Chapter 1

Introductory Chapter: Endoscopy-Novel Techniques and Recent Advancements

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Additional information is available at the end of the chapter

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1. Introduction

Over the years, medicines and the way we approach the patient have evolved from the basic clinical situations and the way we interpret signs and symptoms to imaging technologies that help us provide a faster and more reliable diagnosis. Nonetheless, along with endoscopy appearance in daily practice, patient's survival rate and treatment have improved, and have gradually become the mainstream of current use by introducing screening programs as in colorectal cancer (CRC) [1]. Based on the perceived balance between the necessity and benefits of endoscopy, this technique has prompted its need to be kept in current practice and has become a benchmark for human organs or cavity exploration.

The use of endoscopy within the gastrointestinal tract has been embedded as a welcome development for both diagnosis and therapeutic paths [2]. Continuous research of available technologies has led to a groundbreaking promising foundation to explore new options for patient's condition [3].

A large array of therapeutic alternatives has positioned endoscopy as the cornerstone for most of the diseases of the gastrointestinal tract and gradually has become a technique that may obviate surgery in some situations. From basic tissue harvesting to real-time confocal microscopic assessment [4] or from palliative therapeutic armamentarium to procedures more close tied to surgery procedures, gastrointestinal endoscopy has become more and more popular and along with its advantages or challenges has penetrated the gastroenterology community, becoming the touchstone for this medical specialty [5].

Modern gastroenterology is based on the availability of endoscopy and its secondary features in assessing the gastrointestinal tract. Technological development is a continuous process

in our day-to-day life and has been gradually inserted into endoscopy advances along with high-resolution endoscopes, devices, or accessories. The fact that some organs could have only been accessed by surgical procedures has promoted endoscopy to a level worthy of further appraisal. Among the different steps in endoscopy, the ones that surely changed the way we tend to diagnose or treat patients in daily practice are endoscopic retrograde cholangiopancreatography [6], capsule endoscopy [7], and endoscopic ultrasound [8, 9]. Thus, a new window was opened for both patients and physicians, and allowed the concept of evidence-based medicine to be used in daily practice.

Perhaps the biggest efforts in endoscopy were to improve the diagnosis of gastrointestinal tumors [10]. With various methods which are certified for cancerous gastrointestinal lesions, endoscopy has also become a valuable asset for early-stage diagnosis [10] and is still exploring new therapeutic avenues. Endoscopy screening and treatment of pre-cancerous lesions is part of a growing trend and has been increasing exponentially in many specific lesions due to new technology embedment or transposing current surgical procedures. Thus, a shift has taken place and the use of endoscopic systems has allowed technology to become part of both the physician and patient's life.

2. Diagnostic novelties in gastrointestinal endoscopy

2.1. High-definition endoscopy imaging

Substantial innovations in endoscopy imaging have occurred in the last 30 years, allowing physicians to perform a more personalized therapy for patients. With an increasingly technology-driven field, the current focus is to use high-definition (HD) techniques in a platform that will eliminate all disadvantages and will enhance the gastroenterologist's ability to provide a better diagnosis or therapeutic management [11]. Endoscopy has taken an important leap from basic imaging to digital, high-definition white-light resolution which detects and highlights mucosal changes that were not perceived by the previous techniques.

The use of HD endoscopes and monitors allows substantial image improvements by producing fewer artifacts on rapid movement and when combined with the corresponding processors may reach an image quality of over 2 million pixels [12]. HD magnification endoscopes have the ability of enlarging the image up to 150× with an adjustable focus and to discriminate between lesion's characteristics from 10 to 71 microns in diameter [13, 14]. Topical application of agents such as acetic acid, methylene blue (chromoendoscopy), congo-red, or even hematoxylin has proven beneficial [15].

Narrow band imaging (NBI) was introduced for early detection of lesions. By using a narrow band filter for blue and green, it illuminates tissue at wavelengths absorbed by hemoglobin, showing microvascular patterns (**Figure 1A–E**). This allows better characterization of lesions, which appear darker than the surrounding tissue [16, 17]. A different solution uses algorithms based on mathematical estimations of pixels. This technique has the advantage of generating a large number of wavelength permutations with adjustable settings [18, 19]. The I-scan technology uses three algorithms which may be applied simultaneously or one at a time: surface enhancement, tone enhancement, or contrast enhancement [20, 21].

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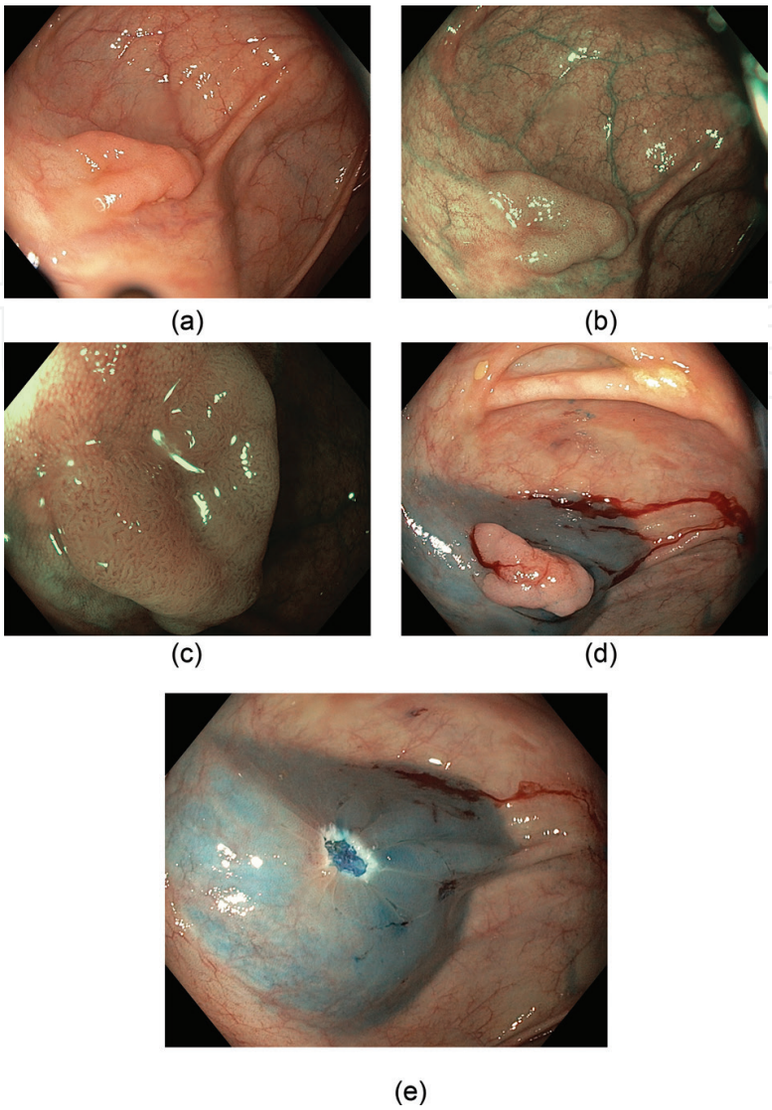

Figure 1. (A) HD endoscopy of a large colonic polyp; (B) NBI view for better characterization of the vessels; (C) HD endoscopy with NBI and magnification for pattern assessment; (D) submucosal injection of methylene blue and epinephrine 1/10,000 for elevation and enhancement in order to perform polipectomy (E).

2.2. Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is a cutting edge technique based on real-time image reconstruction on a subcellular level, in any endoluminal cavity by using flexible endoscopy [22]. The ability to see the microarchitecture in vivo in a non-invasive setting has opened up new windows of opportunity for a faster diagnosis. Thus, providing images of the mucosal layer will not only ensure a rapid assessment of the lesions, but will also have a role in choosing the right therapeutic management [23].

Based on a low-energy light source that enables acquisition of histology-like images, CLE usually requires the use of a dye for a better characterization of morphology or vascular pattern. The most used dye is fluorescein which has a safety profile, and has the ability of highlighting the vessels. However, the direction seems to be toward individualized situations whereas specific antibodies such as CD 31, CD105, and EGFR [24, 25] might be more useful for tissue

architecture description. CLE is considered a valuable tool with great potential that may overcome some of the disadvantages of classic histology such as time waiting or sampling bias, thus facilitating live diagnosis and treatment decisions. Also, its use might also lead to a lower number of biopsies, provide a real-time differential diagnosis in pancreatic tumors or access to the biliary tree, or even reduce the number of noncancerous lesions removed through endoscopic procedures [26, 27].

CLE is available either in an integrated conventional endoscope (Pentax, Tokyo, Japan) or on a probe-based system which is connected to a laser unit (Mauna Kea Technologies, Paris, France). Endoscope-based CLE (eCLE) systems (**Figure 2A, B**) are used for both upper and lower gastrointestinal tract examinations with depth scan images from 0 to 250 μm and scan rate of 1.6 frames/s. However, eCLE is no longer commercially available [28–30]. In contrast, probe-based CLE (pCLE) consists of different confocal miniprobes (Coloflex UHD, GastroFlex UHD, CholangioFlex) which provide images at different depths depending on its use, either for gastric, colonic, or biliary tract lesions. Moreover, a special probe was designed for an endoscopic ultrasound setting through a 19 gauge needle for a real-time assessment of pancreatic tumors. All miniprobes depending on their lesions' objective may be used for a maximum of 10 or 20 investigations.

Various applications have been tested for CLE from early gastric cancer [31], Barrett's esophagus [32], colonic polyps to inflammatory bowel disease (IBD) [33], and biliary strictures [34]. Many clinical settings have confirmed this technique as an evolutionary step and in synergy with histology have led to several atlases for pattern and morphology recognition. Surveillance CLE imaging after polyp resection or IBD therapeutic mucosal assessment has confirmed its success [35]. The advantages of CLE have been recognized by the Federal Drug Administration and it is currently used in some clinical settings and settled by insurance policies [36]. Thus, the field of endomicroscopy, a rather challenging one due to long learning curve and high costs, is on a continuous expansion with multiple methods being tested.

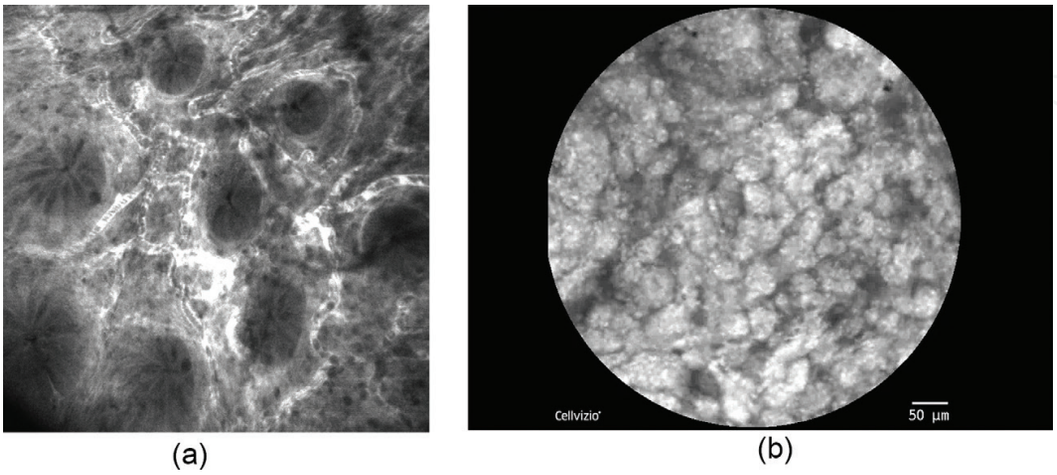

Figure 2. (A) CLE of normal colonic mucosa—the mucosal vessels as honeycomb appearance represented by a network of capillaries circumscribing the mucosal glands. Blood cells can be observed as dark shadows in the lumen; (B) pCLE image of an ex-vivo normal pancreas. Acriflavine staining which emphasize the acini distribution.

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2.3. Capsule endoscopy

Video capsule endoscopy (VCE) has revolutionized the way we explore bowel disease, and has become the reference method for small bowel imaging diagnosis. From its commercial release in 2001, VCE surfaced as the most challenging alternative for upper endoscopy or colonoscopy [37]. However, as it turned out, its full potential is directed toward the small bowel, which until then represented an area difficult to explore.

Over the years, as technology evolved, the optical lenses and image resolution have laid grounds for new improved VCE, now reaching an image resolution of 512 × 512 pixels [38]. Moreover, the use of a dedicated analysis software may enhance the picture quality and provide more details that might suggest a more accurate diagnosis. This facilitated the new ways to analyze patterns and lesions, decreasing inter-observer variability [39].

The main indications are obscure gastrointestinal bleedings, with current guidelines available on Crohn's disease initial diagnosis, suspected celiac disease, and hereditary polyposis syndromes [40–42] (**Figure 3A, B**). There are also some dedicated capsules for the esophagus directed to Barrett's esophagus, esophageal varices or gastroesophageal reflux disease, or the colon, successfully used for CRC screening or adenoma detection. Colon CE (CCE) has also proven its efficiency in unsuccessful colonoscopies, or when patients willingly refused to perform a colonoscopy [43].

The major setback in VCE is the lack of biopsies. This has welcomed the implementation of virtual chromoendoscopy, color enhancement, or flexible spectral imaging. Rigorous colon preparation is required, as movements, washing, or aspiration are not possible [44]. While movement is based on bowel peristalsis or segmentation, future directions focus on systems controlled by active locomotion. Several robotic forms of CE have been developed. External magnetic systems have also been studied, either with direct control by the physician or by using external platforms with a console or robotic arm in conjunction with MRI or CT [45, 46].

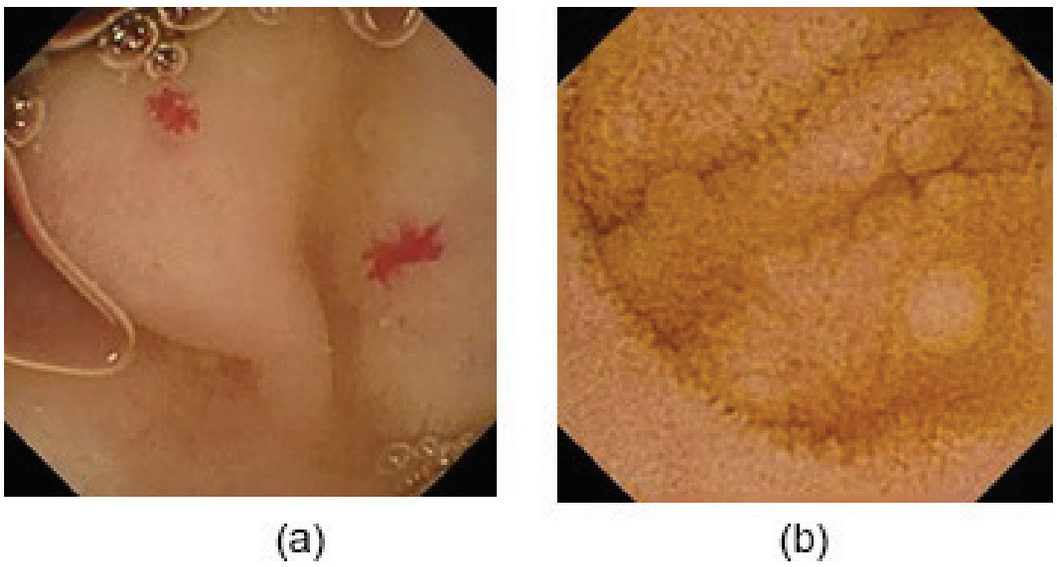

Figure 3. (A) VCE imaging of a telangiectasia and (B) an intestinal polyp.

The future of VCE is directed to remote-controlled tools for both diagnosis and therapy as in drug delivery systems. This will provide a non-invasive and easier management for the patient with potentially less side effects and stress than ordinary procedures.

3. Therapeutic endoscopy

3.1. Endoscopic retrograde cholangiopancreatography (ERCP)

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard method for therapeutic management of biliary disease [47]. Progresses have been met from stone extraction to biliary stenting for both malignant or benign stenosis and even ablation of biliary tumors. On this latter platform, the next step was set to the development of the peroral retrograde cholangioscopy, a technique that can provide direct images of bile and pancreatic duct [48–50]. A single operator device employed through the working channel of the duodenoscope has provided images that changed the way some diseases are managed [51]. It is mostly used for the differential diagnosis of biliary strictures; cholangioscopy decreases perforation and bleeding rates [51–55]. Spyglass digital system technology has stepped into the next generation of devices by providing high-resolution images with a field view of 110 and by eliminating degradation over excessive use [56]. With a friendly-user interface, this technique might solve the so far inaccessible path of biliary irresolute diagnosis (**Figure 4**).

3.2. Endoscopic ultrasound

Endoscopic ultrasound (EUS) development has opened up new horizons for diagnosis and management, especially in pancreatobiliary disease [57]. While on a continuous evolution process, EUS has been introduced as a standard diagnosis technique which provides information

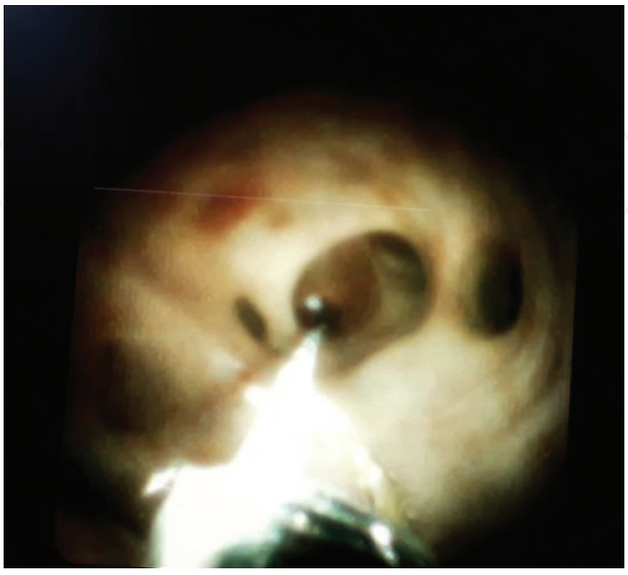

Figure 4. Spyglass endoscopy. Cholangioscopy image with biliary stenosis and dilatation of the biliary tract.

of structures located near the gastrointestinal tract. The arrival of fine-needle aspiration (FNA) has paved the way for various new therapeutic options that may substitute several surgical procedures or provide new options for cancer therapies [58]. EUS-drainage of fluid collections represented the grounds for novel techniques which focus on joining two cavities [59]. Along with the additional growth of the industry of endoscopy supplies, EUS has enabled novel therapeutic alternatives. Lumen-apposing metal stents are highlighting a fine line between the gastroenterology and surgical community [60] (**Figure 5A, B**). EUS-guided gallbladder drainage [61], EUS-choledochoduodenostomy [62], EUS-pancreaticogastrostomy [63], and the most recent EUS-gastrojejunostomy [64] represent some of the challenges that were introduced with focus on minimally invasive therapy.

Cancer-directed therapy has been the EUS objective with several alternatives so far. EUS-guided radiofrequency ablation has been successfully used in pancreatic tumors, along with alcohol injection. However, the most interesting technique seems to be injection of chemotherapeutic agents either directly within the tumor or within the venous system. This setting might provide a larger volume of drugs to the tumor and enhance their effect, while avoiding systemic reactions. Pain therapy has also been a matter of discussion especially in pancreatic cancer with the EUS-guided celiac plexus neurolysis and celiac plexus block after alcohol injection [65–67].

3.3. Submucosal endoscopy

Greater experience in flexible endoscopy and new devices development have gradually introduced the concept of therapeutic endoscopy from endoscopic mucosal resection (EMR) to endoscopic mucosal dissection (ESD) [68, 69]. Recently, the concept of endoscopic full thickness resection (EFTR) has gained attention trying to secure the possible complications [69]. Over-the-scope clips and new suturing endoscopic devices are instruments worthy of appraisal even though it gets us closer to natural orifice transluminal surgery (NOTES) [70]. Currently, peroral endoscopic myotomy (POEM) for the treatment of achalasia represents one of the most advanced NOTES technique performed in gastroenterology, which requires a high level of skill in performing submucosal tunneling, injection, and hemostasis. POEM has prevailed as a new reference method in achalasia treatment [71].

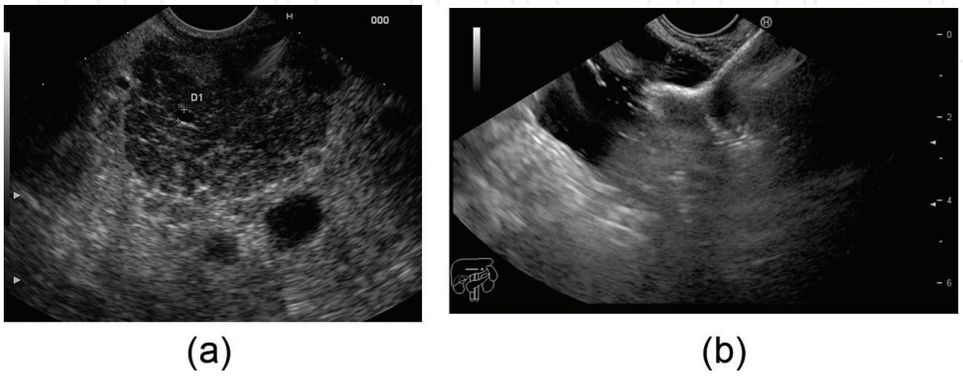

Figure 5. (A) EUS of the pancreas—inhomogeneous tumor with hyperechogenic foci localized at the level of the head of the pancreas; (B) balloon-assisted EUS-gastrojejunostomy in a pig with a hot metal lumen-apposing metal stent.

Conflict of interest

The authors have no conflicts of interest to declare.

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