 90.9% when tested in a dataset with 74 patients [8].

A study by Shichijo et al. tested two CNNs against 23 endoscopists of varied experience on 11,481 images from 397 patients. The second CNN showed better performance than the first. Sensitivity, specificity, and accuracy of the second CNN in comparison to the endoscopists were 88.9% vs. 79.0%, 87.4% vs. 83.2%, and 87.7% vs. 82.4%, resulting in a significantly higher accuracy for the second CNN [29]. A CNN trained with a smaller dataset (149 images) and tested on 30 images achieved sensitivity and specificity rates of 86.7% each [30].

A pilot study on an AI-diagnosing system using DL compared the system's accuracy when analyzing WLI, BLI-bright, and LCI images. The areas under the curve obtained for BLI-bright and LCI were 0.96 and 0.95, respectively, and significantly larger than for WLI [9].

35.4 AI in Lower Gastrointestinal Endoscopy

The role of CAD has been investigated most extensively in colonoscopy where it can aid polyp detection and characterization as well as the assessment of colitis [31].

35.4.1 Polyp Detection

So far, most studies on CAD have been retrospective. Before the advent of DL, CAD algorithms were developed by analyzing scores of WLE images of polyps. This approach had its limitations due to relatively low numbers of polyps, interference by stool, mucosal folds, lighting, and vessels as well as the ground truth being provided by human detection.

DL and the application of CNNs have greatly increased the ability of machines to detect pol-

yps (for a historical overview, refer to[32]). An early study combining the extraction of color wavelet and CNN features from endoscopic videos to train a linear support vector machine gained an accuracy of 98.65%, a sensitivity of 98.79%, and a specificity of 98.52% when evaluating standard public databases [33]. To solve the problem of limited training data, another study employed nonmedical images to train the CNN with millions of images, which resulted in 98% sensitivity and 1.00 area under the receiver operating characteristic (AUROC) curve [34]. This CNN also outperformed endoscopists in terms of accuracy (86% vs. 74%). One of the first studies to apply a CNN in real time achieved excellent diagnostic accuracy of 96% and was superior to conventional colonoscopy in detecting polyps (reviewers identified 36 polyps without and 45 polyps with the assistance of the CNN) [35]. The first and only RCT to date comparing CAD assisted to conventional colonoscopy for polyp detection demonstrated a significantly higher adenoma detection rate (ADR; 29.1% vs. 20.3%; $p < 0.001$). The AI found significantly more diminutive adenomas (185 vs. 102; $p < 0.001$) and hyperplastic polyps (114 vs. 52; $p < 0.001$), while there was no statistical difference in adenomas larger than 5 mm (77 vs. 58; $p = 0.075$) [36].

35.4.2 Polyp Diagnosis

Differentiating non-neoplastic from neoplastic colorectal lesions during screening colonoscopies has the potential to reduce unnecessary treatments and costs. CAD systems have been developed for all available advanced imaging modalities. For the management of diminutive polyps, CAD systems offer the opportunity to meet the American Society for Gastrointestinal Endoscopy (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI) criteria on Real-Time Endoscopic Assessment of the Histology of Diminutive Colorectal Polyps [37].

CAD systems employing WLI, which is per se an attractive modality given its global use, have unfortunately not performed as desired with a reported accuracy of only 70% [38]. Further developments of CNNs include the "deep capsule neural network" whose architecture is further truncated and which has achieved promising overall diagnostic accuracy [39]. This has included the diagnosis of hyperplastic polyps, adenomas, and serrated adenomas, which are traditionally difficult for CAD systems to diagnose.

35.4.3 Narrowband Imaging

CAD systems utilizing NBI have been evaluated in colonic studies most extensively to date. Algorithms based on vascularization as visualized by magnification NBI are capable of differentiating between neoplastic and non-neoplastic lesions with sensitivity rates ranging from 85% to 93% [40, 41]. Retrospective studies on the assessment of diminutive polyps by DL CNNs have surpassed PIVI-2 criteria with sensitivity rates ranging from 96% to 98%, specificity rates from 78% to 83%, and NPV rates from 91.5% to 97% [42, 43]. In a small prospective study ($n = 41$ patients), a real-time image recognition system analyzing diminutive colorectal lesions in NBI magnifying colonoscopy images achieved an accuracy of 93.2% between its predicted diagnosis and the histologic findings (sensitivity of 93.0%, specificity of 93.3%, a PPV of 93.0%, and a NPV of 93.3%) [44].

35.4.4 Pit Pattern

The pit pattern of colorectal lesions can be used to guide endoscopic treatment decisions, but its implementation in clinical practice requires extensive training. A CAD system was developed to classify pit patterns in magnifying endoscopy images. In a retrospective study with 134 images, the system achieved an accuracy of 98.5% [45]. Using a set of texture image features in the wavelet domain, a classifier combination approach also achieved encouraging results [46].

35.4.5 Autofluorescence Imaging

CAD systems using autofluorescence endoscopy may assist in differentiating non-neoplastic and neoplastic polyps. A system performing real-time color analysis and assessing the green/red ratios of colorectal lesions found that the mean green/red ratio of neoplastic lesions was significantly lower than of non-neoplastic lesions (0.86 vs. 1.12; $p < 0.001$) [47]. In a study with 32 participants with 102 colorectal lesions, it yielded sensitivity, specificity, PPV, and NPV of 94.2, 88.9, 95.6, and 85.2%, respectively [47].

A CE-marked and FDA-approved autofluorescence-based system is WavSTAT4, which performs an optical biopsy using a single-use probe and which is capable of differentiating neoplastic from non-neoplastic tissue of colorectal lesions by detecting differences in fluorescence absorption. Biopsy forceps integrated to the probe allow performing biopsies if required. In a more recent study with 27 patients, WavSTAT4 achieved an overall accuracy of 84.7% with sensitivity, specificity, and NPV of 81.8%, 85.2%, and 96.1% [48].

35.4.6 Confocal Laser Endomicroscopy

AI has been applied in the context of confocal laser endomicroscopy with the aim of identifying optimal images and extracting relevant features [49, 50]. A software for automated classification of colonic polyps achieved a performance comparable to expert endoscopists (accuracy 89.6 vs. 89.6%, sensitivity 92.5 vs. 91.4%, specificity 83.3 vs. 85.7%) [51]. CAD of advanced colorectal adenocarcinomas based on a two-layer feed-forward neural network produced an accuracy of 84.5% [52].

35.4.7 Endocytoscopy (EndoBrain)

EndoBrain, an AI system that distinguishes neoplastic from non-neoplastic colorectal polyps, has recently received regulatory approval in Japan. Two initial studies, in which methylene blue was used for nuclear staining, demonstrated that the endocytoscopic CAD system achieved an accuracy of 89%, which was significantly higher than nonexpert endoscopists and comparable to experts [53, 54]. A next-generation endocytoscopic CAD system utilized NBI to replace staining with a dye and achieved an overall accuracy of 90.0%, in high confidence cases of even 96.9% [55]. In a head-to-head comparison, the staining- and the NBI-based method achieved similar results [NPV of 93.7/96.4%, and 95.2/96.5%, respectively (worst/best case)] [56]. In the largest prospective real-time trial with EndoBrain so far, the system identified colon lesions with 96.9% sensitivity, 100% specificity, 98% accuracy, a 100% PPV, and a 94.6% NPV. It also distinguished neoplastic from non-neoplastic lesions with 96.9% sensitivity, 94.3% specificity, 96.0% accuracy, a 96.9% PPV, and a 94.3% NPV [57].

35.4.8 Assessment of Colitis

Achieving mucosal and histological healing is an important goal in the treatment of ulcerative colitis (UC). The use of AI to assess the colonic mucosa may also provide benefits in this regard and has therefore been evaluated for this purpose. For example, one retrospective study constructed and tested a CAD system to predict persistent histological inflammation in patients with UC using endocytoscopy. In a dataset with 187 patients, the systems achieved diagnostic sensitivity, specificity, and accuracy of 74%, 97%, and 91%, respectively, with high reproducibility ($\kappa = 1$) [58]. Furthermore, in a recent retrospective study, a CAD system utilizing a CNN based on GoogLeNet architecture was trained with 26,304 colonoscopy images from 841 patients with UC. The performance of the system in identifying normal mucosa (Mayo 0) and mucosal healing (Mayo 0–1) was then evaluated in an independent cohort (3981 images from 114 patients with UC). The algorithm produced strong results with AUROCs of 0.86 and 0.98 to identify Mayo 0 and 0-1, respectively [59].

35.5 Hypoxia Imaging

Hypoxia is a nonphysiological state that plays a crucial role in inflammation and has been linked to diseases such as inflammatory bowel disease, cancer, and infections [60]. Therefore, measuring oxygen levels in specific parts of the body provides information on the present metabolic as well as inflammatory state. Optical microscopy techniques allow to visualize oxygen levels not only ex but also in vivo. Fluorescent hypoxia stains, fluorescent protein reporter systems, phosphorescent probes, and nanosensors facilitate the mapping of oxygen gradients, qualitatively or quantitatively (reviewed in [61]). In gastrointestinal endoscopy, these techniques can be obviously used to detect cancer and inflammatory bowel disease.

35.5.1 Neoplasia

The assessment of oxygenation in the gastrointestinal tract by measuring hemoglobin oxygen saturation using conventional spectroscopy has not been feasible due to poor image quality, low spatial information, and lack of speed. These limitations have been overcome by a laser endoscope system that is composed of two laser diodes and a color CCD sensor. This system is capable of producing an oxygen saturation map of cancerous lesions and their surrounding mucosa based on the difference in absorption of oxy-hemoglobin and deoxy-hemoglobin [62, 63]. A proof-of-concept study with 40 subjects with known malignancies of the pharynx, esophagus, stomach, and colon demonstrated a significant difference in the oxygen saturation map between neoplastic and non-neoplastic areas in cancers of the esophagus and colon [62]. These results illustrate how functional endoscopic imaging may aid cancer diagnosis and treatment response prediction in the future.

35.5.2 Inflammatory Bowel Disease

Compared to other tissues and organs, intestinal epithelial cells are relatively hypoxic, which is exaggerated in active colitis. This is because inflammation increases the metabolic rate, leading to an increased demand for oxygen and energy supply [64, 65]. In such a setting of hypoxia, the transcription factor hypoxia-inducible factor (HIF) regulates key target genes that promote inflammatory resolution. Accordingly, HIF1alpha and HIF2alpha have been found to be overexpressed in UC and Crohn's disease [66]. In a murine model of colitis, an increase in oxygenation, partial activation of HIF1 signaling, and negative trends in pyruvate dehydrogenase activity and oxygen consumption suggesting a decrease in mitochondrial respiration rate were observed in the colitis mucosa [67]. While these findings require further validation, they set an example for how the detection of hypoxia and related signaling pathways can serve as biomarkers and therapeutic targets in inflammatory bowel disease.

35.6 Three-Dimensional Imaging

The concept of three-dimensional imaging was first applied in laparoscopic surgery more than 20 years ago and has gained a strong foothold in this setting because of the benefits of space perception [68]. To generate 3D endoscopic images, two optical axes are needed that present two separate images matched to the convergence angle of the endoscopist [69]. Apart from pairing two video cameras in one optical system, an alternative approach generates a virtual 3D video from conventional endoscopic images after converting them into a separate pair of images, which has the advantage of being compatible with existing conventional endoscopes [69]. The 3D video can then be viewed using 3D glasses and a 3D monitor. In a first study on 3D vs. 2D imaging for lesion detection during simulated colonoscopy, 3D imaging resulted in a 25.1% absolute improvement in detection with the sensitivity of 3D viewing being twice that of 2D and the specificity being similar between the two groups [70].

35.7 Robotic-Assisted Devices for Endoscopic Imaging

Having been successful in the field of surgery, robotic-assisted devices have been introduced to the field of endoscopy. The promise of robotic-assisted endoscopes is to increase diagnostic yield, cecal intubation rates, and patient comfort, which remains to be translated into routine clinical practice.

The first self-propelling colonoscopes that are remotely controlled by an endoscopist using a handset have become commercially available. One such example is Aer-O-Scope™ (GI View Ltd., Ramat Gan, Israel), which is a CE-trademarked, FDA-approved disposable 360° viewing colonoscope that is navigated through the colon with sequential inflation/deflation of two balloons. In one study, it achieved a high cecal intubation rate of 98.2% [71].

Another device is Endotics® Endoscopy System (EES; CE trademarked, Era Endoscopy SRL, Peccioli, Italy), which incorporates a steerable tip with two mucosal clamping systems placed at both ends that enable it to ascend the colon using an iterative process of mucosal suction for clamping, extension, and retraction. Direct comparison to conventional colonoscopy failed to demonstrate superiority of EES [72]. However, EES achieved cecal intubation in 93% of patients with previously incomplete conventional colonoscopy ($n = 102$) [73].

The NeoGuide™ Endoscopy System (NeoGuide Systems, Los Gatos, CA, USA) is equipped with a tip position sensor to measure its steering and an external position sensor to measure the insertion depth. The system is made of multiple electromechanically controlled segments that follow the movement of the tip during insertion mirroring the shape of the colon and reducing patient discomfort during inspection. In a first clinical trial with 11 patients, the cecum was reached in 10 (90.9%) [74].

The disposable Invendoscope™ (Invendo Medical, Kissing, Germany), a motor controlled device with eight wheels attached to an inverted sleeve propelling the camera, enables faster procedures. In the most recent clinical trial with 61 participants, a cecal intubation rate of 98.4% within 15 min was reported [75].

A prototype of a pneumatic-driven soft earthworm robot with two expanding sections and one extending section with bending function has been shown to be capable of crawling through tubular environments such as the colon [76]. The system, which has a rigidity similar to colon tissue that is meant to minimize patient discomfort during inspection, awaits to be tested in clinical trials.

For the upper GI tract, capsule endoscopes have been developed whose movement can be controlled through an external magnetic force. Examples are the Olympus capsule endoscope [77] (Olympus Medical Systems, Shinjuku, Tokyo, Japan) and NaviCam® [78–80] (Ankon Technologies, Wuhan, China). Both have been designed to examine the stomach. The Olympus capsule endoscope was capable of visualizing the antrum and body reliably (98% and 96%, respectively) but was less suited for the fundus (73%) and cardia (75%) [77]. The mean duration per examination was 30 minutes. NaviCam® detected gastric focal lesions with 90.4% sensitivity, 94.7% specificity, a PPV of 87.9%, a NPV of 95.9%, and 93.4% accuracy with similar performance for the upper and lower stomach and a mean duration of 26.4 ± 5.1 minutes [80]. Of the 350 patients, 335 (95.7%) preferred magnetically controlled capsule endoscopy over conventional gastroscopy.

35.8 Eye-Tracking

Eye-tracking technology allows to study an individual's gaze and record the resulting visual gaze pattern (VGP). This offers the opportunity to analyze and compare VGP of for example, experts vs. nonexperts, which can be used for training purposes [81]. Medical experts have been shown to achieve higher diagnostic accuracy and faster visual search than nonexperts in nonendoscopic studies [82].

VGPs, in particular gaze time per area of interest, significantly correlate with the time spent on the corresponding area of the colonic surface with experienced endoscopists showing

significantly higher percentages of overlap between the measured gaze position and the actual inspected area of the colonic surface [83]. Three different types of viewing patterns have been described (center type, donut type, and defect type), which have been shown to be corrigible in novice endoscopists [84]. A centrally focused gaze fixation has been associated with higher ADR and endoscopic experience [85]. However, in a similar, more recent study, just the opposite was reported: the gaze of experienced endoscopists covered the outer ring and the "bottom U" of the screen more than their inexperienced counterparts [86]. In light of the small scale of both studies, it seems that the true VGP of expert endoscopists remains to be demonstrated. In a study assessing the visibility of colorectal lesions using BLI-bright, LCI, and WLI with an eye-tracking system, the miss rate of BLI-bright and LCI was significantly lower and the detection time for BLI-bright and LCI was significantly shorter than that for WLI [87].

35.9 Discussion and Outlook

Endoscopic imaging has witnessed rapid developments in the field of optical biopsy over the past three decades, which has already impacted the role of endoscopic diagnosis. AI is bringing the next wave of innovation to the realm of endoscopy, and it seems inevitable that CAD will become a part of endoscopic practice in the future.

A known restriction of DL-based AI is the "black box" phenomenon where classifications of the algorithms are not directly evident. To counterbalance this deep layer, decomposition helps explain individual neural network predictions by generating a heatmap that highlights the pixels that are determinants of the prediction [88].

The great advantage of CAD is that it will make advanced endoscopic imaging modalities that have so far been confined to expert endoscopists available to routine clinical practice. However, large, multicenter RCTs are needed to confirm the benefit of CAD over the current standard of care in order to support its transition into global practice.

Yet another wave of innovation will come from robotic-assisted endoscopy, which may help to lower the requirements of conventional endoscopy for the endoscopist's skill. In addition, eye-tracking technologies may improve endoscopy training also contributing to reducing the skill gap. Furthermore, high-resolution spatial imaging using volumetric holographics that provide information beyond the superficial mucosa and functional tissue hypoxia imaging are developments that may increase the value of endoscopic imaging. Taken together, the future of advanced imaging methods looks very bright and promising.

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The Struggle from Idea to Product

36

Yoav Mintz and Ronit Brodie

The essence of the process of innovation was best captured by Albert Einstein who said "If *I had an hour to solve a problem I'd spend 55 minutes thinking about the problem, and five minutes thinking about solutions*". Contrary to common belief, innovation is not simply having an idea, from which you then push to develop a product. This concept of working toward a solution is a perfect setup for failure; instead, one should start with the problem that needs solving. A careful analysis of the problem encountered, combined with a detailed understanding of the solution needed, allows creative people to develop new and improved ways to complete specific tasks. As in any field, surgeons or any member of the operating team often have ideas regarding improving a way of doing things or have ideas for new devices that can solve problems encountered in the operating room. While some people stop at the idea, others take the next step, making a sketch of their idea on paper in an effort to move toward developing it into a working prototype. The process of device development does not occur overnight, and it can only be successful when the inventor understands that the process involves many aspects other than the actual invention/solution at hand. In order to achieve the goal of finalizing the idea, taking it from sketch to actual product, one must recognize and relate to each of these aspects from the very beginning of the process.

Successful development of a medical device is similar to crossing a field of landmines in the middle of a battle. Mistakes made will either blow up the project or cause you to retreat and repeat the attempt to cross the field from a different direction. The best way to achieve this is to gather as much intelligence as possible before you begin. If you recognize the pitfalls in advance and plan how to overcome them, your chances of success in marching through the battlefield are much higher. The structured process of innovation together with the problems needed to overcome can serve as a guide for successful implementation of device development.

Unlike a true minefield, you cannot simply avoid the landmines to successfully cross the field, but rather need to disarm them all. The known landmines or pitfalls, inevitably encountered in the process of device development, include (Fig. 36.1: *the problem, the solution, intellectual property, regulation, business plan, reimbursement, funding, and clinical trials.*

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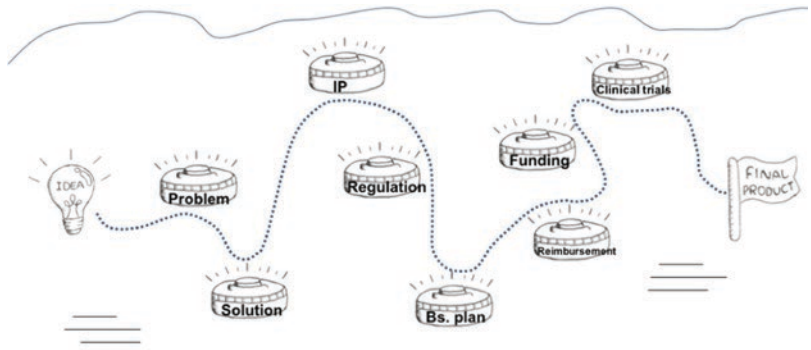

Fig. 36.1 The development process of a medical device resembles crossing a landmine field during battle. Unlike a true minefield, in this complex process all landmines need to be disarmed and cannot just be avoided.

36.1 The Problem

Many medical device startup companies fail because their innovation does not address a "real" customer or market need. As such, the most important landmine to disarm is understanding the problem that needs to be solved. No matter how great an idea is, it does not guarantee a successful development process. Understanding the problem, or more specifically "defining the need," is necessary in order to develop a new improved solution. *Defining the need* means to purify the problem from an entire process or defining an unmet need. For example, if a surgeon is frustrated from the difficulty of suturing an anastomosis in laparoscopy, the problem at hand is laparoscopic suturing; however, purifying the problem is needed to specifically identify the essence of the problem. Necessary questions to be answered should include the following: Is it the needle driver that needs to be modified? Is it the needle designed for open surgery and not for laparoscopy? Is it the positioning of the trocars that constrict the movement of the needle driver? Is it the 2D vision? Is it due to surgeon inexperience? Once the problem is better defined, an actual "*need statement*" can be written. A poor statement would be "there is a need for a better laparoscopic suturing device"; as opposed to a good refined statement such as "there is a need to find a simple way to perform an anastomosis between two bowel loops during laparoscopic surgery." The major difference between the two statements is that while the first statement focuses only on a suturing device, in the second statement the development process is open to exploring all options, causing difficulty suturing an anastomosis. In addition, the second statement suggests that it is open to finding other solution methods such as magnetic compression anastomosis, glues, welding, etc. The better the understanding of the need, the more specific the statement can be, making it easier to focus on a better solution. If the problem is specific to a group of patients such as morbidly obese, the need statement should focus on this specific group. If the problem is more pronounced in a specific type of anastomosis such as gastrojejunal rather than colorectal, attention should be placed on these specific cases.

Once a strong need statement has been formed, the statement should be challenged to ensure that there is indeed an actual universal need. To do this, one must determine if the problem is experienced by others via interviewing relevant personnel such as colleagues (other customers like yourself). Literature searches in journals or websites can also reveal if this problem exists on a larger scale, in the larger community. Once the problem is confirmed as being significant and known, lesser-known existing solutions need to be evaluated. For instance, is there a device that solves the problem, but is not used in your hospital due to contract conflicts with a competitive company, or due to cost limitations (high price), or lack of FDA approval/CE marking. Only after collecting all this information can one move forward, and a "*gap analysis*" should be performed. A gap analysis aids in understanding what is missing from the available solutions, allowing for better resolution of the problem at hand. The gap analysis will determine what specific features the

new device should have to be unique and meet the universal need.

36.2 The Solution

Once the first landmine is disarmed via formulation of a perfect need statement, the next pitfall is proposing the solution. The way to disarm this landmine is rather than charging toward a solution, to generate several *concept solutions* (without going into small technical details). Other than technical feasibility and sound clinical logic, the new concept solutions need to conform with some basic aspects to enable successful adoption by the healthcare community.

A good concept solution should include one or more of the following aspects:

1. Lead to a better clinical outcome
2. Improve safety profile either for the patient or operator, or both
3. Reduce costs
4. Reduce manpower needed for a procedure
5. Simplify the use of a device or simplify a process
6. Reduce the time of a procedure in such a way that it will increase productivity
7. Reduce hospitalization days
8. Reduce intensive care unit days
9. Improve patient satisfaction – shorter recovery, less pain, better cosmetic results
10. Significantly increase the market size or opening a new patient population

Understanding each of these aspects and what they mean for the process of product development provides clarification of the term "innovation" in the MedTech arena. While an *invention* is the creation of a product or introduction of a process for the first time, *innovation* is fresh thinking that *creates value*. This innovation could be a new idea, device, or method that solves unmet needs, or providing better solutions for existing market needs. MedTech corporations often modify their devices incrementally, adding improvements, allowing them to sustain their market presence and maintain profitability. These kinds of innovations, "*sustaining innovations,*" do not require major overhauls of the device, rather small changes. Examples of sustaining innovation include modification of a linear stapler from having only two rows to now having three rows of staples on each side, or having different staple heights within the same cartridge. Another example is the modification of the tip of an energy instrument to be curved with better dissection capabilities rather than just being straight and pointed. The term *disruptive innovation* refers to an innovation that disrupts the current process of a specific treatment, usually very sophisticated, very expensive, and accessible to only a small patient population. This kind of innovation usually does not include a breakthrough technology to make it a superior product, rather a product (even inferior than the existent and, therefore, ignored by industry leaders) that improves accessibility to a much larger population. In time, this innovation usually undergoes more modifications until it outperforms the primary product disrupted, overtaking a significant market share.

As physicians, we have been trained to suggest differential diagnoses for every clinical situation. We work toward confirming the working diagnosis while ruling out the others. Generation of concept solutions works much in the same way. A main concept solution is generated; however, multiple more concept solutions should be generated in order to understand which concept is better or which concept could be better adopted. The best way to generate new concept solutions is to form a team and brainstorm for possible solutions. For MedTech innovations, a core team usually includes a physician, an engineer, and a business oriented person (aka businessman). The members of this team will eventually be the founders of a startup company as such selection of the right people for the task is crucial. While this sounds like an easy task, there are a number of factors that must be taken into consideration: there is a significant "language" barrier between the three, in the early stages work will need to be performed for free, and money as a universal obstacle between friends is involved. As such, it is imperative that there is a good relationship between the people involved and that each

member of the team is dedicated and loyal to the project and the group. The physician should be fluent in the clinical problem; the engineer should be knowledgeable in the area of the technology in question, but also able to provide knowledge in other areas if needed; and the businessman should be able to perform a market analysis and suggest some business plan options. As engineers and businessmen rarely understand anatomy, physiology, or medical procedures, the physician must engage the team into the development process, beginning with laying out the clinical problem. Here is where the "language barrier" comes into play as all the team members need to explain in simple terms, their thoughts, and recommendations. The same way that an engineer may not understand the disadvantages of pneumoperitoneum and what an anastomosis is, the physician and businessman may not easily understand complex definitions of forces applied and nonparametric Kernel regression graphs. The best way to present the problem is through vivid presentations, that is, take the team to the operating room and have them see first-hand the problem encountered. Additional opportunity may be to take the team to a lab to demonstrate the problem on simple simulators, allowing for hands-on opportunity to feel and see, and understand exactly what the problem is. Furthermore, providing and displaying the available devices, and techniques related to the problem to be solved, will maximize contribution of each team member to the project.

Once the team has a sound understanding of the problem, and is fluent with the specific nomenclature, it is time to go on to the stage of brainstorming. *Brainstorming* is based on three foundations: facts, ideas, and solutions. Each foundation deserves quality time, and the tendency to skip from facts to solutions should be discouraged. This is the fun time to explore all ideas, even if they seem silly, or seem like ideas that will never work. The goal of the brainstorming session is to have as many ideas as possible, so judging the ideas presented is done only at the end of the session. One way to generate ideas is to adapt technologies used for other purposes, to the medical need, or reformulating a silly idea into a more feasible one, by taking some useful concepts and modifying it. Once you have developed multiple ideas, a selection process takes place. The ideas are judged by technological feasibility, clinical probability, cost-effectiveness, and patentability. Most importantly, it must be determined whether the idea conforms with the previously developed need statement. Typically, a group will continue to work on developing three to four concept solutions. The final concept solution will be the one that solves the unmet need, makes medical sense, with feasible technology, and is reasonable in terms of cost (production and potential marketing).

A common mistake at this stage is thinking that once there is a concept solution the road is paved and is smooth sailing toward developing a product prototype. This mindset, however, is a recipe for failure. The design process should take into account not only technical issues, but also the patentability (as well as how to avoid infringement of existent patents), the regulatory process, and the business plan. An amateur mistake is thinking that these three issues should be addressed only after the prototype is produced, so it will guide these processes – the opposite is true. Rather than being constricted by the product design, the design process should be shaped to enable patentability and to fit in the desired regulatory path. In a sense, one must constantly look at the larger picture as how to cross the landmine field using the smartest strategy, not the fastest. The next landmines to diffuse therefore are intellectual property, regulatory process, and the business plan.

36.3 Intellectual Property

Intellectual property (IP) is the core strength of any MedTech company; it is the basis upon which the founders acquire funding to continue the development process, eventually allowing them to sell their product for profit. IP refers to creations of the mind and includes patents for inventions, trademarks, industrial design, and copyrights for artistic work and architectural design.

A patent is a legal document enabling the owner to prohibit others from commercial use of the invention for a set period of time, usually 20 years. Existing patents in the field of invention can block the ability of inventors to commercialize their inventions. As such, it is of utmost importance to be familiar with the patents already in place and design the new invention in a way that it does not infringe upon those already in existence, thereby enabling patenting and commercialization. Having a strong patent portfolio is of great value as it creates a barrier to entry for competitors.

A common mistake made by entrepreneurs is to refrain from patenting their invention, avoiding disclosing the details of the invention, to prevent them from being copied and bypassed using different approaches. While this may be true in rare instances, most of the time an IP is the heart of the value of a company. Investors would rarely invest in a company without a strong IP portfolio. As an example of the importance of IP, a company may successfully sell a non-IP-protected product, but may be prohibited from further sales if a competitor enters the market with a similar, but patented product. The competition can claim that your product infringes their IP even if their product was developed years after yours. In such cases, disclosure of the invention should take place, and patenting applied for, if possible, until resumption of sales is permitted. It would be prudent, then, to have a patent in place, but in order to prevent others from exploiting the company's patent, additional confidential *know-how* should remain within the company only. Such confidential know-how could be a special process of welding, or metal sanding that is absolutely necessary in the assembly process, and without this knowledge, the production would fail.

The process of patenting can be very long and very expensive; as such, without substantial funding innovation can be very difficult. In an effort to promote inventions, despite the high costs, the patenting process enables an inventor to submit a provisional patent first. A *provisional patent* is a preliminary description of an invention, which, once filed, establishes a priority date. Filing a provisional patent is relatively inexpensive, and may be written by the inventors themselves, without the need for a patent attorney. It is wise though to have a professional review of the submission, which can then ease the way for a full patent application in the future.

Generally, assessment of patentability should continue throughout the process of development, adding more patents to the portfolio, as the development process advances. A patent attorney would advise whether it would be smarter to gather the inventions combining them into one larger patent or keep as several separate smaller ones. More patents increase the patent portfolio; however, it also increases the cost. To assess if an invention is patentable, three questions need to be answered favorably: Is the invention useful? Is it new? And is it not obvious? The first and last criteria are often easily answered; however, the novelty of the invention is sometimes more difficult. In order to assure novelty, a *patent search* needs to be performed. As a professional patent search may prove to be expensive, especially in the early process of development with no significant funds, a preliminary superficial search can be performed by the inventors themselves. A simple search could be performed using "Google patents search" with adequate keywords, known inventor names in the field, or companies in the field. Searching the USPTO (United States Patent and Trademark Office) and EPO (European Patent Office) websites may also be useful. These preliminary superficial searches enable the inventors to understand how unique their invention is and learn from other inventions in the field. It is important to understand, however, that a professional search would probably yield many more patents related to the invention. In addition, it is important to note that provisional patents are not public, therefore do not turn up in searches. A literature search should also be performed, for if the invention is mentioned in an article it is considered public knowledge and therefore cannot be patented. While searching patents in the field of invention, *freedom to operate* should be assessed. This means that the invention may be novel; however, an existing patent may have claims that could block the commercialization of your product. In cases of existing patents similar

to your invention, or problems with freedom to operate, it is important not to get discouraged. At this early stage of the development process, the opportunity remains to modify your invention to allow you to bypass these hurdles or even license/partner with owners of an existing patent.

In the United States, once a provisional patent is filed, the inventors have a period of 12 months to file a full utility patent in order to keep the priority date. During this period, the inventors should accomplish significant progress in the development of the product; as such, the utility patent should include specifications of the invention, drawings, and claims. Claims are written statements defining the invention, providing the actual aspects that can be enforced; as such, they are the primary components to concentrate on while writing a patent. Once the utility patent is filed and accepted, it usually becomes accessible to the public within 6 months from the filing date. To obtain further protection outside of the United States, corresponding patent applications should be filed in each country desired, while the US priority date will be the effective date if the filing is within 1 year (under the Paris Convention Treaty). To facilitate this process, a unified patent filing can be applied for through the International Patent Cooperation Treaty (PCT), which represents most major nations including the United States and an additional 153 countries to date. The cost of covering a patent worldwide is extremely expensive; therefore, this *national phase* of patent processing may be delayed up to 30 months from the priority date. This allows the inventors to advance substantially with the development and testing, prior to making a major financial commitment.

One cannot underestimate the importance of IP protection. As entrepreneurs seeking funding for the development process, investors are presented with some details of the proposed invention. Having a provisional patent application in place can protect the IP to some extent; however, it is still advisable not to disclose sensitive information. Another way to protect the IP is to have potential investors sign a Non-Disclosure Agreement (NDA, sometimes referred to as CDA – Confidential Disclosure Agreement) prior to meeting with them. While NDA does not guarantee prevention of breach of confidentiality, it does however fall into a category of confidential information exchange preventing from qualifying as public disclosure. When seeking funding from Venture Capital (VC), who interview many entrepreneurs on a daily basis, NDAs are rarely signed as there is a strong possibility they have been exposed to the same problems and solutions from several groups. In these cases, the inventors should only disclose what is absolutely necessary, and in the event of document exchange, the documents should be clearly marked as "confidential."

It is important to note that simple interactions may be considered public disclosures including casual conversations with colleagues, submitting an abstract or a manuscript describing the invention – even if the manuscript has not been published. As such, prior to submissions of such abstracts or manuscripts a provisional patent should be in place in order to safeguard one's concepts. In the United States, there is a grace period of 1 year to submit a patent application from the date of public disclosure; however, internationally there is no grace period, and in the event that the invention was publicly disclosed, it cannot be patented outside of the United States.

36.4 Regulatory Process

An unavoidable and significant landmine to defuse in the battle of product development is the regulatory process. In order to market a device in the United States, a Food and Drug Administration (FDA) clearance is necessary, while in Europe, a European Union approval, Conformite Europeenne (CE) marking is necessary. In other countries of the world, either national regulation approval is necessary or approvals are granted based on the FDA/CE mark.

Some inventors assume that the regulatory process should only begin after the prototype is designed, hence one will know exactly which regulatory path to take according to the function of the device. While this may be the strategy of a new Commander, the veteran Commander will

act exactly the opposite way. He will first determine which regulatory path is desired and adequate for his device and design the device in a way that will suit this regulatory pathway.

Determining the regulatory pathway for a device and going through the process is best done with the aid of an experienced combat tracker who has already marched down this path before. This professional and experienced person from within the field of invention will help you classify your device and guide you through process. In short, the FDA classifies devices into three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. Device classification is based on the risk posed to the patient or user by the device, so that Class I includes the lowest risk devices and Class III includes those with the greatest risk. Well-known examples of Class I devices include surgical clamps, suction catheters, and stapler appliers. Class II devices include implantable devices such as surgical meshes, staples (while the applier is Class I), or radio frequency (RF)-based energy devices, and esophageal stents. Class III devices include pacemakers (cardiac, phrenic, bladder), vascular stents, and thermal ablation devices.

Classification is also dependent on the intended use of the device. A scalpel blade intended for skin incision would be classified differently than a scalpel blade for making corneal incisions. A trephine intended to perform punch biopsies of skin lesions would be classified differently from a puncher intended to create a hole in the aorta for creating an anastomosis.

Understanding how device classification is determined aids in the decision as to which regulatory path to choose for FDA clearance for market. Most Class I devices and some Class II devices are exempt from premarket notification process and do not require the FDA review before marketing. Most Class II devices are subject to premarket notification *510(k)* process if a substantial equivalent device (predicate device) is legally marketed and is demonstrated to be equivalent in terms of intended use, safety, and efficacy. All Class III devices are subject to premarket approval (PMA) process due to high risk involved. *PMA* by FDA is the required process of scientific review to ensure safety and effectiveness of the device. While this is the most rigorous, lengthy, and costly process, it is necessary in order to receive FDA clearance for high-risk devices. It is not uncommon for a device to qualify for regulation via both the 510K and the PMA pathways, and a decision should be made which is the best route to use. Generally, the 510K route is a quicker route to market, is less expensive, and usually does not require clinical data. Competition, however, can more easily follow to market, and the device may be limited in the indications for use because it must follow the indications of its predicate. The PMA route is much more expensive and rigorous, safety and efficacy must be proven, and clinical data is required, often through randomized controlled studies. The PMA route, however, has significant advantages as it constitutes a high entrance barrier for competition, the indications for use can be tailored to the product and potentially protects the company from liability cases.

Mobile medical applications or software, as well as artificial intelligence (AI) and machine learning software, are all considered "*software as medical device*" and regulated separately. In short, software classification is according to the probability of harming the patient; as such, Class A cannot cause any harm; Class B may cause minor harm such as minor injuries; and Class C may cause major harm such as severe injuries or death.

It is imperative to choose the correct regulatory pathway to avoid rejection and the need for resubmission, which can not only lengthen significantly the development timeline, but also compromise the ability to maintain the necessary funding for the process. Therefore, as mentioned earlier, these decisions should be made by experts in the field and as early in the process as possible.

The regulatory process in Europe was once believed to be easier and faster; however, this is no longer true. In the European Union, the *CE mark* is obtained from one of many *Notified Bodies* (NB), indicating that the device conforms to the relevant Medical Device Directives (MDD) with regard to safety, manufacturing, labeling, and expectant per-

formance. The NB are thereby the premarketing assessors responsible for higher risk devices. They check the development and device designs, review the clinical studies, and monitor the quality control procedures and the production of the device. As opposed to the FDA, this includes on-site visits and performing unannounced audits. Once the device is granted a CE mark in one Member State, it can be marketed in all the other European Member States without further controls or evaluations via a Competent Authority (CA) in each country. The government integrates (legally termed as transpose) the MDD into the national law, for which the CA is tasked with ensuring compliance with, as well as responsibility of post-marketing surveillance of the medical devices.

Similar to the FDA, the classification of devices in the EU is also based on risk, but is composed of four classes and with different definitions. A Class I device is a low-risk, noninvasive device that does not interact with the body. If the device is nonsterile (i.e., Class Is), is not a measuring device (i.e., Class Im), or is not a device that can be reprocessed (i.e., Class Ir), then it does not need approval from the NB. It can be self-registered and declared that it complies with the applicable requirements of the MDD. Examples of Class I devices are wheelchairs and plasters. If the device is sterile, certification of sterility from the NB is necessary and subsequent registration is through the CA only. If it is a measuring device such as a stethoscope or thermometer, the science of measuring needs approval from the NB, and subsequently registered through the CA only.

Class II and Class III devices are medium- and high-risk devices (respectively). These devices are further classified according to the duration of use, invasiveness, whether they are implantable or active, and whether they contain a medicinal substance with additional action. The classification of the device is determined by the intended purpose of use by the manufacturer, so two similar devices can be classified differently according to the intended purpose. As such, manufacturers are able to successfully avoid higher classification by clearly defining the intended purpose in such a way that if falls under the lower class.

The regulatory process does not have to start in all locations at the beginning of the process; however, it is dependent on the inventors' location, hospital connections, and capabilities to push their product forward into clinical studies. Since time to market is usually a significant factor in device development, once the product design is mature, even if not finalized yet, it is wise to begin the regulatory process.

36.5 Business Plan

While one might think that a business plan is not related to clinical outcomes of a new device or to the regulatory process or how the device functions, it is imperative to understand that any new device has to be financially lucrative. A device that performs better or even leads to better clinical outcome would never enter the MedTech market if it there would not be any financial benefit for the stakeholders. The business plan should be an integral part of the design process as such decisions made along the way should take into consideration the potential profitability of the device. For example, if an innovator develops laparoscopic scissors with the capability to function well every time for more than a 1000 operations, this would be a great tool; however, with a business model of reusable instruments only, there would be no substantial profit from this device and it will fail before reaching the market. In this situation, one might consider designing the scissors to be partially reusable and partially disposable (insertable blades). The business plan in this case comprises "Razor-razor blade" type, with accrued revenue from the continued purchase of the disposable inserts.

Common business models in the MedTech field include disposables, reusables, implantable, and capital equipment. Unless there is a good reason for an extremely high cost, such as for MRI or CT scan machines, profit should rely on continuing transactions. A business plan relying on sales of capital equipment, such as energy instrument generators alone, would not be profitable enough. This is why companies who develop these generators, develop them to be spe-

cific to the companies disposable instruments. The revenue is based heavily on the disposable devices, rather than the generator itself. In some cases, local company representatives sign contracts with institutions where the capital equipment would be free of charge if the institution commits to purchasing a predetermined amount of disposables. This business plan is very attractive to institutions as they believe they are being charged only for the use of the disposables, hence a cost reduction for them. Another way to profit from capital equipment is by providing a service contract where a monthly fee is paid.

With the emergence of AI and machine learning technology, a business model of fee-per-use may also be utilized. A software-based technology typically does not have any maintenance cost and often has no need for capital equipment, rather the software itself. Other than fee-per-use, the development of such technology should incorporate continued transactions, such as software upgrades, or cloud-based technology necessary for operations. A company can even offer the institution some revenue as well. If the medical software device includes using medical records data, radiology images or even procedural videos, the company can offer the institution revenue from their data if it is sold for use to a third party. With the institution holding such a financial incentive to supply as much data as possible, this may appear to be a win-win situation both for the institution and the company.

While the business model must enable profitability, it should also make sense to the customer as well. There is no reason to dispose of a perfect laparoscopic scissor insert if it can function well for many times, being easily sterilized. If however the insert cannot be sterilized, due to heat-sensitive parts, or long small tunnel cavities, then it needs to be disposed of, and the single-use device makes sense. The concept design of the device therefore is dependent also on the business model and should be incorporated into the design before the final concept. When choosing a business model, one does not need to choose the most profitable one, rather the one most likely to be adopted by the customers while providing a sustainable revenue.

36.6 Reimbursement

Some landmines in the battlefield are very sophisticated requiring careful deciphering, sometimes with much ingenuity. This is the case with reimbursement strategy in medical device development. A careful plan and even out-of-the-box solutions are necessary to successfully decipher this critical obstacle.

Integration and adoption of a new technology into practice is dependent on the capability of the institution and/or physicians' ability or willingness to pay for it, without compromising their current income. In the United States, the cost of a procedure is determined based on the ICD9-CM codes (International Classification of Diseases, 9th Revision, Clinical Modification) and CPT codes (common procedural terminology code). The ICD9-CM code specifies the diagnosis of the patient and the procedures that can be provided for this diagnosis. The CPT codes specify the actual procedures performed. The reimbursement is then calculated according to the approved CPT codes for that ICD9-CM code. The procedure reimbursement includes a component for the hospital and a component for the physician performing the procedure, when not performed in the physicians' office.

The reimbursement cost is fixed according to the procedure and does not change according to the devices used. Therefore, any institution aiming to profit from procedures tends to lower the expenses of the procedure in order to expand their profit margin. An example of such a problem lies with operative gastroscopy, which is reimbursed according to the CPT codes available. If a company develops a new disposable device for endoscopic sleeve gastroplasty, to be performed as a same day procedure in the endo-suite the cost of the new device would need to be absorbed within the existing reimbursement rate. Since the rate of an operative gastroscopy is only a few hundred dollars, the company would not be able to maintain profitability without additional reimbursement. The inventors therefore would need to find a way to get sufficient reimbursement for their procedure. The most simple way is to compare the cost of the new device to the exist-

ing device used. Novel devices, however, usually cost more than the ones they replace; therefore, this strategy is not always possible.

Another option is to apply for a new CPT code; however, this is risky and time consuming with much uncertainty for success as reimbursements are based on procedures rather than new technologies. A final option is to find a more appropriate CPT code and compromise on some advantages that this device may have or even change the physician performing the procedure (which is a risk by itself). If the CPT code chosen is the one for laparoscopic sleeve gastrectomy, the reimbursement will be more than enough to cover the cost of the consumables, as well as leave room for hospital cost savings. The problematic issues in this route are as follows: first and foremost whether this will this be approved by the payors (insurance companies) as this is not laparoscopy and, second, whether the procedure would probably need to be performed in the operating room by surgeons rather than gastroenterologists. In some extreme cases to enable the procedure to qualify for the CPT code of laparoscopic sleeve gastrectomy, a 5 mm trocar may be inserted for laparoscopic surveillance or guidance. This, however, necessitates anesthesia with muscle relaxation and adds unnecessary risk of laparoscopy, raising ethical issues as performing unnecessary laparoscopy to justify the reimbursement.

Other creative ways may include reduction of the overall costs of the procedure, directly attributed to the new device, due to reducing hospitalization days, reducing medication use for both pain and anesthesia, and reducing expensive procedures or surgery, etc.

Since deciphering the reimbursement code is a critical component for the successful adoption of a new medical device, the reimbursement strategy should be determined early on in the process and incorporated into the device design.

In the United States, the government is the single largest entity providing health insurance, covering approximately 40% of the population (Medicare, Medicaide, and Military healthcare). More than 50% have medical insurance through their employer and overall more than 70% have private health insurance, which are more oriented for profitability than the governmental insurance. In general, private insurance companies follow the direction of governmental insurance policy in reimbursement even using the same coding system. However, the large number of health insurance companies makes it very difficult for young startup companies to seek reimbursement approvals from each payor separately.

In Europe, the reimbursement policy is different, taking into account the medical device used, rather than the procedure alone. There are relevant codes for specific medical devices, and if the new device code description is similar, it may be possible to be reimbursed using this specific code. A code description indicates a specific technology (pneumatic, electric, mechanic), certain features (number of channels, pressure ranges), material (type, size, characteristics), etc. The new device needs to comply with the description in order to qualify for the code.

Having an appropriate code, however, is not sufficient. The payors need to decide whether to cover the new device in the reimbursement payments for a specific diagnosis/treatment and what the payment rate should be. Reimbursement for a device is granted when it provides significant clinical benefits when compared to the current alternatives or if the new device provides economic benefits compared with the current medical pathway.

In the EU, the exact wording of the description of the medical device is crucial. The decision for reimbursement is evaluated according to the wording used in the regulatory approval. Therefore, it would be wise to first decide which reimbursement code to seek, and only then start the regulatory process using the appropriate terms and words. Doing it the opposite way could result in compromising the ability to fall under specific desired codes.

36.7 Funding

Just as in a battle, without continuous logistical support to the troops in the field, the soldiers on the front lines would not last long, resulting in losing the war. This holds true in the development

process of a medical device. The process begins with no expenses, simply the investment of time by the inventors, but as the innovation process progresses, funding becomes necessary to continuing development. Expenses include salaries, IP protection, regulation process, manufacturing of the prototype, animal, and clinical trials. Up to 90% of startup companies fail, eventually due to lack of sufficient funding or lack of a well-established business plan. Significant funds are necessary for various stages of development, and one of the major roles of the CEO is continuous fund seeking. As a gross estimation, medical device startups in the United States require 30 million US dollars from proof of concept to market in case of 510(k) approval, and three times as much for a PMA. The first stage that requires funding is for a "quick and dirty" proof of concept. This stage, considered as "pre-seed," usually comprised funding from the "3F's" – Family, Friends, and Founders. Having some form of an initial proof of concept leads to the first official equity funding stage termed "seed funding." Investors at this stage include "Angel Investors" who are willing to take higher risks in return for equity in the company in its early stages. In certain countries, where governments support and stimulate innovations, incubators or accelerators are also an option, although they usually require a higher equity stake. Rarely, Venture Capital (VC) participate in seed funding as well. Another possibility is crowdfunding, typically obtained via the Internet in which small amounts of money from a large number of people is pooled together to reach the desired funding goal. There are many mechanisms of rewarding the investors, either presale of the product, reward-based or equity. Keeping in mind that most novel medical devices have a substantial confidential component, using crowdfunding is a limited option.

Other options for funding include competitive governmental grants intended for small businesses and academic-based innovations, and may serve as seed funding. In the United States, for example, the National Institute of Health (NIH) offers innovation research grants, and in Europe the European Union Horizon 2020 program offers grants for various business projects as well.

A high percentage of startup companies fail to maintain funding throughout the entire process of development, the result being they simply cease to exist. The period between the initial investment and the creation of a commercially viable product therefore is known as *The Valley of Death*. Only companies who succeed in surviving this period are faced with the challenge of raising a more substantial funding termed as Series A funding.

With Series A funding, the company has already demonstrated a good track record and begun to show some revenue. The goal of Series A funding is to further optimize its user base and product offerings. In this round, it is important to have a plan for developing a business model that will generate long-term profit. In Series B rounds, it is all about taking businesses to the next level, past the development stage expanding on personnel, business development, sales, and advertising. Series C rounds are for companies looking for additional funding in order to develop new products, expand into new markets, or even to acquire other companies.

Raising funds along the Valley of Death is an art in and of itself, in which the inventors must be concise and clear when they approach investors for the first time, as investors are flooded with groups seeking funds, sometimes even for the same ideas. Investors' decision to invest in a startup company is not only dependent on the technology itself, rather on multiple factors. The most important factors taken into consideration include:

1. Is there is a significant market size or potential for significant market growth?
2. Is there technical feasibility for the technology within the desired funding and time to market?
3. Is there a demand for the technology, or does it solve an unmet need?
4. Are the team members qualified for the job according to their personal track record, their enthusiasm, and dedication for the project?
5. Does the investors' funding policy fit with the device and area of expertise including the stage of the company, the specific investment

Table 36.1 Members of stakeholders and potential benefits held by each one

Stakeholder	Potential benefit
Patients	*Better clinical outcome, improved quality of life, better cosmetic results*
Physicians	*Better performance, increase safety, improve consistency, higher reimbursement*
Providers	*Lower cost than currently available solutions, reduces manpower, reduces hospitalization days or ICU days, increases productivity, reduces potential complications, reduces overall hospitalization costs*
Payers	*Reduce late complications and readmissions, transfers inpatient to outpatient treatments, lowers the cost of treatment*
Policymakers	*Lowers overall healthcare cost, political concerns*

area (medical device, pharmaceuticals, digital technology, etc.)?
6. Is the stakeholders' analysis favorable?

In the MedTech industry, there is never just one customer, rather there are multiple stakeholders. Stakeholders are those affected by the medical need, holding a stake in the implementation of the technology and holding a role in the adoption of the technology. Stakeholders can benefit from the technology or it can be detrimental for them; therefore, a stakeholder analysis must show a high probability for technology adoption. The major stakeholders (the 5 P's) that need to be addressed in the analysis, and their stake in the new technology are depicted in Table 36.1. The relationship between the stakeholders is complex, with each one influencing the others. For example, private payers are dependent on the income from patients, which is dependent on the policymakers who determine which services should be provided and paid for. The patients choose the payers, vote for the policymakers, and are dependent on the providers and physicians.

In the stakeholders' analysis, innovators should evaluate not only the benefits for each stakeholder driving for adoption of their new technology, but also the potential barriers that would make them resist adoption. In general, if there are revenue losses for one stakeholder, there should be a compensatory mechanism lowering the opposition for adoption. For example, physicians are the ones who recommend the medical treatment options. Although the desire to provide patients with the best possible treatment is their primary concern, these decisions are also dependent on income from procedures. If a new procedure would benefit them via some incentive either financial, or improved efficiency, etc., it is more likely to be adopted. If, however, the new procedure would be detrimental either financially or loss of patient base secondary to a procedure being transferred to another specialty (i.e., from surgeons to gastroenterologists or from cardiothoracic surgeons to cardiologists), there would be strong opposition. The entire picture of benefits and drawbacks, including all stakeholders, will determine the adoption rate of the new technology and innovators should present a favorable stakeholders analysis to potential investors in order to receive investments.

36.8 Clinical Trials

Clinical trials are studies performed on humans to determine specific outcomes of a new medical treatment. The major objectives of clinical trials are to demonstrate safety and efficacy of the new product in order to receive the necessary regulatory approval for marketing. In complex cases, however, the clinical trial may be important for reimbursement and marketing matters as well. In such cases, the trials may be performed in several stages each time concentrating on the specific goal of the company.

Most landmines are passive; however, some are active, meaning they sense your presence and are activated – even if you do not touch them. In order to avoid activation of such landmines, one must know where they are, their mechanism of action, and how to diffuse them. Clinical trials can be thought of as an active landmine. Failure

is destructive. The innovators must know and expect all the potential pitfalls that can go wrong during the clinical trial and avoid such problems. Other than anticipating which problems may be encountered, prior to human experience, a simulation can help to elucidate potential problems. Therefore, the way to diffuse this landmine is performing preclinical trials.

The concept of preclinical trials includes bench testing, software simulations, animal trials, and cadaver testing. Any problems encountered should be resolved, and testing is repeated until no more failures are demonstrated in the same simulation study, confirming the modification did not result in a different new problem. Once these repetitive tests are completed, assuring safety and efficacy in animal models, the human trials can begin, with an initial experience being limited to a small number of patients, called a "First-in-Man" study. This specific step is for medical devices that need to have their safety determined on a small subset of patients when the device is for immediate performance. The effectiveness can also be measured, but due to the small number of patients, it is insignificant.

Preclinical studies should be performed gradually increasing the cost and risk from inexpensive, and lower risk to more expensive and higher risk. With more experience and elucidation of problems in the early stages, the device can be modified, avoiding those issues in the next more expensive stage. Following the first prototype production, bench studies are performed first. For medical devices, these usually include trainer box studies and studies on explanted organs. A novel anastomosis device could be tested via creation of an anastomosis on two explanted animal bowel loops using a laparoscopic trainer box. Following the anastomosis, a burst test can assess the integrity of the anastomosis. Once the size, angles, and function of the device is confirmed, the next step is acute animal studies. This stage will test the device in vivo, meaning that the device will be tested including the effects of true physiology such as bleeding, temperature changes, blood flow, and immediate physiological consequences (vessel sealing, lateral thermal effects, ablation capabilities, etc.). In acute animal studies, specimens can be removed and tested, to determine immediate effectiveness (burst pressure for anastomosis or vessel sealing, depth of ablation, strength test for sutures, tacks, etc.). The next and more expensive stage are survival animal studies. In this stage, all the previous tests are repeated, but safety and efficacy are also tested long term. This stage is the most important stage of the animal model preclinical trial as it tests safety for a prolonged time period, as well as functionality. For example, the creation of an anastomosis can be evaluated longer term for leaks, stenosis, and function. At the end of the study, the animals are sacrificed, so that histological evaluation of the anastomosis can be performed. Vessel sealing can be evaluated for late bleeding, lateral thermal effects, or infections. Ablation catheters can be evaluated for completeness of ablation (size) and for adjacent or distant complications.

According to the FDA, animal model studies are necessary for medical device development, either to determine biocompatibility when new materials are incorporated into the device for which biocompatibility has not yet been proven or to assure device function without injury to surrounding tissue. Animal studies should be performed according to the Good Laboratory Practice (GLP) guidelines with the Institutional Animal Care and Use Committee (IACUC) guidelines and approval. Many inventors erroneously think that animal model studies are easily achieved. Following the global framework for the elimination of animal testing at the International Cooperation on Cosmetics Regulation and the Animal Welfare Act, specific regulations on animal testing were put in place. These regulations ensure that research animals receive humane care and include regulations for the transport, housing, care, handling, and treatment of specific animals. In order to get approvals for animal testing, the innovators should specify why animal testing is necessary, how the specific animal model chosen will serve the objectives of the study, what studies were performed prior to the animal testing stage, and that there are no alternative routes to obtain the objectives other than animal testing.

These concepts are commonly referred to as the three R's of humane animal experimentation: Replacement, Reduction, and Refinement.

Replacement The innovator should justify the use of animals instead of substitutions like inanimate systems or computer programs. If large animals are chosen for the studies, justification is needed for the use of vertebrate animals with greater cognitive awareness, rather than animals with significantly lower potential for pain perception, such as some invertebrates.

Reduction The innovator should specify the strategy for reducing the number of animals used to obtain sufficient data for the research question. One strategy is to use the device multiple times in the same animal. For example, if the device is a novel anastomosis device, the study should include multiple anastomoses in the acute study, and more than one in the survival study. This has an implication on the prototype production and preparedness, and should be established prior to beginning the study. If the device is a new tracker for positioning mesh during hernia repairs, instead of one 10×15 cm mesh in one animal, the study should be designed to use multiple 4×4 cm meshes.

Refinement The innovator should lay out the modification of the experimental procedure to minimize the severity of procedures in order to reduce the pain and distress experienced by the animal. This is achieved via acute studies, in which the animals are euthanized following surgery. In survival studies, the welfare of the animals should be maintained with adequate postprocedure care, sufficient analgesics, and specific time points to finalize the study and sacrifice the animal when animal welfare is unacceptable.

In cases in which there is no suitable animal model or animal research is forbidden, *cadaver studies* are a possibility. Such is in cases for GEJ studies. Dogs have been the preferred animal models for endoluminal gastric devices, as their anatomy closely resembles the human stomach. However in most countries today, it is almost impossible to receive approvals for dog studies. Substitute animals, such as sheep and goats, are ruminants and have a different anatomical stomach. Pig stomachs can be useful for simulation in limited procedures, however not for the GEJ. For endoluminal GEJ procedures, for example, cadaver studies are best for preclinical simulation studies. In Europe, some states enable animal use only for educational purposes, imposing major restrictions on animal research. Major European grants like Horizon 2020 strongly discourage animal testing assessment for medical devices and promote the use of inanimate simulators, software simulations, or cadavers. For cadaver studies, there is no need for any ethical approvals; however, real-time physiology, which is a large part of the study, is not possible. *When performed correctly, preclinical testing should successfully reveal most of the potential problems encountered in the development phase of the device prototype.*

Reaching the point of clinical trials is a significant milestone in the device development process. It is an extremely stressful stage for everyone involved, with patient safety being the top priority and primary concern. Mitigating complications at this stage include making the following decisions:

1. Choosing the facility for the clinical trial wisely. The facility should be one that is familiar and experienced with clinical trials for medical devices.
2. The physician carrying out the procedure should be well informed and well-experienced with the device. Actually the best way is to have the same physician perform a preclinical study on animal models prior to human experience, giving them hands-on in vivo practice.
3. The physician in charge of the trial, and the one who is actually using the new device, should have a strong desire for the success of the device. It is very easy to give up and declare failure if actions are not smooth, and patience together with dedication is mandatory for successful implementation. One way to ensure dedicated physicians is to involve them from the beginning of the development

or from the preclinical trial stage. The problem, however, is if a physician holds significant ownership or stock in the company, the hospitals IRB (Internal Review Board) that approves the trial, will not allow this physician to participate in the trial, thereby preventing him from being the primary investigator (PI). This is rightfully so and is an effort to avoid bias and unnecessary patient risks. The physician involved in this case should involve his colleague friends to support him in this clinical trial, so the desire for success is based on friendship, with the clear limit of patient safety. The company should also make sure that the physicians using the new device do not have any conflict of interest as this is an easy way to give up once there are some difficulties.

Designing a clinical trial should not just concentrate on the functioning of a device and clinical outcome. The clinical trial should be coordinated with the necessary documentation for regulatory purposes, the economic benefit, reimbursement strategy, and data needed for marketing the device. It is important to design the clinical trial to answer the questions needed for these areas, occasionally being performed in a stepwise matter. The goals of the clinical trials should be specified in such a way that they are feasible at that point in the process and formulated in a way that the outcomes measured would not interfere with the development process. For example, if the new device performs a semiautomatic gastrointestinal anastomosis that is anticipated to be faster, safer, and with decreased incidence of leak, the outcome measured *should not* be faster time, less complications, and less leaks. A better way is to determine the outcome measures to be as safe as the stapled anastomosis, comparable leak rate, and comparable time creation. Basically, it is better to have a noninferiority study, rather than insufficiently reaching the goals due to many issues that can arise. If the device performs better, as anticipated, the company goals are achieved – even if it was not specified as the primary outcome measured. If it does not show a better performance, then the trial could be considered a failure and serve as a hurdle for continued development either clinically, or for the ability to raise funding for the next stage. However, if one of the goals of the company is to have data relating to improved cost-effectiveness for reimbursement purposes, the clinical trial should include rigorous financial reports in order to demonstrate superiority over the current technology or treatment. Usually marketing is also an issue that needs to be addressed; therefore, the trials could be performed by key opinion leaders who can assist in marketing by publishing the results in the relevant literature or presenting them in conferences. Before designing a clinical trial, it would be prudent to consult with the regulatory agency (FDA in the United States) and reach a consensus of how many patients are needed, as well as what exactly should be studied in order to receive the necessary regulatory approval. This will avoid misunderstandings, potentially eliminating the need to repeat the study.

36.9 Summary and Personal Insights

Bringing a product to market is a serious struggle, and the analogy to a battle in war highlights this anticipated tortuous path, highlighting in particular the need to visualize all influential aspects at once, thinking ahead for success (Fig. 36.2). Innovation is a process that needs to be learned. Multiple programs offer innovation courses like the "BioDesign" programs offered by leading universities worldwide, potentially increasing the success rate of those who partake in these courses. The need assessment is fundamental, and the key for decision-making throughout the development process. A well-defined need statement guides the entire design process.

A worthy innovation should have a significant value. Either improve clinical outcomes, increase revenue or reduce costs, increase patient safety, or improve patient satisfaction. The chosen concept solution should contain these added values, have a clear regulatory pathway, and the best probability for adoption due to reimbursement policy.

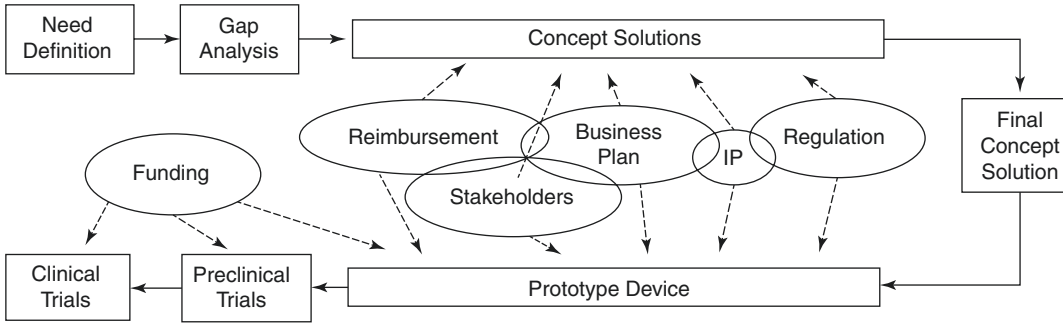

Fig. 36.2 The process of device development is complex, and many factors should be taken into account for successful development

This short chapter is far from being a comprehensive guide for device development; it only underlines the complexity of this process and attempts to highlight the most important components. Many obstacles arise on a daily basis while developing a novel device potentially, resulting in the destruction of the young startup company. In order to succeed, innovators should anticipate obstacles and know how to deal with them individually. A few of the insights from previous personal mistakes and successes are presented here to highlight that there is much more to this process.

- More than three founders of a startup company will lead to many conflicts, increasing the risk of failure.
- Equity split between partners should be decided upon early in the process, in particular before the first investment.
- Always document progress and modifications. This is mandatory for the regulatory process, as well as to avoid repeating mistakes.
- Focus on the need and keep it simple to reduce complexity.
- Early collaboration with experts leads to enhanced solutions and performance.
- Hands-on experience in animal models is priceless.
- It is never a straight road.
- You need more money than you think.
- It takes more time than you think.
- The end result will not be what you thought it would be. Do not be afraid to make changes and adapt. Be flexible.
- Failure is part of the development process. Do not give up. You can lose some battles as long as you win the war.

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Artificial Intelligence

37

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37.1 Introduction

Artificial intelligence (AI) is a new tool of computer science and associated fields to create the ability for machines to establish reasoning and perform cognitive functions [1]. One can differentiate in "strong AI" and "weak AI." Strong AI would be involved performing complex workloads on a similar level as humans, while weak AI would focus on special problems, which often occur and have to be solved in medicine. The aim of these applications is the support of human thinking in connection with technical processing. A major element of AI is the process of learning by these machines, which will build experience and improve the process and which should be able to handle "uncertainties" based on learned and generated probabilities of signs and events.

Most people connect AI with computer science, but it should be noted that AI is associated with mathematics, statistics, computer science, philosophy, psychology, neurology, neurobiology, neurophysiology, communication science, linguistics, and computational neuroscience [2]. Within these areas, AI has shown to be capable of accomplishing very specific tasks. For the clinicians, it is important to learn about these new chances of improving medicine and to understand the possible applications. At the same time, it is important to also understand what AI may be able to help and what are the limitations. AI has entered the medical arena years ago and is here to stay. The Food and Drug Administration (FDA) approved the first diagnostic utilization of an AI algorithm in 2018 – a program that assists in screening for diabetic retinopathy through automated analysis of images of the fundus [3]. The number of FDA-approved algorithms is growing with approved applications in radiology, cardiology, pathology, and other subspecialties [4–10]. Several techniques of AI are known such as machine learning, neural networks, neural networks, and deep neural networks.

37.2 Machine Learning

The term "machine learning" is characterized by studies of algorithms and statistical models, which enable machines to learn and perform special tasks, for example, surgical tasks [11]. Algorithms for machine learning use features and/or properties within the data to learn tasks without explicit programming. In this machine

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learning, the involved features are selected by humans to guide the algorithms during the analysis in evaluating specific components within the data. The tasks to be learned can require a certain classification (data divided into classes) or they may require a regression (relationship is modeled between continuous variables). One can differentiate in machine learning in two most common learning types, which is supervised and unsupervised learning [11].

Supervised learning is a task-driven process, in which an algorithm is trained to predict a prespecified output, such as identifying a stop sign, recognizing a cat in a photograph, or identifying a polyp in the colon during colonoscopy. In this case, the "supervision" is based on the need to feed labeled data in the system to allow for learning the associations between inputs and the desired output. During this learning process, datasets must be provided initially with labels (training set) for learning and, in addition, a test set with no labels, which allows for the assessment of the performance of the algorithm on new data [2, 11].

Unsupervised learning does not require prelabeled training sets or a prespecified annotation. Unsupervised learning is based on drawing inferences from unlabeled data to identify patterns and/or structure within a dataset. This type of learning can be very useful in identifying relationships between groups and/or may be helpful in generation further hypotheses. This unsupervised learning technique can be helpful in managing applied to typical, endoscopic or surgical patient's outcomes databases. Furthermore, it could be also applied to unique datasets such as surgical motion and activity. This technique has been used to identify high-risk cardiac surgery patients and to automatically identify suturing motion in surgical videos [4, 11, 12].

Another technique of unsupervised learning is "reinforcement learning." In this technique, learning occurs through successive attempts via trial and error and subsequent rewards and punishments, which guides the behavior of the model to optimize rewards [2, 13]. A famous example of reinforcement learning has been demonstrated in "AlphaGoZero" by Google, a reinforcement learning algorithm designed initially to play "Go" [14]. In many earlier computer games, the machine was taught a series of moves or was fed past examples of moves played by master players. In AlphaGoZero, the system was only given the rules and subsequently it learned from self-play, becoming one of the top players in the world [14].

Given the vast amount of possible moves in the game, one should expect a substantial learning ability of these systems for the application in endoscopy and surgery. However, expectations for the application of this technology in endoscopy surgery must be kept on a reasonable level. Games may be complex, but they usually follow well-defined rules, which can be incorporated in algorithms quite easily.

In contrast, medical processes such as endoscopic and surgical therapies are subject to all kinds of uncertainties and random interferences, which cannot be foreseen. Many features are required to appropriately model a medical phenomenon, increasing the dimensionality of a problem and the difficulty of accurately modeling the phenomenon itself. On the other hand, performing medical technical steps or recognized important medical findings by an AI-driven system does not allow failures, especially when a new method such as machine learning is involved [2].

In addition, one must be careful when describing medical phenomena and running into potential methodological pitfalls, such as overfitting of data. Overfitting describes a model that too closely fits the data on which it was trained, resulting in predictions that are very high but do not generalize well to outside datasets [2, 11]. The model may memorize the training dataset itself very closely, instead of modeling the phenomenon. As a consequence, in addition to testing performance of a model on a test dataset after running the original training data, it is important and advisable to have another independent dataset on which to validate model performance and assess its general usefulness. This is especially important in clinical applications in medicine.

37.3 Neural Networks and Deep Neural Networks

Neural networks are inspired by biological neural networks and structures. They process data in different layers of computational units that are intended to be analogous to neurons. In classical machine learning, variables are selected and hand-engineered by competent individuals to optimize the performance at a special task chosen for the project. In contrast, neural networks can extract variables from data and use them as inputs, adjusting the weights of those features accordingly to be used within an activation function to achieve some output [15]. Thus, the system automatically, using predetermined mathematical functions, finding and optimizing weights to strengthen or weaken connections within the network to gain optimal results.

Deep neural networks represent neural networks with more than three layers, which allows for learning more complex patterns. Neural networks with deep learning will select variables that have a high probability to achieve best results. This technique can handle unstructured data such as audio, images, and video [5]. Each layer of a deep neural network performs a set of operations to generate a representation of the data that is then fed feeds to the next layer. With each layer of the network, the representation of the data becomes more abstract though with increasing ability to distinguish different data classes [6].

37.4 Application of AI in Medicine

37.4.1 Natural Language Processing

Natural language processing is around since many years and has supported and replaced work processes in many ways. Those systems focus on machine understanding of human language beyond identification of vocabulary. Natural language processing provides machines the ability to approximate the understanding of human language as it would be used in day-to-day life. It strives to achieve understanding of syntax and semantics to approximate meaning from phrases, sentences, or paragraphs [16]. Basic analogous functions are seen in digital systems for operative dictation such as Nuance Dragon software (Nuance, Burlington, MA, USA). Currently, most popular are home assisting devices such as Amazon Alexa (Amazon, Seattle, WA).

Natural language processing is utilized commonly in the analysis and connection of data within electronic medical records, which an important issue in many countries. In these systems, management is needed to analyze segments of human language, unstructured free text such as radiology reports, progress reports, and operative notes. These can be structured and further processed in an automated manner. As examples, it can be utilized to assess for sentiment in patient notes for the prediction of patient health status, to analyze records for risk prediction in cancer patients, or to detect surgical-site infection based on some notes [17–19].

37.4.2 Computer Vision

Computer vision can be described as machine understanding of images and videos [2, 11]. Computer vision is part of AI and is also associated with signal processing, pattern recognition, and image processing. In this context, machine learning means integrating information from pixels, which make up an image, detecting objects within such an image, and potentially even engaging in analysis of open spaces within an image.

All these features can result in complex applications such as autonomous driving systems. In the latter, the computer is able to identify obstacles versus open roads, pedestrians, traffic lights, and other special road characteristics. For these systems, deep learning techniques are essential.

In medicine, the majority of progress applications of computer vision have come from radiology and pathology, probably due to the readily available, digital images in these subspecialties. Computer vision has also demonstrated advancement with screening applications in ophthalmology, such as through automated detection of

diabetic retinopathy. Furthermore, automated recognition of benign versus malignant skin lesions has been described [8]. Computer vision and deep learning have been applied to create a system to predict radiation and magnetic exposure to staff persons in computed tomography, fluoroscopy, and/or magnetic resonance imaging, which may be very important for the involved persons [9].

37.4.3 Special Application of AI in Surgery

With the increase in imaging and visual findings in medicine as well as more storage capacity of diagnostic and therapeutic procedures, the basis for big data collections is secured. This may lead to more surgeons choosing to record their operations for teaching, education, and research purposes.

This process will help establishing a large database of recorded visual material, which can be used for AI involvement [2, 11, 20–22]. AI, through computer vision, allows computers to comprehend visual cues and therefore interact with the world in real time [11, 20–22]. With sufficient training and incorporation of thousands of operations, an AI model could guide surgeons during an operation in real-time mode. AI will support and assist the surgeon since AI is based on input from thousands of operations just like a world expert in surgery giving advice based on a large experience. There is evidence based data that experience matters with an inverse relationship between a surgeon's case volume and their patient's mortality [23]. Studies have shown that the surgeon's ability on visual insights alone is even predictive of a surgeon's rate of complications [24].

It seems very much desirable to develop a system, which could guide surgeons (or endoscopists) and take their performance from a lower level to the top quartile. The patients would receive immediate improvement in their care. It is known in a substantial percentage of cases. It is known that a "near-miss" event may happen during procedures, which may even cause further interventions. A computer vision model could warn the endoscopist or surgeon in a critical moment and prevent "near-miss" events in the first place [25].

With the advent of minimal invasive surgery, it became much easier to record operations over the full length of the procedure. A few authors around the world have tried to tackle the problem of teaching a computer to see and think like an experienced surgeon using computer vision. These applications of computer vision are quite new [25, 26].

This initial work has focused on the analysis of laparoscopic cases, for example, select and identify phases with high accuracy during laparoscopic cholecystectomy (in 86.7%), sleeve gastrectomy (in 85.6%), and sigmoidectomy (in 91.9%) [27–29]. Additional applications have been investigated for its potential impact on improving operating room workflow and logistics by prediction of remaining operative time from intraoperative video [30]. In this context, accurate phase recognition within a given procedure is mandatory.

Furthermore, the next important steps could be development of intraoperative decision support. For example, applications include some guidance for port placement in the beginning of the operation and/or the confirmation or warning during the phase of the "Critical View of Safety in Cholecystectomy" [31]. A future vision could be real-time intraoperative "GPS" to guide surgeons during their dissection, especially during critical steps [2, 11].

A prerequisite of translating computer vision to the operating room is the establishment of clear labels for operative videos. Hashimoto et al. demonstrated that surgeons, even within the same institution, can differ in performing standardized uniform operative steps during a procedure [27]. As previously described, for supervised learning, defining a "gold standard" or ground truth is important to be able to train a model to recognize aspects of surgical video [20–22, 31]. This requires in establishing the "ground material" a certain discipline among the contributing surgeons to feed the learning process and model.

Another option is the usage of humanoid robots in preoperative patient counseling.

Fig. 37.1 A humanoid tablet-based robot used in preoperative patient counseling by a team at the University of Cologne, Germany

Different manufactures allow simple tablet-based machines that may include different AI-based software tools. The University of Cologne has started a pilot project with Mr.Pepper™ (Humanizing Technologies GmbH, Olpe, Germany) (Fig. 37.1).

Another application of AI in surgery could be preoperative risk prediction by learning from the analyses of patients clinical courses. Surgery is a controlled insult on the human physiology that is not without risks: 20% of surgeries have complications [28]. More accurate risk prediction would both guide patient-centered decisions to evaluate both operative candidacy and predict possible postoperative complications. Many risk calculators and decision algorithms exist on the market, but these systems are often insufficient [32–35]. Frequently, systems use cardiac parameters and events. Other risk calculators incorporate more than cardiac factors alone to predict risks for the patients. Most famously, the American Society of Anesthesiologists has created a classification system to predict risk [36]. Recently, the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) released a risk calculator. This model had good performance, with a c-statistic of 0.944 and 0.816 for mortality and morbidity, respectively [37]. With the advent of machine learning, new methods for better approximation of the nonlinearity of patient risk factors were applied. Three different methods on single-institution database of 100,000 patients were tested and showed better postoperative mortality and morbidity prediction for a sample of 75 patients [38].

Similar work has been done at the University of Florida with their MySurgeryRisk score [39]. The objective of this study was to develop an algorithm that could fulfill this role by being universally applicable for any type of surgery, while using all available data within any Electronic Health Record (EHR) platform, and by having the capacity for automation and implementation in real-time clinical workflow. A risk prediction was performed using "machine learning techniques" [39]. Interestingly, their risk prediction was particularly patient-tailored since they linked training data to census data tied to ZIP codes and to surgeon-specific outcomes. Beyond just the creation of a risk calculator, they also created interfaces for seamless EHR integration, so that not only risk prediction happened in real time,

but their models underwent continuous learning and tuning from physician feedback [39].

A group from the Massachusetts General Hospital created another risk prediction calculator called POTTER. They used the "machine learning technique" of Optimal Classification Trees trained on 7 years of ACS-NSQIP data, which they packaged in a smartphone application for ease of use and deployment [40]. Unlike the other previously discussed scores, they compared their technique to multiple scores, including the ASA and ACS-NSQIP with superior results [40]. With continuous integration of Electronic Medical Records and even deployment to smartphones, this amount of information is immediately available and creates the vision of the future that we may be able to more exactly determine the exact risk of the patient for a given procedure in a given situation.

The application of AI in gastrointestinal endoscopy is emerging quickly [41, 42]. An ideal field for help from AI is endoscopic detection of lesions. This issue is extremely important for the patients not to miss any lesion during routine prophylactic investigations such as screening colonoscopy [43, 44]. Enormous efforts are done to improve the accuracy of these investigations. The modification of colonoscopes can compensate only to a certain degree [45]. The integration of AI in the investigation shows very promising results in increasing the diagnostic yield, especially in incomplete colonoscopies [41, 46–48].

Similar experience has been made with the detection of lesions in other areas of the gastrointestinal tract such as hard-to-find gastric cancers [46]. It is important for the endoscopist and surgeons to understand that AI is not taking away the role of the involved physicians, but will help to improve their professional results [11].

In conclusion, artificial intelligence as applied to endoscopy and surgery is early in its development. While significant advances are being made in AI, these advances are focused on narrow applications of the technology to specific problems within endoscopy and surgery. This represents a new field, which still needs to be explored and tested and re-evaluated to establish these systems to achieve the results that look so promising in the future. As with any new technology, a healthy level of skepticism is necessary to guard against hype.

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