Endoscopic Follow-up of Digestive Anastomosis

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Editor

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Preface

There are undoubtedly several books and atlases, available on the shelves of scientific bookstores, regarding digestive endoscopy and investigating both diagnostic and therapeutic techniques, and all those publications are surely very useful from a didactic and technical point of view.

What is, then, the rationale of this new text? My purpose in undertaking the editorship of this volume was to develop a monograph about a topic often treated in a superficial or even vague way.

The study of anastomosis is one of the most frequent indications in diagnostic digestive endoscopy, and the endoscopist is frequently asked to treat some complications of the surgical interventions, such as bleeding, benign strictures, neoplastic recurrences, and dehiscences, by the means of operative procedures. Moreover, the evaluation of a digestive anastomosis can represent a source of worries and anxiety, especially for the junior professionals, because they are confronted with the new anatomy modified by the surgeon.

In spite of this, in most cases, textbooks and atlases available for practitioners devote just a few pages or short paragraphs to the endoscopic follow-up of digestive anastomosis and to the endoscopic treatment of their complications.

Finally, beyond the technical aspects of the topic, it appears very important to clarify the logistic points of view of the problem: what is the appropriateness of the endoscopic follow-up, who should be put under surveillance, how and when to perform surveillance, has biopsy been performed, and what about the useful tools of endo-ultrasonography, chromoendoscopy, and magnification?

The main goal of this text is to present the knowledge about endoscopic follow-up of digestive anastomosis as much completely as possible, both illustrating diagnostic protocols and operative techniques, in the global perspective of a systematic and multidisciplinary monograph.

I would like to seize the opportunity to express my thankfulness to collaborators and colleagues. In the first place, my sincere thanks go to all the authors and contributors of the book: with their efforts they have been able to share and communicate their scientific knowledge and enthusiasm to all those who will read and study this volume. Secondly, my thanks to the Springer editorial team, who believed in this endeavor and followed it with professionalism. Finally, my thoughts go to the readers: we hope this volume will be a contribution to their professional growth and foster a comprehensive vision of digestive endoscopy.

Naples, Italy — Giuseppe Galloro

Contents

Part I

Diagnostic Procedures and Follow-Up

Analysis of Surgical Risk Factors in Tailoring Digestive Anastomosis

1

Mario Testini, Ilaria Fabiola Franco, Valentina Ferraro, Angela Gurrado, and Germana Lissidini

Failure of gastrointestinal anastomosis results in *leaks*, *fistulas* and dehiscence, still representing the major complication following abdominal surgery. Despite the improved perioperative assessment, the standardization of surgical technique, and the use of innovative devices, reported incidence of gastrointestinal anastomosis leakage ranges from 2 to 12 % [1–4], significantly increasing mortality (7–12 %), morbidity (20–30 %), and hospital resource utilization [5].

The anastomotic leakage rate is highly variable and strictly depending on the anastomotic site [6]: failure of esophagojejunostomy is a potentially catastrophic event, as a missed leakage of a colorectal anastomosis; on the contrary, gastroenteric or entero-enteric anastomosis leakage could be more often managed by a conservative approach. Therefore, anastomotic leakage represents one-third of overall mortality in colorectal surgery [6] and even more in esophagectomy and total gastrectomy [7–9].

The *risk factors* for anastomotic failure in digestive surgery (Table 1.1) can be divided into two groups:

(a) General
(b) Local also including factors related to surgical technique

Diabetes mellitus seems to have an important role on the anastomosis healing. Experimental studies demonstrated an increased anastomotic leakage in untreated diabetic rats vs diabetic one

Table 1.1 Risk factors of anastomotic leakage

General	Local
Age	Bowel preparation
Sex	Surgical technique
Diabetes mellitus	Mechanical or manual anastomosis
Nutritional state	Emergency surgery
Blood transfusion	Surgical skills
Uremia	Comorbidity
Anemia	Peritonitis
Preoperative radiotherapy	Bowel obstruction
Chemotherapy	Antibiotic therapy prophylaxis
Chronic obstructive pulmonary disease	Operative time
Cardiopathy	Protective ileostomy
Hypotension	Use of drain
Weight loss	High tension at anastomosis level
Obesity	Vascularization
Coagulopathy	Anastomosis site and number
Smoke	Positive surgical margins after resection (Flogosis, necrosis, neoplasia)
Corticosteroid therapy	
Metastatic disease	
Fluid and electrolyte disorders	

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treated by insulin therapy. Obesity, anemia, hypotension, uremia, coagulopathy, age, and male sex are also reported in some experiences [1–5, 8]. Otherwise, a prolonged nonsteroidal anti-inflammatory drugs (NSAIDs) use yields a higher risk of anastomotic breakdown. NSAIDs result in an increased rate of anastomotic leakage after colorectal surgery during the postoperative treatment too; consequently, cyclooxygenase-2 selective NSAIDs should be used with caution after colorectal resections with primary anastomosis [10, 11]. Moreover, some authors [12, 13] consider intraoperative blood loss of 200 mL or more, blood transfusions (more than 2 U/24 h), and low albumin serum level (inferior than 3.0 g/L) as significant factors. Conversely, chronic hypovolemia and weight loss don't seem to be significant factors, while vascular disease, advanced tumor stage, radiotherapy (Figs. 1.1 and 1.2), and chemotherapy are associated with increased anastomotic leakage. However, localized and generalized leaks also have a significant negative impact on overall, cancer-related, and disease-free survival [1–8, 12–14].

Among the local factors, compelling evidence exists that intestinal bacteria play a predominant role in the pathogenesis of anastomotic leakage [15]. Moreover, some authors consider bowel obstruction (Fig. 1.3), while others don't confirm its relevance [13]. Sepsis appears to be associated with anastomosis leakage, also enhancing the collagenolytic effects of the collagenosis [16]. We believe that sepsis still represents an absolute contraindication to a single-stage anastomosis during emergency colorectal surgery, above all in the presence of endoabdominal multiple abscesses and collections. In these pathological evidences (Fig. 1.4), a prudent behavior is mandatory, with the performance of a *Hartmann* procedure. The leakage rate appears significantly higher in patients undergoing to emergency surgery than elective one [12, 17] (38.1 % vs 13.3 % in *Kim* experience [18], 13 % vs 3.9 % in our [13]). Moreover, a full bowel preparation allows greater intraoperative cleaning, reducing fecal contamination, even if *Harris* [19] suggests elective colon resection performed safely without preoperative mechanical bowel preparation.

The decrease of *mortality* and *morbidity* due to anastomotic leaks can be also gained by performing intraoperative pneumatic test, defunctioning ileostomy, and drain tube insertion, as reported by *Boccola* [14, 20].

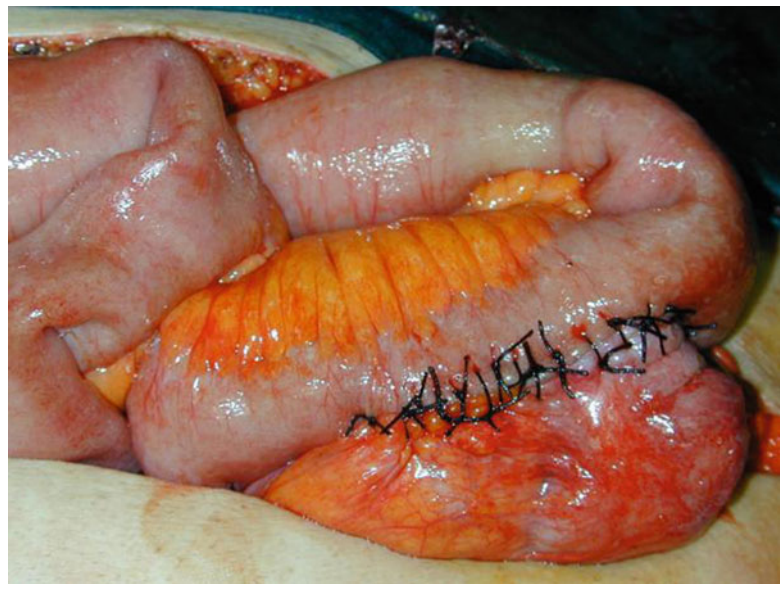

Fig. 1.1 Small bowel side-to-side anastomosis in a patient affected by volvulus following radiation enteritis

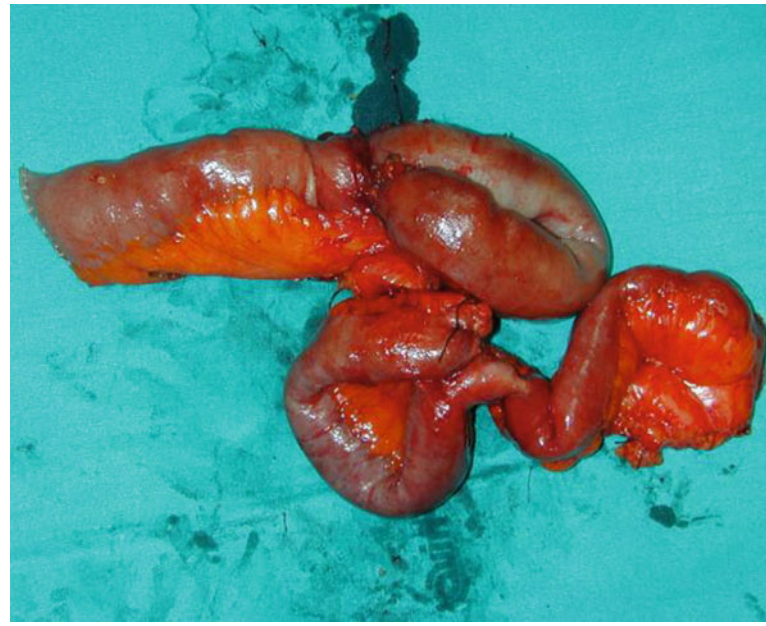

Fig. 1.2 Small bowel volvulus caused by radiation enteritis

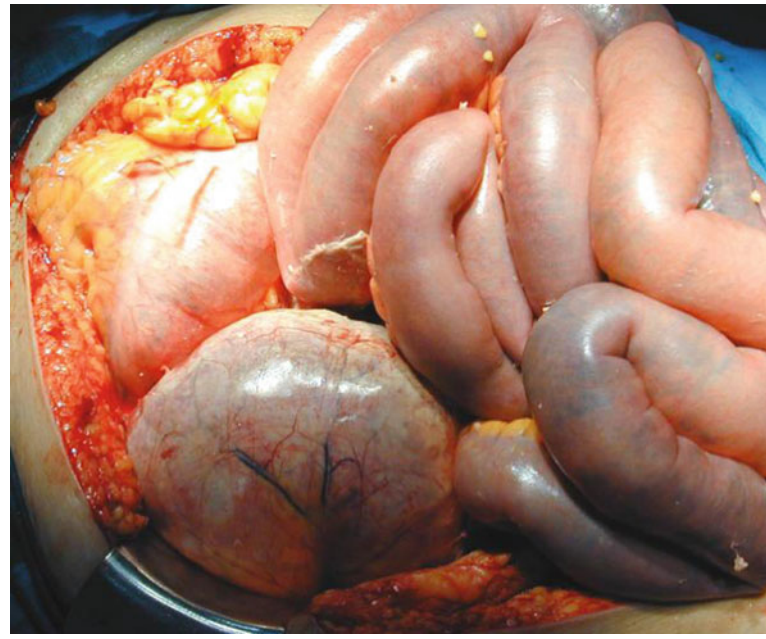

Fig. 1.3 Mechanical bowel obstruction with cecum diastase due to stenosis by carcinoma of the rectum

The choice of anastomosis remains at the discretion of the surgeon, largely depending on experience, patient's characteristics, and operative setting, even if there isn't a clear evidence for one technique over another [20]. Stapled anastomoses is associated with a significant lower leak rate regardless of anastomotic location [21], even if, as recently surprisingly reported by *Korolija* [21], anastomotic failures can be more than twice with stapled than hand sewn in the emergency general surgery.

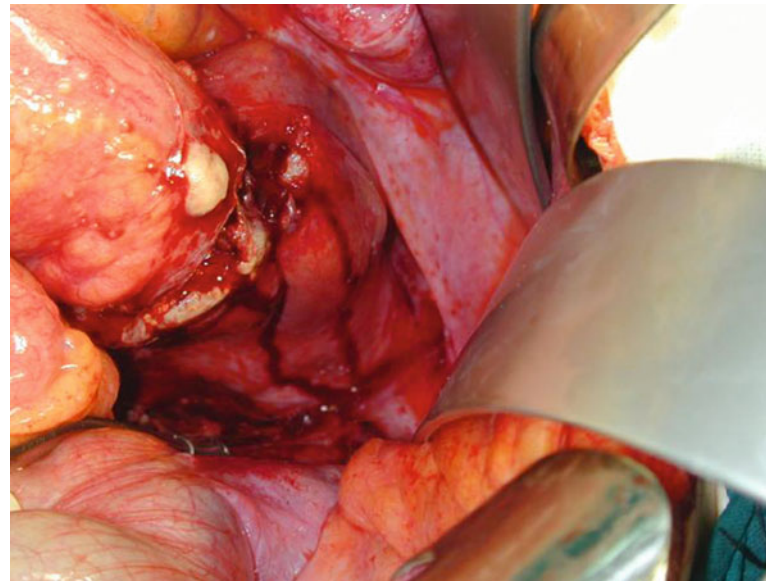

Fig. 1.4 Pelvic abscess from perforated carcinoma of the rectum

The anastomosis site represents one of the main problems in the digestive surgery. In fact, low colorectal [12, 14] as well as esophagus–jejunal [8, 9] anastomoses are associated with a higher incidence of failure. In this regard, *Montesani* reported re-peritonealizing and technical changes in the mechanical suture as useful in order to reduce failures following low anterior resection [22]. No differences in anastomotic colorectal leak are reported between laparoscopic and open surgery [23], even if a lower incidence in the laparoscopic one is reported in a recent review (3.0–17 % vs 0–23.0 %) [24]. The use of a protective stoma is controversial, with widespread use in some experience and markedly reduced or abolished in other [25]. In our opinion, according to *Hansen* [25], we justify the use of a protective ileostomy or colostomy only in situations with a high risk of failure as low colorectal anastomosis, difficult pelvic dissection, and risk patients. However, it is important to consider also the morbidity related to re-surgery and to the stoma management. Therefore, we believe that when an anastomotic failure appears, a late opening of a ghost-ileostomy could be not useful. A tension at the level of anastomosis resulting from an incomplete mobilization, an insufficient blood supply, and the absence of margins' integrity for necrosis, inflammatory disease, or cancer are univoquely accepted as high-risk local factors [1]. For these reasons a proper mobilization of the splenic flexure is essential to prevent the stretching on the anastomosis in left colon *resective surgery* [12]; otherwise, the low percentage of splenectomies of necessity reported in the literature does not justify different behaviors. Instead, the kind of disease does not seem to constitute a risk element [22] but a higher incidence of tumor recurrence resulting from the onset of dehiscence is reported in literature [14]. In univariate analysis [8], the patient age, the pulmonary insufficiency, the lymph node dissection, the combined resection of other organs, the omental resection, the operative time, the blood loss, the intraoperative blood transfusion, and the postoperative creatinine level were reported as significant factors influencing anastomotic healing. Also, a multivariate analysis [1] identified *pulmonary insufficiency* and duration of operation as predictors of anastomotic leakage.

Assembling the general and loco-regional with technical factors, we still agree with the multivariate analysis of *Golub* [3] that selected five statistically significant predictive parameters: chronic obstructive pulmonary disease (COPD), bowel obstruction, peritonitis, corticosteroids use, blood transfusion >2 U, and serum albumin level <3.0 g/L. Furthermore, a supplemental 80 %

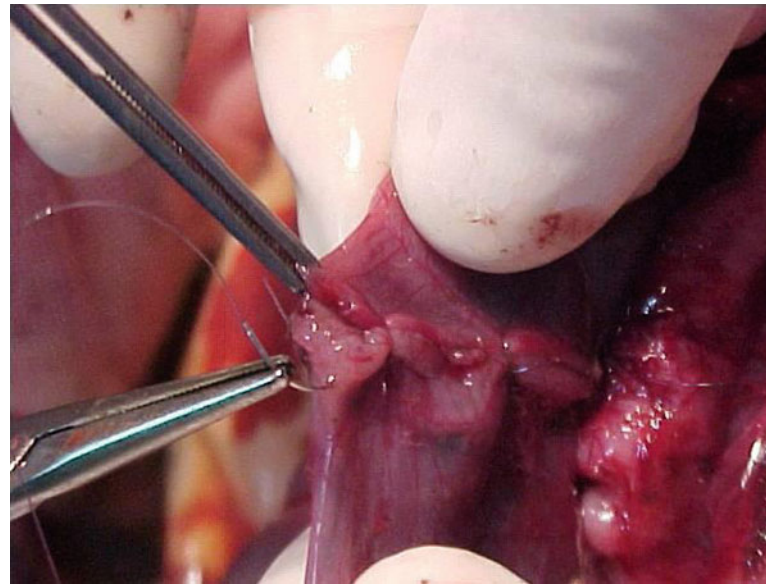

Fig. 1.5 Experimental study: small bowel anastomosis in the rabbit

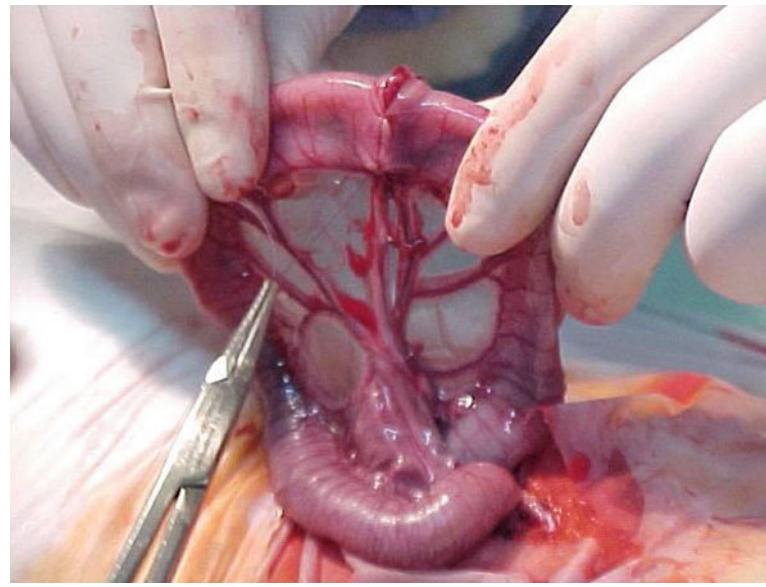

Fig. 1.6 Experimental study: colo-colic anastomosis in the rabbit

FiO2 during the rectal cancer surgery and immediate postoperative period reduces anastomotic failure [26].

Despite of the importance of general, local, or technical factors, at the base of the anastomosis failure could be an "innermost" *primum movens*, to look for both at the pathophysiological and biochemical levels. In fact, it is not otherwise possible to explain leakage in anastomoses performed under optimal conditions of elective surgery, using perfect technique, in patients without general risk factors.

Starting from this *rationale*, and from the higher leak rate in large than in small bowel anastomoses, we performed experimental studies comparing resected and anastomosed segments of small and large bowel (Figs. 1.5 and 1.6) using biochemical and tensiometric methods [27–29].

Previous experimental studies showed an early and massive deposition of collagen and a greater distress of the large compared with the small bowel. It is also well known the importance of the maturation of collagen in the anastomosis *healing process* and that an adequate *metabolic energy* is needed to realize healing process. Starting from these assumptions, our first study [27] was to analyze the process of oxidative phosphorylation (mitochondrial function) in colon and small bowel during the anastomotic process. The results of polarographic, spectrophotometric, and gel-electrophoresis analysis showed a prevalence of oxidative metabolism in the colic mitochondria compared with the small bowel, demonstrated by an increased activity of oxygen consumption and enzymatic respiratory. On the contrary, the small bowel showed a prevalence of glycolytic metabolism. Summarizing these results, the small bowel burns sugars through anaerobic glycolysis to produce energy for collagen deposition and healing process of anastomosis, and therefore is less influenced by the decrease of available oxygen occurring in the anastomotic area during surgical stress. By contrast, colon shows a metabolism mainly linked to the oxidative phosphorylation, presents a more difficult anastomotic healing process in absence of oxygen, and shows a greater risk of leak. This observation is confirmed by the decrement of biochemical parameters in colonic cells. In fact, at the end of the study, we observed a small bowel tissue biochemically identical to the preoperative one, while the colon tissue showed marked differences.

In the second phase of our experiments [29], we investigated if *biochemical differences* were also associated with motility and peristalsis. In fact, the aim was to verify in vitro how much the surgical stress could affect contractility of the smooth muscle (both spontaneous and agonist induced) of both organs, correlating these results to the biochemical parameters too. The results showed an anarchist contractility and late restart of colic peristalsis compared with an early and regular contractile activity of the small bowel. Such motor abnormalities may be the consequence of abnormal biochemical changes, because the ATP is necessary in the maintenance of membrane potentials, in calcium homeostasis, and in the actin–myosin interactions. The study showed that surgical stress determines abnormalities in the mitochondria of the smooth muscle, damaging the contractility. In consequence of a difficult process of collagen maturation and deposition, these changes are prevalent in the colon and may explain unexpected anastomotic leakage in the absence of apparent risk factors.

At confirm of these experimental results, an other retrospective study [30] showed a significant leakage rate (24.1 % vs 2.7 %, $P=0.001$) in patients who underwent colic resection, affected by COPD compared with patients not affected by COPD. COPD is characterized by a condition of chronic hypoxemia that determines a reduced peripheral oxygen delivery (DaO2). However, the mechanism of control of blood flow and of oxygen extraction at intestinal level let the consumption of oxygen (VO2) to be independent from DaO2; thus, the reduced DaO2 does not influence the VO2 in patients with COPD. On the contrary, during the healing process of colic anastomosis, the need of oxygen increases, both for higher metabolic request related to the oxidative phosphorylation and for the synthesis of collagen. In patients with COPD undergoing to resective surgery and colic anastomosis, these pathophysiologic changes inevitably relate the VO2 to the insufficient DaO2. Therefore, the correction of impaired oxygen tension could reduce the high incidence of anastomotic leak in patients with COPD. On the basis of these results, a preoperative evaluation of respiratory tract (chest X-ray, CT, spirometric tests, hemogasanalysis) is essential before colic resective surgery, especially in aged patients affected by COPD. Moreover, a perioperative oxygen therapy also may facilitate anastomotic healing.

In a further *experimental study* [31] we investigated in pigs if *pericardium bovine patch* (Tutomesh®) wrapping ileoileal and colo-colic anastomosis seals the suture line and promotes anastomotic healing. By using integrated and translational methodologies, we described intraoperative, histological, biochemical, tensiometric, and

electrophysiological evaluations performed on intestinal specimens.

Biologic materials have been introduced in general surgery as reinforcement of abdominal wall hernia in contaminated or potentially contaminated settings, when the use of alloplastic meshes is contraindicated [26–31]. In this respect, an innovative application of biologic patch could be their use as reinforcement of the gastrointestinal anastomotic suture line [7–9]. Therefore, the aim of the study was to verify if bovine pericardium patch improved the healing of anastomosis, when in vivo affixed on the hand-sewn suture line of large and small bowel anastomosis of the pigs.

A further end point was to verify if the patch was able to avoid anastomotic leakage in the presence of a deliberately incomplete left suture.

The results showed that the application of a patch wrapping the colic anastomosis produces a positive effect in the healing compared with untreated samples also showing, during follow-up, an almost full recovery [1–3, 26]. In the large bowel patch anastomosis group, the delay of oxidative stress in the early stage of reparative processes could prevent the damage of noble cells (like tissue stem cells), allowing a full restoration of tissue functions and also decreasing fibrotic reaction during the next stages of healing process. Under a condition of cellular oxidative stress, the protective effect of the patch is compatible with the histological observation of a moderate inflammatory infiltrate; moreover, the late increase of reacting oxygen species can be correlated with an appearance of a granulation tissue, without damages during the repairing process. Therefore, tensiometric evaluations in colic specimens suggested that the use of patch can preserve smooth muscle response to acetylcholine similar to the response of controls (specimens without anastomosis) in the early postoperative time (48 h–14 days), while the colic preparations with traditional anastomosis showed contractility alterations. In the ileum, the presence of pericardium bovine patch clearly prevents the alterations following the traumatic effect of surgery. However, pericardium bovine patch appears to modulate and counteract the traumatic effect of surgery. Overall, our results suggest that the application of the patch also improves the intestinal mucosal function, restoring the almost normal transport properties. In conclusion, the use of the pericardium bovine patch as *reinforcement* of the intestinal anastomosis could be safe and effective. Moreover, the leakage prevention in the presence of iatrogenic perforation is also unpublished before and it represents a surprising histopathological data. On the basis of these experimental results, we started a multicenter-controlled clinical trial in humans, comparing the outcomes of intestinal anastomosis performed with and without the bovine pericardium patch in risk patients.

In conclusion, despite studies regarding risk factors and prevention, the anastomotic leakage continues to be the most serious *complication* after *gastrointestinal tract surgery*. A thorough surgical technique, avoiding hazardous anastomoses without protective stoma, or without two-stage surgery in patients at risk, could allow a significant reduction of healing process failure. A tailored surgical approach to both patient's physiology and disease is the most important factor that influences anastomotic integrity after resective surgery. Further studies regarding innovative devices able to improve the healing process of anastomosis are needed.

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2 Impact of Flexible Endoscopy in the Evaluation of Digestive Anastomosis

Antonello Trecca, Raffaele Manta, Amitabh Naik, Mario De Bellis, Alberto Arezzo, and Giuseppe Galloro

2.1 Introduction

Flexible endoscopy plays a fundamental role in the clinical monitoring of surgical digestive anastomosis [1]. Careful endoscopic exploration is essential for the recognition of the linked intestinal segments and for the description of the type of anastomosis (end to end, end to side, side to side), providing both an accurate evaluation of the new digestive anatomy and the early detection of any postsurgical complications or recurrence. Close monitoring of the surgically treated disease, both neoplastic and nonneoplastic, can be realized by an accurate and scheduled follow-up which should consider all the imaging modalities available nowadays in clinical practice, such as radiology and endoscopic ultrasonography. A functional evaluation of the reconstructed segment can be provided by an accurate endoscopic technique aimed at observing caliber, patency, motility, response to the air insufflation, and flexibility of the anastomosis. On the other hand, prompt detection of any pathologic pattern of the anastomosis (stenosis, dehiscence, fistula, recurrence) is the key factor for the choice of any further and appropriate treatment. Our chapter is aimed at defining the key factors of an accurate endoscopic evaluation of surgical anastomosis and at discussing the clinical criteria for an accurate follow-up.

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2.2 Endoscopic Evaluation

An accurate endoscopic technique is the first step in order to describe the morphology of the new intestinal tract. Bowel preparation of the patient is one of the key factors, as the intestinal damage during surgery can induce a reduction of bowel segmentation and movement. Tailored preparation should be sought after, in order to reduce the missing rate of recurrence and to avoid any further reevaluation of the patient [2]. Administration of a cholinergic blocking agent or glucagon to reduce spasms can be of added value in close observing the intestinal mucosa.

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Some authors underline possible side effects and suggest the intracolonic administration of peppermint oil during colonoscopy for the control of colonic spasms. Asao [3] refers on a satisfactory spasmolytic effect in 88.5 % of the patients treated with a mixed solution of peppermint oil, water, and indigo carmine by using a hand pump attached to the accessory channel of the colonoscope, with a continuing effect of at least 20 min. Endoscopic observation should consider the useful role of the air in the evaluation of intestinal lumen with its adequate introduction and aspiration during the exploration of the anastomosis. Injection of a saline solution directly or using an irrigation pump through the accessory channel of the endoscope is another tool in the hand of the endoscopist to improve the quality of gastrointestinal exploration. Flexible endoscopy should always evaluate the caliber of the intestinal lumen which can be measured by using an opened biopsy forcep and the main longitudinal axis of the new reconstructed intestinal tract (Fig. 2.1). The description of the type and morphology of the surgical anastomosis should always be provided in the endoscopic report. After a complete evaluation of the functional status of the anastomotic site, including its patency and motility, flexible endoscopy should be prolonged to the evaluation of the proximal and distal parts and to all the reconstructed segments in order not to miss any morphologic change of the intestinal tract. The presence of metallic clips or suture stitches along the border of the anastomosis are often visible during upper and lower endoscopy as far as the presence of connecting venules, which reflects the healing process of the mucosa and rarely can cause impairment of the anastomosis. After an accurate cleaning of the intestinal lumen, the surgical anastomosis should be accurately checked for any mucosal defect such as discolorations, atrophic changes, and nodular irregularities which can be the expression of a redundant mucosal response or can mimic the presence of an endoluminal recurrence (Figs. 2.2 and 2.3). In this scenario the role of histology is mandatory to complete the endoscopic

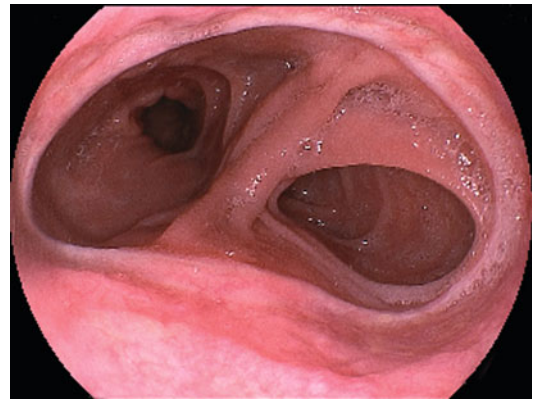

Fig. 2.1 Esophago-digiunal anastomosis after total gastrectomy: normal endoscopic findings

evaluation of the anastomosis and to detect any inflammatory or neoplastic change. We have to consider that any surgical intervention creates a new and different environment, and it should be taken into account when we study upper or lower gastrointestinal tract. So far the gastric remnant has been considered at higher risk for gastric cancer with an increasing postoperative interval, with a well-established clinical entity after remote surgery for peptic ulcer, called gastric stump carcinoma [4]. Many factors are involved in the pathogenesis such as achlorhydria, hypergastrinemia, biliary reflux, Epstein–Barr virus, atrophic gastritis, and also some polymorphisms in interleukin-1β and maybe cyclooxygenase-2. The microscopy of the anastomosis changes from the chronic active *H. pylori* gastritis into the typical reflux gastritis with foveolar hyperplasia, congestion, paucity of inflammatory infiltrate, reactive epithelial change, and smooth muscle fiber proliferation which slowly evolve to preneoplastic conditions, particularly dysplasia. Endoscopic surveillance is mandatory particularly in this clinical condition where the detection of premalignant or early neoplastic lesions is more frequent [5]. Concerning the lower tract, ileal-pouch anastomosis after proctocolectomy represents another example of how the modified clinical environment can lead to a new disease condition, named as pouchitis and

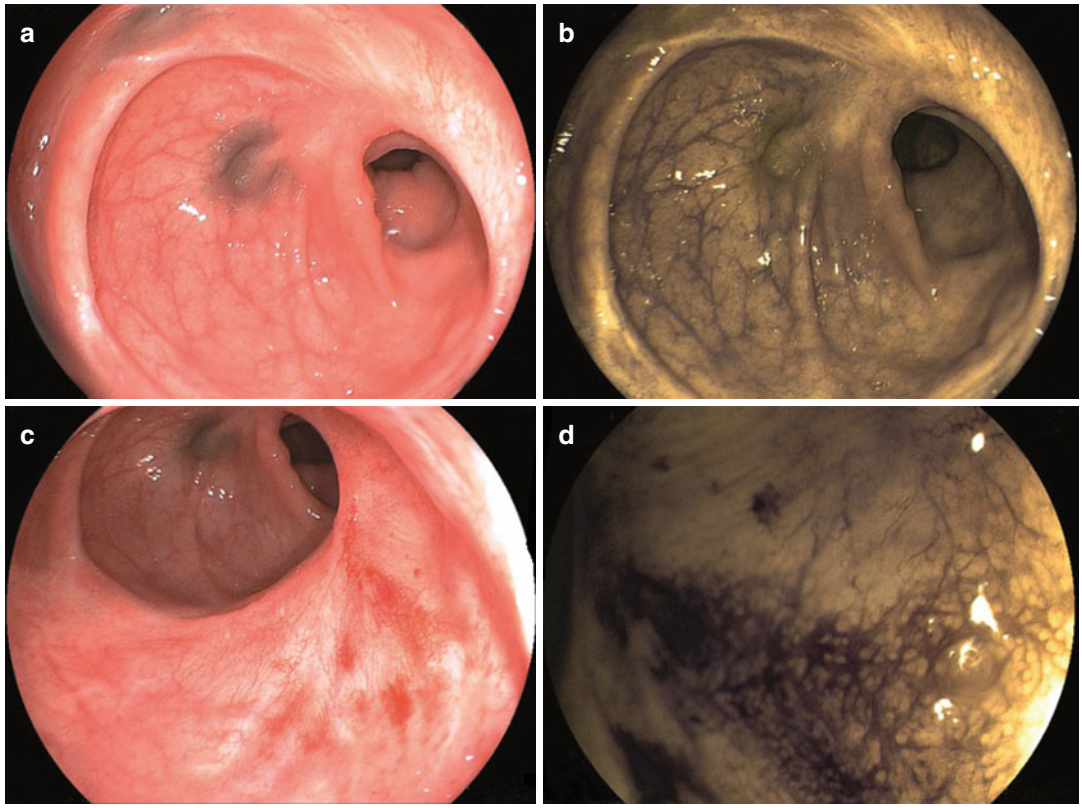

Fig. 2.2 Lower colonic anastomosis with a small reduction in caliber (**a**). Electronic chromoendoscopy (FICE-system evaluation) with negative findings (**b**). Slight hyperemia is visible at the edge of the anastomosis (**c**). Electronic chromoendoscopy confirmed negative findings (**d**)

characterized by a nonspecific inflammation of the ileal reservoir. Bacterial overgrowth, chronic inflammation, and villous atrophy, even if always present, can evolve in pouchitis in some cases, mainly after surgery for ulcerative colitis, and for this reason pouchitis is considered an inflammatory bowel disease. Lower endoscopy, together with an accurate histopathological evaluation, is mandatory for studying and monitoring this condition [6].

A significant reduction of the intestinal lumen, even if asymptomatic, should be described and monitored, while in case of intestinal stenosis, fistula, or dehiscence, other imaging modalities together with prompt treatment should be scheduled and selected among the different options (endoscopic dilation, stent placement, or surgical reconstruction) (Fig. 2.4).

2.3 Oncological Criteria of Follow-Up

Endoscopists should keep in mind clinical criteria for an accurate follow-up of the patient: synchronous cancer is defined as a cancer detected within 1 year of follow-up, while metachronous cancer is that one detected after 1 year of follow-up, while concomitant cancers are defined as multiple cancers detected before the surgical treatment. In this setting, we define the miss rate as the proportion of missed cancer out of all

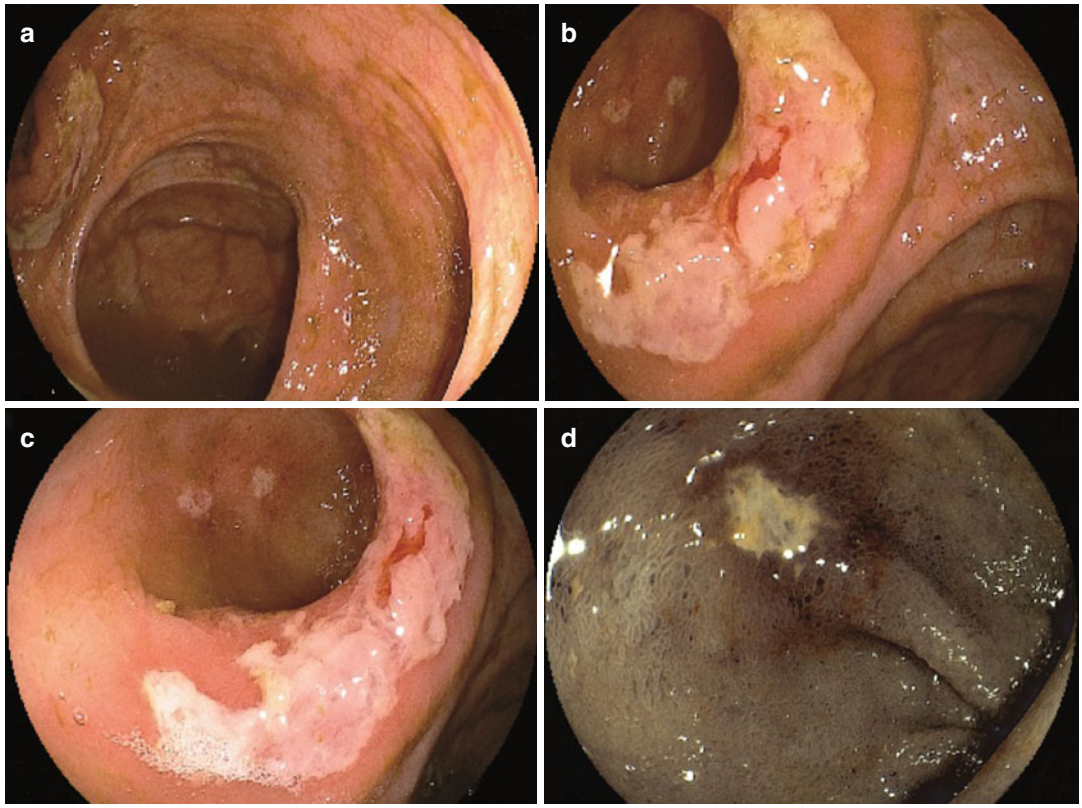

Fig. 2.3 Ileocolonic (side-to-side) anastomosis after *right* hemicolectomy (**a**). Whitish discoloration involving half of the anastomotic border (**b**). Conventional close-up view with evidence of superficial erosions of the ileal mucosa (**c**). Electronic chromoendoscopy (FICE system) of the ileal erosions with negative histologic findings (**d**)

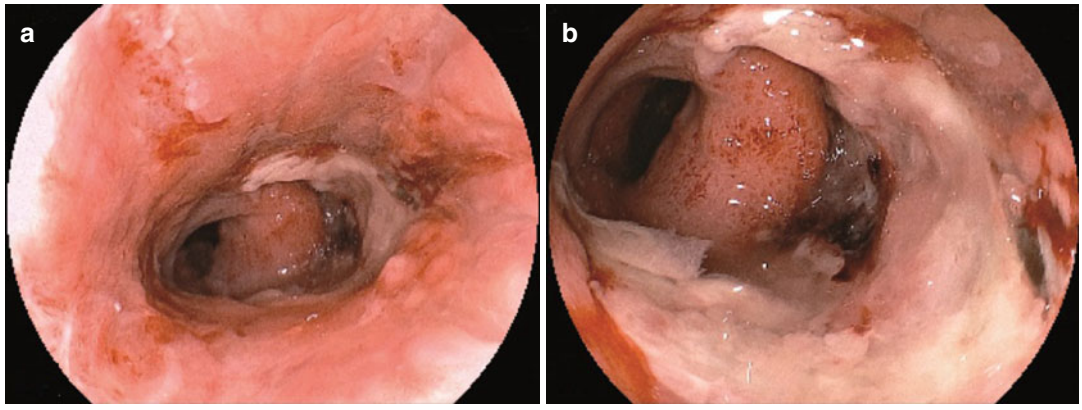

Fig. 2.4 Coloanal anastomosis with dehiscence and large amount of fibrin deposit (**a**). Close-up view with evidence of anastomotic leakage and necrotic area (**b**)

synchronous cancer [7]. These parameters have been introduced in order to better define the oncological criteria of the endoscopic follow-up. Timing of the first endoscopic evaluation has been questioned as a risky procedure particularly when dealing with difficult anastomosis such as esophageal ones. Maish [8] reports as early endoscopy after esophagectomy provided reliable identification of graft ischemia in 63 over 102 patients of his series. Upper flexible endoscopy performed a median of 9 days after operation was safe and with no anastomotic injuries. In another UK series [9] esophagoscopy was attempted within 1 week of esophagectomy in order to check the anastomosis and the reconstructed stomach of 79 consecutive patients. A total of 15 patients with gastric ischemia, two with a leak, and four with ischemia and leakage were detected, thus confirming endoscopy as a safe and accurate procedure. Intraoperative endoscopic diagnosis has been questioned to evaluate circular-stapled colorectal anastomosis during laparoscopic surgery and as a possible resource to prevent bleeding and possible leakage [10]. The patients with and without routine intraoperative endoscopic assessment were compared regarding postoperative complications, and even if the postoperative rate of bleeding and leakage was not significantly reduced, intraoperative endoscopy was accurate in the early detection and treatment of these complications. The implementation of new imaging modalities such as dye-spraying technique, virtual chromoendoscopy, and high-resolution endoscopy not only in eastern countries increases the early detection of neoplastic disease. These techniques made a much accurate diagnosis of neoplastic disease possible even in the endoscopic follow-up of surgically treated patients, so far improving the early detection of neoplastic recurrence. Endoscopic surveillance with chromoendoscopy in a Japanese series of 97 colectomized with ileorectal anastomosis ulcerative colitis showed definite dysplasia in four patients, who received IRA; among them two were adenocarcinoma with submucosal invasion [11, 12]. Postoperative surveillance endoscopy performed by an experienced endoscopist and with dye-spraying technique was useful to detect cancer at an early stage.

Conclusions

Flexible endoscopy is of pivotal importance in the evaluation of surgical anastomosis, in the definition of early recurrence, and in the diagnosis and treatment of complications. Clinical follow-up of treated patients should be implemented together with other imaging modalities, even if early postoperative endoscopic evaluation can be scheduled in selected cases without anastomotic injuries and with no further risk for the patient. Accurate endoscopic technique is mandatory for early recognition of the reconstructed anatomy and to detect any anastomotic defect, while endoscopist should consider the primary disease responsible for surgery, the timing of the endoscopic surveillance, and the role of other imaging modalities. Diagnostic accuracy of conventional endoscopy can be improved by new emerging modalities such as chromoendoscopy and enhanced endoscopy, even if these results should be confirmed in larger series.

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3 Methodology and Appropriateness of Follow-Up in Digestive Endoscopy

Gianluca Rotondano, Stefano Sansone, and Claudia Cesaro

3.1 General Criteria

Endoscopic follow-up is defined as the performance of endoscopic examination(s) subsequent to an *index* endoscopy aimed at both:

(a) Monitoring neoplastic or pre-neoplastic conditions or patients at increased risk (more properly termed "surveillance")
(b) Monitoring the therapeutic response to a determinate treatment (be it pharmacological, endoscopic, or surgical)

The end point of any endoscopic follow-up is that of reducing morbidity and mortality associated with or deriving from the pathologic condition that is under specific surveillance.

Examples of surveillance of pre-neoplastic conditions are Barrett's metaplasia of esophagus, inflammatory bowel diseases, colorectal adenomas, and polyposis syndromes. Another type of follow-up is the surveillance of patients submitted to surgery for a malignant disease, where the patient undergoes scheduled periodical postoperative examinations aimed at early identification of any recurrence of the primary cancer.

Among the endoscopic controls to assess the outcome of a treatment are the healing of gastroduodenal ulcers or erosive reflux esophagitis, the mucosal healing in patients with ulcerative colitis or Crohn's disease, a second look after endoscopic hemostasis of bleeding peptic ulcers, the eradication of esophageal varices, the histological control of gastritis or of the eradication of *H. pylori*, etc.

As a general rule, the rationale for any follow-up in digestive endoscopy raises from the epidemiologic evidence of its necessity and clinical benefit: the disease under surveillance should, in fact, be epidemiologically relevant (it would be illogical to monitor patients to identify a rare disease) and its detection and subsequent early treatment should entail a prognostic gain or advantage for the patient as compared to the treatment of the same condition identified when symptomatic.

The sticky issue of endoscopic follow-up would inevitably lead us to face up with two awkward truths that are overuse of surveillance and poor quality of surveillance. In fact, not only do we perform too much surveillance, with inevitable working overloads for our endoscopy services, but the quality of surveillance is often poor. This last condition can be due to conceptual deficiency (inconsistent evidence of clinical utility of the follow-up or inadequate knowledge of guidelines) or sometimes due to professional and/or supply shortage (technical competency not homogenous between different operators, equipment not always adequate for the specific needs of surveillance of specific conditions).

In general, the appropriateness is the quality of being just right for the requirements. In clinical medicine, it means that a test or an intervention is adequate and pertinent, i.e., suitable for a

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Table. 3.1 Domains of the appropriateness

Clinical appropriateness	Organizational appropriateness
Benefits overcome risks	Provide procedures really useful individually
Endoscopic follow-up	
Appropriateness = why and who	
Methodology = when and how	

particular subject and performed for a correct indication in a given moment with the aim of producing health without wasting resources.

Appropriateness has two inherent domains: clinical and organizational. Clinical appropriateness means that the expected benefits overcome any possible risks (or negative outcomes), while organizational appropriateness indicates the ability of a determinate health facility to provide medical procedures that are really useful to the individual cases treated. The key concept is therefore that any diagnostic and therapeutic procedure should be offered or required ONLY IF this alters the clinical management of the patient.

The appropriateness of any endoscopic follow-up is related to two essential aspects, which are as follows: why perform the examination and who should be surveilled. Besides, when and how to perform the surveillance are the two substantial domains of the methodology of follow-up (Table 3.1).

3.2 Indications to the Follow-Up in Digestive Endoscopy

The indication to perform an endoscopic follow-up examination is acceptable when decided by the physician on the basis of strong evidence of clinical utility (i.e., effectiveness). Any follow-up endoscopy required only for physician's personal serenity, to stay on the safe side in a concept of "defensive medicine," is unacceptable and inappropriate. Nonetheless, it may happen that the patient asks for a possibly inappropriate surveillance endoscopy: in such cases, the request should not be rejected a priori, it should rather be judged carefully on individual basis, considering the potential for reassurance and its important psychological impact. Nowadays, many scientific societies consider appropriate an endoscopic examination performed to reassure those particularly anxious subjects, whose distress about health status cannot be completely quietened by verbal reassurance of the specialists.

3.3 Why an Endoscopic Follow-Up Examination?

When assessing the rationale of an endoscopic surveillance examination, it is mandatory to ask oneself whether the condition or disease deserves any surveillance. Such judgment inevitably arises from the presence of scientific evidence of clinical utility, from the knowledge of the natural history of the disease, as well as from the epidemiological relevance of the expected event that is under surveillance.

Establishing if these criteria can always be satisfied is not an easy task. As a general rule, endoscopic follow-up of benign conditions is considered appropriate only within the framework of clinical studies. On the reverse, such criteria are fully satisfied for post-polypectomy surveillance: there is, in fact, compelling evidence of its clinical utility [1]; the natural history of colonic carcinogenesis (through the adenoma–carcinoma sequence or the serrated pathway) is recognized and because the incidence of colorectal cancer is high.

The same does not hold true for Barrett's esophagus, where evidence of clinical utility is weak, natural history of the condition is still poorly understood, and the incidence of esophageal adenocarcinoma has long been overestimated due to the poor quality of the studies, often underpowered [2–5]. Even less known is the natural history of Barrett's dysplasia; also, ablative therapies such as radiofrequency ablation will likely modify the cost–utility and cost-effectiveness of surveillance in the future, leading to a paradigm shift in the need for surveillance of these patients [6–11].

As mentioned, the question about why perform endoscopic follow-up does not always have a clear, explicit, and definitive answer: conditions

that today are kept under surveillance may in the future be not as the progress in medicine removes the grey shadows from our knowledge.

3.4 Who Should Be Surveilled?

Once established that the condition actually deserves surveillance, the other key question is the selection of candidates, i.e., which patient affected with a given risk condition should be really kept under surveillance?

Such judgment can be drawn by an accurate assessment of the individual risk profile, including age, comorbidities, and capacity of the subject to sustain the therapeutic intervention(s) driven by a positive follow-up examination. Practically speaking, if the patient is too old or frail to resist surgery, is there any sense in surveillance for colorectal cancer recurrence? Progress in endoscopic techniques of ablation or resection of early gastrointestinal neoplasia, may transform patients *"unfit for surgery"* into good candidates for mini-invasive forms of treatment.

A possible algorithm is depicted in Fig. 3.1, which takes into account patient's risk profile, age, and comorbid conditions as decision knots or filters to pass judgment on the appropriateness of an endoscopic follow-up.

3.5 How to Perform Surveillance?

As for the methodology of the endoscopic follow-up, the seminal importance of the operator and the facility is intuitive. Technical competence together with adequate technology equipment are crucial factors for the safety and efficacy of follow-up endoscopy, minimizing potential complications while in the meantime maximizing potential benefits deriving from an early intervention.

Besides, follow-up endoscopy should be modulated to the needs of individual case. Such a modularity of follow-up (patient-tailored) entails that the surveillance protocol can be deviated or rerouted according to the incidence or identification of lesions (e.g., high-grade dysplasia in Barrett's esophagus or dysplasia-associated lesion or mass in patients with ulcerative colitis) that require either an increased level of complexity of the follow-up, with need for referral to tertiary centers more equipped in terms of technology or manpower, or a modification of surveillance intervals.

In particular, technical competence expresses the level of application of scientific knowledge, professional abilities, and available technology to improve health conditions. The competency of those who perform the endoscopy and those who

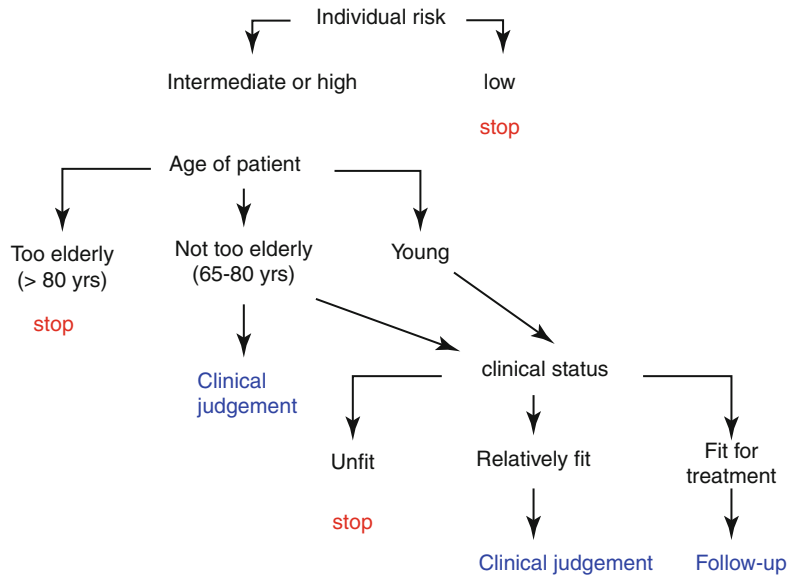

Fig. 3.1 Decision tree or algorithm on the appropriateness of endoscopic surveillance on patients with diseases deserving follow-up

draw the histology report that influences all the subsequent decisional chain is by no way a secondary aspect. This represents a big problem at all latitudes: *ability to match up with the situation should never be taken for granted*.

A major aspect in terms of operator's competence for surveillance endoscopy is the diagnostic accuracy and particularly its negative, i.e., the rate of missed diagnosis of pre-neoplastic or neoplastic lesions (missing rate). Any cancer detected within 3 years of a previous "negative" colonoscopy is termed "interval" cancer and should be considered as a missed lesion [12–18]. The missing rate is not a trivial problem: also, in expert hands, it can be as high as 25 % for small or flat adenomas [19–21] and can reach up to 7 % for overt cancers [15–17]. While the missing rate may not heavily impact efficacy of screening endoscopy, where majority of patients are healthy and does not have cancer, it is potentially devastating in the field of surveillance, which, in turn, is directed toward subgroups of patients at risk of having or developing cancer.

The critical question: is this exam really negative? It urges that everyone performing a surveillance colonoscopy knows and applies those techniques allowing for an accurate evaluation of bowel mucosa during apparently negative examinations (chromoendoscopy, magnification, light technology, etc.) [22, 23]. Such competency requires formal and adequate training and continuous updating (maintenance curve), possibly periodically audited or assessed by external independent subjects (credentialing) and that is when things begin to get difficult.

Health systems often taken as an example in terms of quality have made tremendous efforts to improve patients' outcomes through systematic quality improvement programs. In UK, screening colonoscopists have improved their overall cecal intubation rate from less than 60 % in 2006 [24] to over 90 % in 2011 [25] thanks to a nationwide training and retraining process of all those involved in CRC screening. Improving colonoscopic skills and bowel preparation may also decrease nonadherence to the recommended post-polypectomy surveillance interval. Inadequate *training* and absence of *retraining* inevitably lead to insufficient endoscopic practice not up to the high-quality standards often required by an accurate follow-up.

3.6 When to Perform Surveillance?

Last but not least there is the issue of when to perform surveillance, that is, the appropriate timing of endoscopic follow-up start up and the optimal interval between examinations. Such information, at best, can be derived by specific guidelines on the disease, when available [26, 27]. The personal clinical practice should then be tailored accordingly.

As a paradigmatic example, follow-up after curative surgery for colorectal cancer remains controversial, with no consensus on a protocol. Its evolution has largely lacked an evidence base. Current guidelines from the UK, the USA, Europe, and Canada all have differing recommended schedules for clinic visits, carcinoembryonic antigen (CEA) levels, colonoscopy, and abdominal and chest imaging [28]. However, there is a global lack of consistency. Standardized follow-up regimens need to be developed. Many institutions continue to have their own follow-up regimen. As life expectancy increases, with a reduction in all-cause mortality and spiralling costs of sophisticated imaging modalities, intensive follow-up regimens are becoming more expensive. The cost-effectiveness and cost benefit of such regimens are still unevaluated. The economic burden of this unsystematic follow-up is immense.

A further blow to the faith in follow-up comes from the awareness that cancers can arise between follow-up examinations. This may have an important effect on how patients perceive the benefits of follow-up. When faced with a risk, people tend to assign great value to the complete abolition of risk. For example, when asked how much they would pay to reduce the risk of a hypothetical disease, they would be willing to pay significantly more to reduce the risk from 10 to 0 % than they are willing to pay to reduce the risk from 20 to 10 %, a reduction of the same magnitude.

Although people are willing to pay a higher premium to achieve certainty, such certainty is rarely achievable in real life. Colorectal cancer cannot be completely eliminated as a possibility, even with very intense surveillance. Oncologic surveillance is often perceived by patients as "insurance" against future cancer. I would argue that their enthusiasm for follow-up endoscopy would be greatly mitigated when realistically informed on its true potential benefits.

Another important burden is cost evaluation. The potential costs of surveillance are not only direct and indirect health-care costs for the society or related to the occurrence of complications but also patient's personal costs that cannot be priced, represented by the burden of anxiety and concern regarding their specific pathologic condition requiring surveillance. It is therefore self-evident that the more inappropriate the follow-up procedure, the more unacceptable is the induced waste of health resources along with the risk of adverse events to which the patient is exposed.

Overused procedures are those unnecessarily repeated: the excess number of post-polypectomy surveillance colonoscopies is a suitable example [29] or a colonoscopy repeated 1 year after a negative examination in the absence of a specific objective (identification of early *missed* neoplasia).

3.7 Conclusions and Perspectives

Notwithstanding the absence of a grade A level of evidence (i.e., derived from properly conducted randomized clinical trials or meta-analyses), endoscopic follow-up will likely continue to be a recommended strategy for the surveillance of many conditions.

In this view, every physician involved in the clinical management of cancer patients or patients with precancerous conditions should assure that all potential beneficiaries of the follow-up have access to the procedures, with an inevitable improvement in communication whenever those who require follow-up endoscopy are not those who perform it.

If the desirable aim is to improve both appropriateness and efficacy of follow-up endoscopy, we then need to:

- Determine the true incidence and prevalence of the primary/recurrent cancer and identify predictive factors
- Define the most appropriate modality of follow-up (be it radiologic imaging, endoscopic, laboratory, or else) and the optimal interval of surveillance examinations
- Increase the adoption of risk stratification systems and then propose a selective follow-up program only to the high-risk subgroup(s)
- Periodically update guidelines and protocols for surveillance on the basis of new clinical proofs of efficacy

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4 Timing and Protocols of Endoscopic Follow-Up in Operated Patients After Esophageal Surgery

Giorgio Battaglia, Matteo Cagol, Stefano Realdon, Carlo Castoro, Giorgio Diamantis, and Alberto Ruol

4.1 Introduction

The reconstructive techniques used to restart feeding following a total or partial esophagectomy are as follows: stomach interposition, colon or jejunal interposition, cervical and intestinal loop autograft, and musculocutaneous flap. According to the reconstruction technique used, the anastomosis can be at the intrathoracic or cervical level [1, 2] and if a colon or jejunal segment is used, a second distal anastomosis is placed under the diaphragm. The indications may be benign diseases like refractory peptic stenosis, decompensated achalasia, caustic ingestion, etc., but, above all, esophageal surgery is linked to a neoplastic disease which is the aspect which mainly concerns us.

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Despite the improvement in surgical techniques and materials over the last 10 years, complications in interposed viscera (necrosis, fistulation, perforation, stenosis, obstruction, and esophagitis reflux) still remain a problem even if less common in centers with more experience and treated cases [3, 4]. Furthermore, in patients who have undergone an esophagectomy for esophago-cardio malignant cancer, the risk of local neoplastic recurrence and metachronous neoplasia in the residual esophagus has to be considered.

Finally, even if rarely, surgically induced esophageal reflux could lead to cancer through the well-known chain of esophagitis → intestinal metaplasia → dysplasia → cancer. The failure to diagnose these complications in the early stages after surgery or during follow-up can lead to a serious outcome which could be fatal [5].

A consensus on a regular postoperative follow-up exists, but there is no consensus on the type and the frequency.

Despite endoscopy being undoubtedly the best technique to diagnose and, in many cases, to treat the majority of local early and late complications (both benign and malignant), clear indications for endoscopic controls are lacking. As Park and colleagues underlined in a recent study, in many centers, the majority of complications, including neoplastic recurrence, are only diagnosed when clinical symptoms appear and at this time the treatment is very difficult and in some cases useless [6].

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4.2 Literature Search

With the aim of finding follow-up indications in literature, a research was carried out in the Medline, Embase, and Cochrane databases which include publications in English language since 1980. The research was done by using the terms MESH "esophageal cancer," "adenocarcinoma of gastroesophageal junction," "follow-up guidelines," "disease recurrence," "clinical practice guidelines," "prognosis," and "survival." All correlated articles on these subjects were analyzed. In this ample literature, four guidelines were chosen, dealing with the follow-up of patients who had undergone curative esophagogastric resections: the guideline by the British Society of Gastroenterology 2002 [5], the Scottish Intercollegiate Guidelines Network (SIGN) 2006 [7], the European Society of Medical Oncology 2009 [8] and the National Comprehensive Cancer Network (NCCN) release 2–2011 [9]. Only anecdotal data from individual centers was found, while no randomized or controlled studies, which specifically investigated the duration, the frequency, and the type of follow-up (in particular through endoscopy investigation) after esophageal surgery for cancer, were made available.

Therefore, in the absence of precise indications, it is difficult to present sound scientific data to back a follow-up program for asymptomatic patients in order to detect complications or disease recurrence. This is also because according to related literature, early diagnosis does not seem to affect survival.

Nevertheless, several studies have shown that cancer patients prefer a regular follow-up for treating benign complications, for feeding management, and as psychological support [8, 10, 11].

The aim of this paper is to verify if and when, in association with other procedures, there is indication for an endoscopic follow-up after esophageal surgery, combining published data with our findings, based on a long and considerable experience acquired at the Centro Veneto for esophageal diseases, which has treated and followed 4,681 patients since 1980 to 2011[1] (Fig. 4.1).

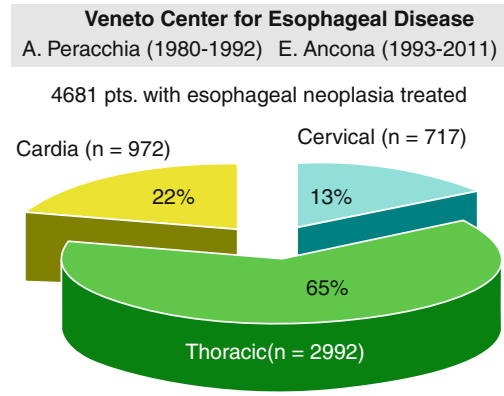


Fig. 4.1 Patients with esophageal/cardia cancer treated at the Veneto Centre for esophageal disease

4.3 Complication After Surgery and Surveillance Endoscopy

In the anastomotic context, endoscopy is able to reveal complications which can appear in the first postoperative days (such as fistulae and interposed viscera necrosis) or in the long term (such as stenosis, esophagitis, and recurrence in cancer patients due to not complete resection or relapse) (Fig. 4.2).

4.3.1 Fistula

Fistula is the most serious complication due to diagnostic difficulty, clinical management, and mortality. It appears in the early postoperative period, usually within 10 days but in some rare cases even later. It always causes a worsening of the patient's condition, ranging from prolonged hospitalization to a life-threatening condition. When appearing in the very early stages (second

[1] The Clinicians that, over the years, performed the procedures on which this study is based are: A. Peracchia (surgeon), E. Ancona (surgeon), A. Ruol (surgeon), C. Castoro (surgeon), M. Cagol (surgeon), L. Corti (radiotherapist), V. Chiarion Sileni (oncologist), G. Battaglia (endoscopist).

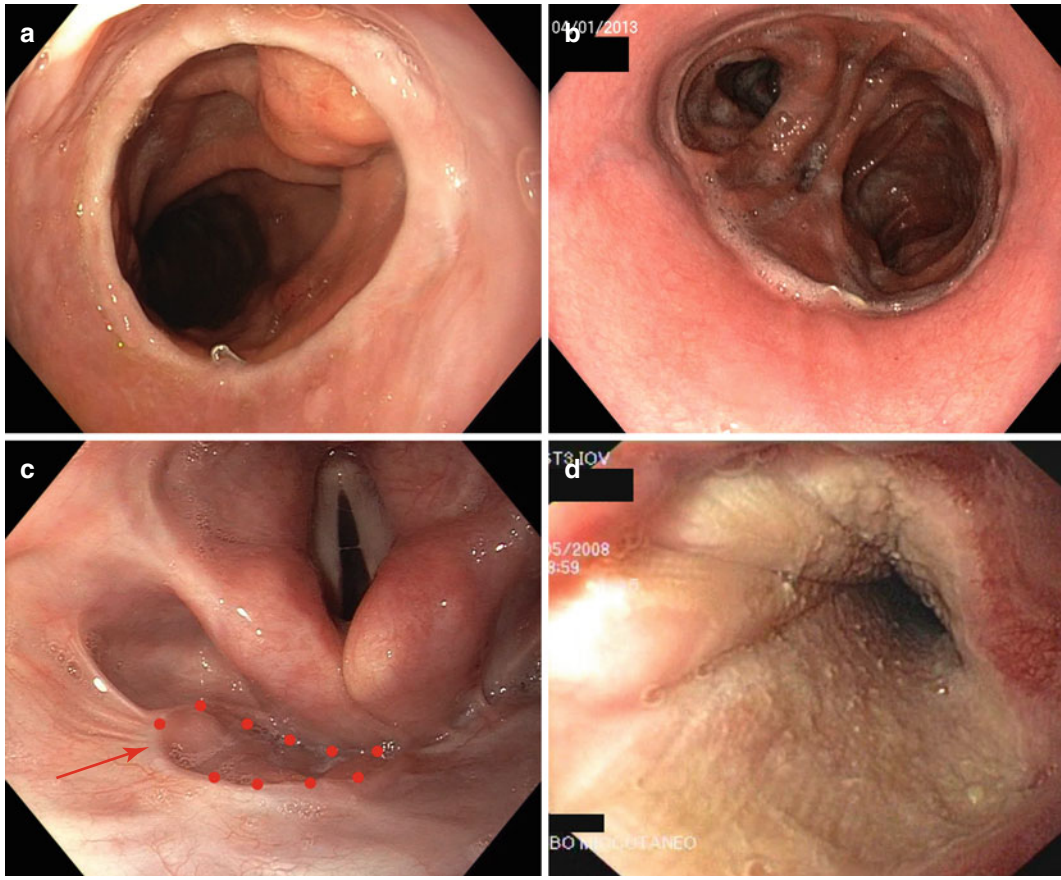


Fig. 4.2 Esophageal anastomotic variants: intrathoracic esophagogastric anastomosis (gastric pull-up) (**a**), esophagojejunal anastomosis (**b**), pharyngo-colonic anastomosis (highlighted by the *red arrow*) (**c**), and musculocutaneous graft (**d**)

or third postoperative day), it implies a particularly serious condition as the visceral contents can easily spread to the mediastinum; in this case it is associated with significant high mortality ($P = 0.013$) [12]. In our case records, we have distinguished three types of fistulae (Table 4.1).

In the literature, the global incidence of esophageal fistula goes from 4 to 14.3 % and represents the most important postoperative factor influencing mortality; the mortality linked to this complication ranges from 16.7 to 50 %, in relation to local factors (fistula gravity, associated necrosis of the tubule), general factors (associated diseases, vascular pathologies, dermatosclerosis, etc.), and the number of surgical procedures [13, 14]. There are many factors playing a role in determining the development of fistulae: they could be due to the adopted techniques such as the type of anastomosis (mechanical or manual) or the tension caused by a too short tubing (if taken to the neck) or due to functional factors leading to ischemia of the gastric tubing, which can depend on either general causes (systemic vascular pathologies) or local causes (a tight diaphragm passage, previous radiotherapy treatment, or the type of viscera used—the ileal and colon segments are the more sensitive whereas the stomach seems to be less sensitive).

Table 4.1 Fistulas classification employed at our department

1	Subclinical (radiologic)	
2a	Minor without borders ischemia	Affects less than ¼ of the esophageal circumference and mainly caused by a technical error; the borders are well vascularized
2b	Minor with ischemic borders	Affects less than ¼ of the esophageal circumference; may be related to an insufficient vascularization of the graft or a prolonged hypotension during or immediately after surgery
3a	Major with necrosis of borders	Affects more than ¼ of the esophageal circumference; related to an important non-transitory vascular insufficiency; necrosis of the anastomotic borders
3b	Major with extensive necrosis of the graft	Affects more than ¼ of the esophageal circumference with an extensive wall necrosis of the graft

Thanks to new techniques, above all the mechanical suturer, a technical error while making an anastomosis is rare to observe today. A more common problem is the ischemia of the mobilized viscera which, to a certain degree, happens in all patients but rarely leads to the inability of healing. Therefore, when a combination of ischemia and mechanical stress has a negative effect on the anastomosis, a fistula can occur. According to some authors, but without clear scientific evidence, radiotherapy may represent another risk factor, especially for an anastomosis at the neck.

A meta-analysis by Biere et al. [15] on four randomized studies analyzing anastomotic risk factors, showed that fistula incidence was significantly higher for cervical anastomoses in respect to intrathoracic ones (2–30 % vs 0–10 % $P=0.03$), even if the thoracic ones generally have a more complicated course. The author explains that this difference could be due to the vascular suffering caused by tubing or to the manual technique that is used for performing a cervical anastomosis. On the contrary, in another study by Kayani et al. [16] examining 47 published articles, no clear evidence was found concerning a higher incidence for cervical anastomoses, but the studies comparing the two types of anastomoses are few, with a low number of cases, and they are not standardized concerning surgery approaches, anastomosis techniques, and the neo-adjuvant therapy.

Analyzing the gastric tube preparation, Collard showed 1 % fistulae with the whole stomach vs 7.9 % with tubular stomach while, regarding the intrathoracic interposition, Shu observed less fistulae with the tubular stomach (5.5 % vs 9.3 % ($P<0.05$)) compared to the whole viscera [17]. Age does not appear to be a risk factor if vascular diseases are not involved; Tapias observed anastomotic leakage in 4.8 % of patients <70 years 4.8 % in 70–80 age and 0 % < 80 years ($P=0.685$).

Regarding seriousness of fistulae, Price and colleagues [18] report a global incidence of 11 % with a superior incidence of neck anastomoses (6/34, 21 %) against intrathoracic (16/268, 5.9 %) but without significant difference regarding the percentage of more serious fistulae with partial or extended necrosis of the viscera (4.8 % vs 4.8 %). In our global experience, we have had 7.3 % of fistulae of which only 1.1 % were serious, with a significant reduction to 5.9 % over the last decade. The level of the anastomosis was decisive for the development of a slight fistula (11.3 % cervical vs 4.3 % thoracic ($P=0.0001$)), as it was also for the type of viscera interposed at the cervical level, even if not significant (colon 16.8 % vs stomach 10.7 % ($P=$NS)).

Whenever an interpositioning is performed with the colon or the jejunum, the lower anastomosis also needs to be monitored as it is the area where, in our experience, there is a fistula incidence of 4.7 % (12/255: 8 slight 4 serious).

Appearance of necrosis has a low rate (1.1 %) and here as well a significant difference between cervical and thoracic levels is to be found (22/774 vs 6/1,468 ($P<0.001$)). Our study did not observe a correlation with comorbidities like cirrhosis, diabetes, obesity, nephropathy, or arteriopathy as shown by the following data:

- Cirrhosis (1/48 (2.1 %) in patients with cirrhosis vs 27/2,194 (1.7 %); $P=0.46$)
- Diabetes (3/159 (1.9 %) in patients with diabetes vs 25/2,083 (1.2 %); $P=0.44$)

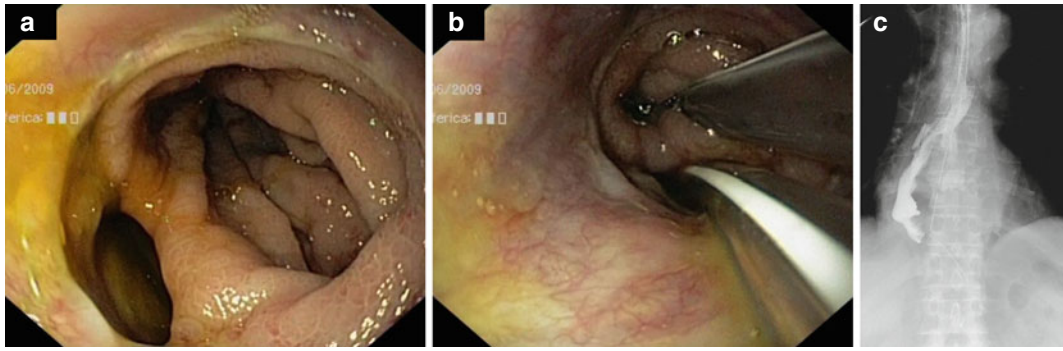


Fig. 4.3 Large anastomotic fistula without necrosis (**a**), conservative treatment by positioning one tube in the stomach and the other one in the mediastinum (**b**), and X-ray control after 10 days of parenteral nutrition (**c**)

- Obesity (0/21 in obese patients vs 28/222 (1.3 %); $P=0.99$)
- Nephropathy (1/55 (1.8 %) in patient with nephropathy vs 27/2,187 (1.2 %); $P=0.50$)
- Arteriopathy (2/93 (2.2 %) in patients with arteriopathy vs 26/2,149 (1.2 %); $P=0.32$)

Anastomotic fistula diagnosis may be difficult [19]. Normally surgeons control the anastomosis with a digestive tube on the seventh day before feeding starts and the control is mandatory in the presence of risk factors like a difficult anastomosis or a serious blood pressure decrease in the early postoperative period or a suspected septic state. These are the conditions to be aware of as the anastomotic fistula or tubular necrosis has to be diagnosed as early as possible in order to quickly start the appropriate treatment.

In suspect cases, as the first approach, a digestive tube and, if positive, a CT scan should be requested; even if 50 % of fistulae are not detected with these exams, they are the basis for the next endoscopic exam. Endoscopy is the only exam able to show suffering in the interposed viscera or am anastomotic leakage: it should be performed by an expert endoscopist using a weak insufflation and, possibly, a hood placed on the tip to enable the detection of the suture line. While performing the retroversion (which is a very risky maneuver), the gastric side of the anastomosis and any eventual vascular problem or necrosis should be described. This procedure allows to determine the presence a critical anastomosis before fistulization in order take the correct measures that often can be done only to delay the refeeding (Figs. 4.3 and 4.4).

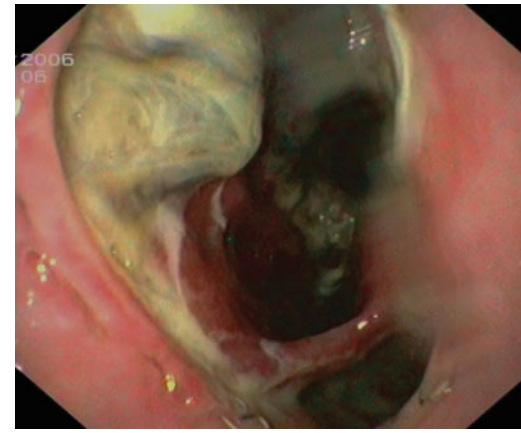


Fig. 4.4 Anastomotic leakage with necrotic tissue

Once the diagnosis has been done, the monitoring of the clinical process of the viscera can be done by daily endoscopic controls if a conservative treatment has been decided. In fact there is not always an indication to surgical treatment even when there is a major fistula, especially if the patient's general condition is not serious and if the disassembling of the anastomosis is technically difficult.

In our experience, if there is no extended necrosis; we always prefer a conservative treatment which includes internal drainage placed endoscopically in the fistula and a gastric tube. We monitor the clinical state carefully and the viscera with daily endoscopic exams, if necessary, and surgery is performed only if the clinical parameters get worse.

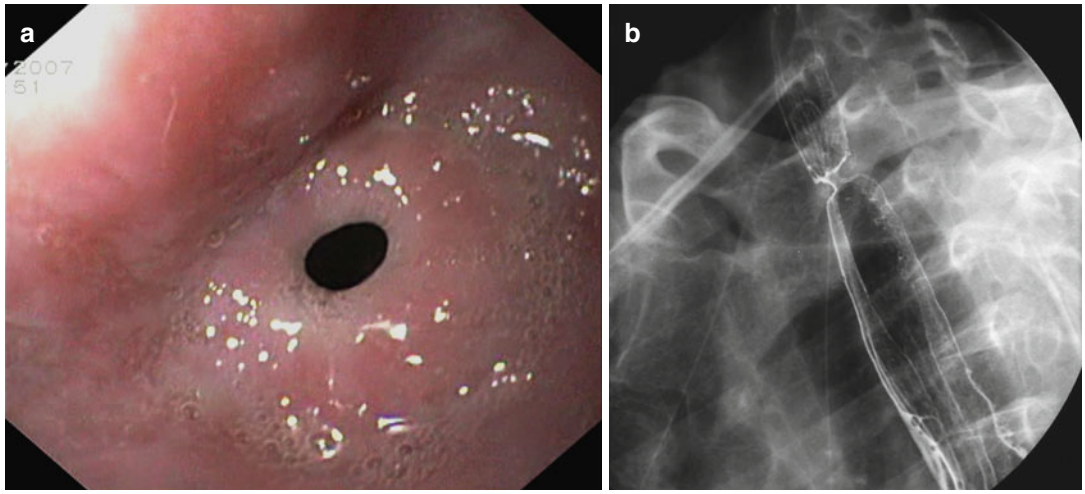
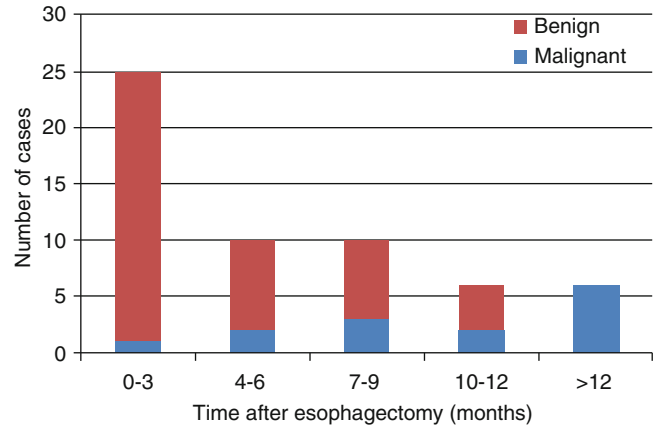


Fig. 4.5 Tight anastomotic stenosis: endoscopic (**a**) and radiological vision (**b**)

Fig. 4.6 Timing of anastomotic strictures after esophagectomy (Reproduced with permission from [21])



4.3.2 Stenosis

The incidence of benign anastomotic stenosis after an esophagectomy and gastric tube reconstruction reported is 10–15 %. They are associated to fistula recovery, ischemia, or the surgical technique used. However, in some cases, these are not the causes, and gastroesophageal reflux is the determinant (Fig. 4.5).

In a Dutch study, carried out on 80 patients who did not complain of an anastomotic fistula in the postoperative period, reflux weighs heavily upon the development of a stenosis (13 % vs 45 %, $P=0.001$): another factor is the use of a 25-mm caliber mechanical suturer compared to a 28 mm or 31 mm one, with the first mentioned the risk was 2.9 times higher [20].

In Sutcliffe's study [21] 177 patients were followed for 3 years; 48 (2.7 %) developed a stenosis which was the result of an anastomosis tightening enough to provoke clinical symptomatology; 40 were benign and 14 were malignant (6 benign developed into malignant ones). Of those which developed within 3 months, 96 % were benign; within 1 year, the benign were 83 %. All cases of stenosis present after 1 year (6/6) were caused by tumor recurrence (Fig. 4.6).

Due to the fact that the principal cause was a fistula, the authors recommended early dilatation

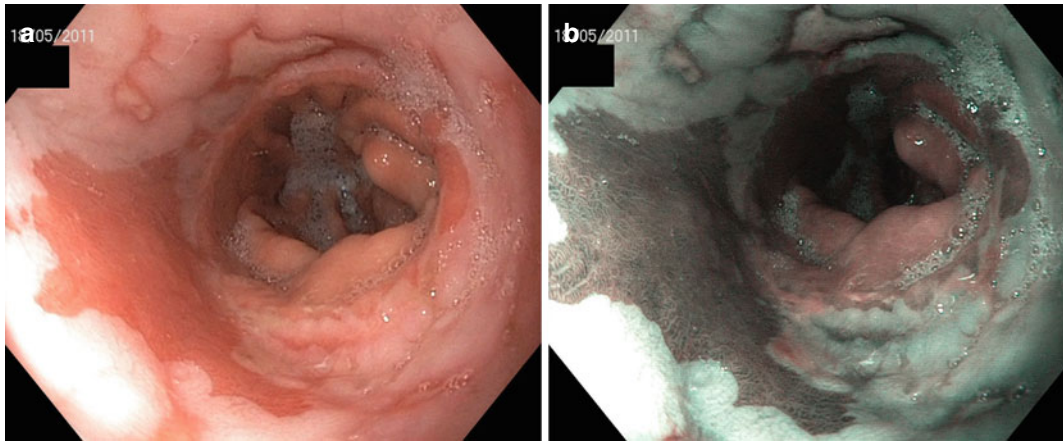


Fig. 4.7 Severe esophagitis of the remnant esophagus with an area of columnar metaplasia (**a**), clearly visible in NBI modality (**b**)

after healing, even without symptoms, to prevent its possible development [22].

In our patients the stenosis occurred early in 3 % of cases with a sufficient difference in the cervical or thoracic sites (4.4 vs 2.65 $P < 0.02$) [23].

The long-term difference is even more significant (15.5 % cervical vs 7.6 % thoracic $P < 0.001$); this would suggest that the gastroesophageal reflux (more frequent in thoracic anastomoses) is not very important in the development of the stenosis, but other factors, such as reduced vascularization or type of suturing, may be determinant. The neo-adjuvant radiotherapy does not enhance the risk of cervical stenosis but it does play an important role in the causing of thoracic stenosis ($P < 0.02$).

4.3.3 Esophagitis

After an esophagectomy, gastric tube reconstruction is the preferred technique, but esophagitis is one of the more frequent complications. In fact on one side, at the anastomosis level, the squamous epithelium is in direct contact with stomach mucous and, on the other side, the pyloroplasty (which is performed to help gastric emptying) facilitates the development of a duodenum gastric reflux of bile and pancreatic juices; esophagitis incidence is therefore high in a range from 38 to 71 % [24, 25] (Fig. 4.7).

The anastomosis level seems to be the principal determining factor: the intra-abdominal pressure favors the reflux of acid and bile through the anastomosis, and therefore the majority of authors describe that the lower is the anastomosis, the higher is the frequency of esophagitis. Others [26] find a major incidence in cervical anastomoses, with the explanation that there is a more feeble clearance of acid through the anastomosis.

Despite retrosternal and cervical "burning" has always been well described [25, 27] a precise correlation between symptoms and reflux or reflux and mucosal damage usually does not exist [25, 28].

The incidence progressively increases in time, passing from 28 % at a year, 49 % at 2 years, and 76 % at 3 years if the esophagitis was untreated. The severity of mucosal damage above the anastomosis can progress from a flogistic state to an intestinal metaplasia of which the incidence follows the same trend (13 %, 34 %, 40 %) [29]. To avoid this evolution also in the case of asymptomatic esophagitis reflux, it is recommended to modify patient's lifestyle, encouraging smaller and more frequent meals and the assumption of *PPI*, even if the reflux symptom response to these drugs is about 60 %. Probably what causes the onset of this pathology is not only acidy secretion but also delayed gastric emptying, as described in 13 % of our patients after 6 months [22]. Our

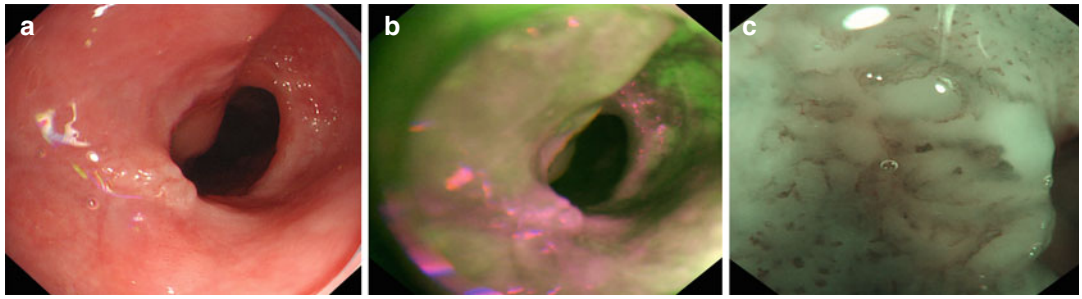


Fig. 4.8 Early anastomotic recurrence 2 years after esophagectomy for cancer (**a**). In A.F.I. modality a hypofluorescent area is seen suggesting a bigger neoplastic area than in white light modality (**b**). Zooming the area, a complete disrupted microvascular surface is seen (**c**)

experience confirms this hypothesis as we found that in patients with various degrees of esophagitis 80 % were treated with PPI, only 53 % presented gastroesophageal reflux symptoms and 37 % had delayed gastric emptying.

4.3.4 Recurrence

Neoplastic recurrence at the anastomotic level or of the esophageal remnant is a common problem after an esophagectomy for cancer. This occurs in the majority of cases within 2 years with a percentage which varies from 3 % [30] to 18 % [31, 32] and is higher when associated to a head–neck cancer.

The presence of disease on the margin of section is an important factor in recurrence. In our experience when a disease-free margin of resection is achieved the recurrence rate is 1.9 % and it develops even 3 years from the procedure. Conversely if a disease-free margin of resection is not achieved the recurrence rate is 15 % and it develops within 12 months from the procedure ($P = 0.001$).

A regular endoscopic follow-up can identify recurrence in the initial stage even if in different series the survival after local recurrence is however 5–7 months. In our center, within the 40 patients with a recurrence after a margin free resection, 6 are still alive with a median survival of 21 months from the date of recurrence, whereas 34 are dead with a median survival of 12 months.

When neoplasia recurs several months after treatment, it is probable that the mucosal damage caused by the reflux could play an important role; for this reason endoscopic controls should be performed routinely. This would confirm D'Journo's [25] observations which show different esophageal mucosal alterations whether the anastomoses is cervical or thoracic, with an intestinal metaplasia transformation at 2 years of 18 % for a neck anastomosis and 40 % for a thoracic one (Fig. 4.8).

Another interesting fact emerges from this study: the only data which seems to be important in the transformation of esophageal mucosa after multi-varied analysis (other than the anastomosis level) is the presence of a presurgery Barrett, as if there were a genetic predisposition toward this alteration.

Conclusions

The timing for endoscopic follow-up for esophageal–intestinal anastomosis cannot be predicted: it depends on the patient's basic pathology (benign or malignant), the type of surgical procedure, the occurrence of perioperative complications, and patient's or doctor's level of anxiety.

Too many controls might create anxiety in patient, whereas a normal finding has a soothing effect. On the other side, the finding of a recurrence and the awareness of probable death can help the patient to modify his lifestyle and help him to organize the future of his family.

In the period immediately after surgery, as the majority of authors, we think that upper endoscopy is superfluous in the absence of clinical symptoms even if it has recently been proposed that upper endoscopy could be useful within 4–5 days instead of the radiological control, in order to accelerate the beginning of refeeding and hospital discharge.

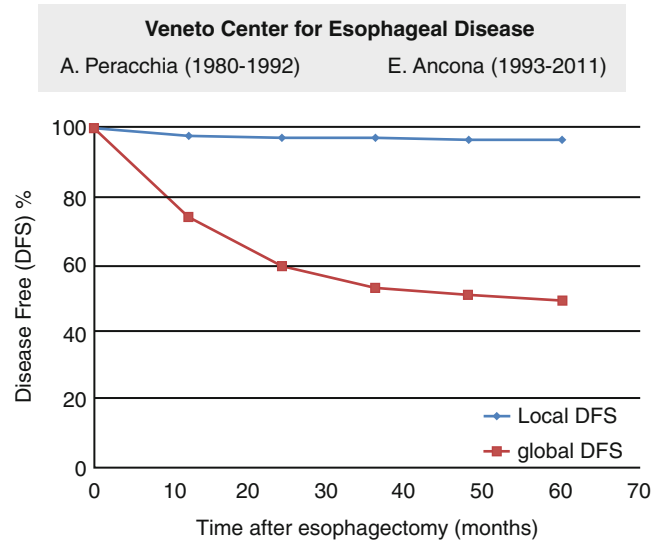


Fig. 4.9 Incidence of local recurrence and global recurrence

For the long-term period, we should distinguish between benign and malignant pathology. In the first case, upper endoscopy should be reserved for symptomatic patients, even if we have seen that symptoms are not always related to the actual state of the esophagus. In case of malignancy, endoscopy is only one of the postoperative diagnostic tools because recurrence could be local but might involve other different and more distant body areas (metastases) (Fig. 4.9).

According to the data we presented, it can be understood that early local anastomotic recurrence diagnosis can be obtained only through an endoscopic exam and such an exam must be accurate and rigorous especially if there is a strong possibility of local recurrence.

In partial resections when the tumor is found on the margin of section of the esophageal remnant, recurrence tends to appear within the first 12 months; therefore, controls at 6 and 12 months are highly recommended. Nevertheless, all the other patients should not be neglected; therefore, we recommend that after 12 months controls should continue every 6 months for 3–5 years. The importance of annual controls has recently been defined in the NCCN guidelines [9]. Instruments should be, at least, high definition with enhanced images through electronic elaboration imaging (NBI, FICE, I-scan).

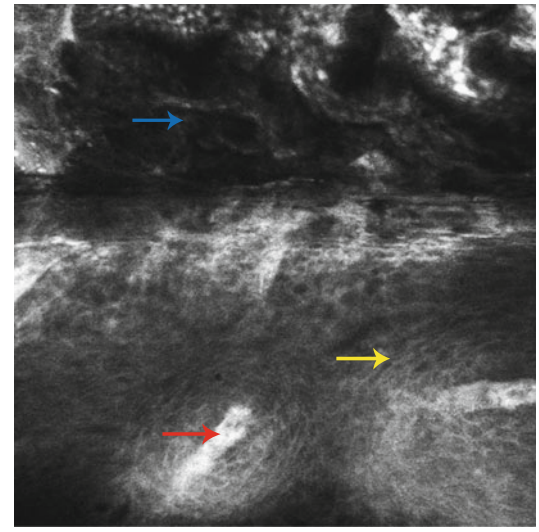


Fig. 4.10 Confocal laser endomicroscopy of the anastomosis with the neo squamo-columnar junction. *Blue arrow*: columnar gastric epithelium. *Red arrow*: squamous epithelium with intrapapillary loops. *Yellow arrow*: dilated intracellular spaces within the squamous epithelium

Specialized centers could perform more refined diagnostics with more sophisticated instruments in suspect cases: in our center, such patients, according to the specific case, undergo endoscopic exams using confocal endomicroscopy or autofluorescence imaging (Fig. 4.10).

In conclusion, even if it is not unanimous that early diagnosis may increase survival, our

experience suggests that a standardized follow-up program could help monitoring and possibly improving results of esophageal surgery.

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5 Timing and Protocols of Endoscopic Follow-Up After Gastric Surgery

Rita Conigliaro, Angelo Caruso, and Marzio Frazzoni

5.1 Introduction

After gastric surgery, indications to endoscopic follow-up have not yet been definitely established. We will consider the most common gastric surgical interventions and indications of endoscopic follow-up will be based on available literature.

5.1.1 Partial Gastrectomy

The question of whether partial gastrectomy carries an increased risk of subsequent development of stomach cancer is debated.

A number of studies have reported an increased risk after Billroth-II gastrectomy compared with Billroth-I gastrectomy [1]. The exact mechanism for the development of gastric stump cancer (GSC) remains unclear, although many causative factors have been reported. It is widely accepted that the predominant factor underlying the development of GSC is duodenogastric reflux including bile and pancreatic juice, reportedly carcinogenic and related with GSC [2]. GSC has been used to define all cancers occurring in the remnant stomach after gastrectomy, regardless of whether the primary disease was benign or malignant [3].

The incidence of GSC following distal gastrectomy has been reported to account for 1–2 % of all gastric cancer in Japan [4]. Specifically, GSC is commonly found at an advanced stage, resulting in low rates of curative resections (38–40 %) and a consequently poor prognosis [5]. However, the incidence and etiology of GSC have changed in recent years because of the long latency periods, the decreasing prevalence of gastrectomy for benign disease, and the early detection and improved outcomes in patients with gastric cancers [6]. Despite the previous reports where GSC was commonly found at an advanced stage, resulting in poor prognosis, recent advances in diagnostic methods and less-invasive treatment techniques have led to a higher detection rate of early GSC following distal gastrectomy and decreased mortality and morbidity rates. Consequently, endoscopic therapy such as endoscopic mucosal resection or submucosal dissection can be adopted for treatment of early-stage GSC [7].

Thus, oncologic and mainly endoscopic follow-ups are important in all patients after

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gastric surgery. Data from literature should be subdivided as follows:

- *Risk* of *GSC* after *gastric surgery* for benign peptic ulcer (partial gastrectomy was the treatment of choice for ulcer disease until the development of antisecretory drugs)
- Risk of GSC after gastric surgery for gastric cancer

Retrospective cohort studies in patients operated for benign disease found mixed results: increased [8], unaltered [1], and decreased [9] risk. Overall, results from the five largest case control studies indicate that the relative risk of GSC after gastric surgery for benign peptic ulcer is two (RR=2).

Twelve prospective studies on patients operated on for peptic ulcer have been published. These studies are based on the follow-up of a cohort over a certain period of time. Results are expressed and analyzed using the incidence ratio observed in the cohort, comparing observed with expected cases in a similar general population. The results of seven of these studies favor the hypothesis of an increased risk of stomach cancer in patients operated on for peptic ulcer disease, while those of five do not support this hypothesis. The results of two of these studies were obtained by multivariate analyses, which represent the best statistical methodology known for assessing the respective role of confounding variables. Authors believe that the evidence is good enough to identify patients who underwent partial gastrectomy more than 20 years previously as a high-risk group for the development of carcinoma. Therefore, it is recommended that these patients should be offered regular endoscopy, especially if they underwent a Billroth-II surgical procedure [10].

Green et al. [11] suggested endoscopic and histological surveillance to enable early diagnosis. Seven early gastric adenocarcinomas were detected in 163 patients followed up for a mean duration of 8 years with yearly upper GI endoscopy gastroscopies. Screening was commenced at least 10 years after surgery.

More recent studies, mostly from Japan, have been published on patients operated on for gastric cancer. Thanks to recent advances in diagnosis, an increased early detection of gastric cancer has been found. Consequently, the number of cured patients has increased and some of these patients are at risk of acquiring a second primary cancer in the remnant stomach. This implies that more cases of GSC will be encountered in the future [12].

Surveillance systems for early detection and curative treatment of GSC with periodic endoscopic examinations of the gastric remnant are mandatory. The time interval to the occurrence of GSC in patients with previous benign and malignant disease was 23.8–32.4 and 6.8–18.8 years, respectively [13]. In the study of Komatsu et al. [14], the follow-up interval was significantly associated with the stage of progression in remnant gastric cancer: an early detection of GSC required less-invasive curative treatment (endoscopic submucosal dissection) and a better prognosis (Fig. 5.1). More than half of the GSC cases were T1 or T2 undifferentiated, node-negative, and early-stage cancers. Accordingly, *annual surveillance* endoscopy *is recommended* for at least 12 years following distal gastrectomy to obtain an early diagnosis of GSC Thereafter, surveillance endoscopy could be performed every second year (Table 5.1). According to authoritative suggestions, careful endoscopic examination should be performed near the suture line and the remnant gastric wall after Billroth-I reconstruction and near the anastomosis after Billroth-II reconstruction [15]. However, more cohort studies are warranted to define optimal surveillance and treatment strategies.

5.1.2 Total Gastrectomy

After total gastrectomy, tumor recurrence can be subdivided as follows:

- Distant tumor recurrence
- Peritoneal tumor recurrence
- Loco-regional tumor recurrence

Loco-regional tumor recurrence includes both endoscopically accessible tumor recurrence (at the anastomosis site or within loop) and endoscopically inaccessible tumor recurrence (lymph nodes or mass near the resected site) [16].

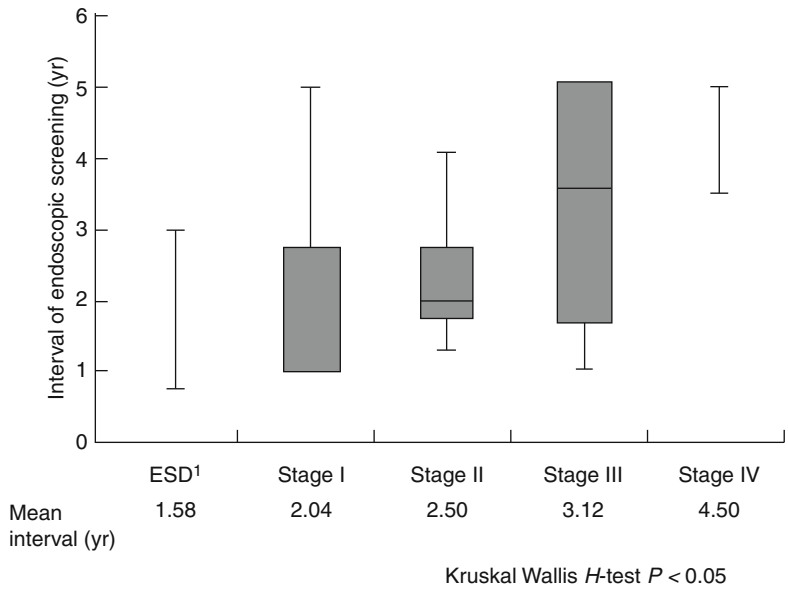

Fig. 5.1 This graphic represents the correlation between less-invasive curative treatment of gastric cancer recurrence after partial gastrectomy and timing of follow-up

Table 5.1 Timing of follow-up: EGDS + biopsies (in anastomotic site and in the remnant mucosa)

Surgery	Follow-up
Billroth-I/Billroth-II	
(a) Benign	(a) Every 2 years 15–20 years after the initial surgery
(b) Malignant	(b) Every 2 years 8–10 years after the initial surgery
Total gastrectomy	
(c) Benign	(c) No data
(d) Malignant	(d) Every year 1–2 years after surgery
Bariatric surgery	(e) On demand (clinical symptoms)

In the study of Lee et al. [17], among 215 patients with *early* gastric cancer submitted to total gastrectomy, there were no endoscopically accessible loco-regional tumor recurrences, while distant large masses were found in two patients at a 36-month follow-up. Among 622 *advanced* gastric cancer cases, 233 patients had tumor recurrence, in 24 of whom recurrence was endoscopically accessible. The endoscopic findings revealed stenosis in ten cases, mass in eight cases, ulcer in three cases, discoloration in two cases, and mucosal nodularity in one case.

Thus, distant tumor recurrence is more common than loco-regional tumor recurrence after total gastrectomy [16]. Endoscopic examination after total gastrectomy for gastric cancer has an important but limited role in the management of tumor recurrence.

5.1.3 Bariatric Surgery

The *performance of bariatric surgery* is escalating in order to treat the obesity epidemic, with multiple procedures that include:

- Roux-en-Y gastric bypass (Fig. 5.2)
- Vertical banded gastroplasty (Fig. 5.3)
- Laparoscopic adjustable gastric banding (Fig. 5.4)
- Sleeve gastrectomy (Fig. 5.5)
- Sleeve gastrectomy with duodenal switch (Fig. 5.6)

Formerly, many of the complications following bariatric surgery were approached by reoperation, but currently, endoscopy plays an important role in the evaluation and management of postoperative upper gastrointestinal symptoms. Endoscopic examination is warranted in patients who present postoperative symptoms including abdominal pain, nausea, vomiting, dysphagia, hematemesis and melena, or even heartburn and regurgitation [18, 19].

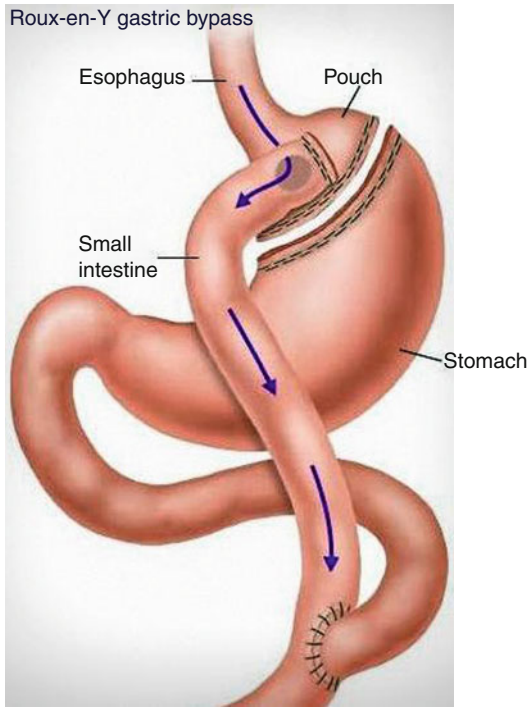

Fig. 5.2 This figure depicts the stomach's appearance after Roux-en-Y gastric bypass

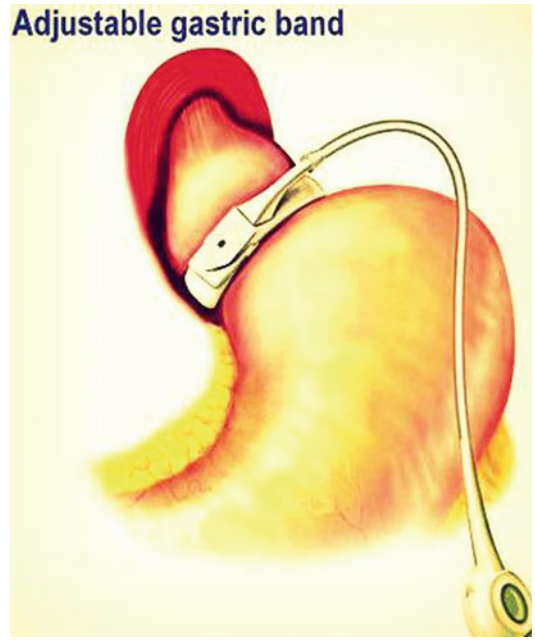

Fig. 5.4 Laparoscopic gastric banding is a purely restrictive procedure in which a prosthetic band is positioned around the entrance to the stomach

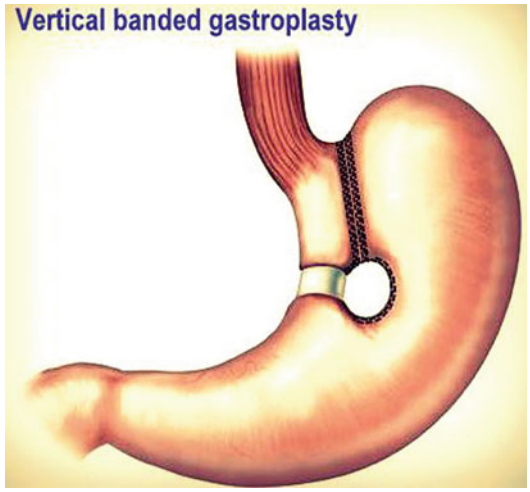

Fig. 5.3 Vertical banded gastroplasty is a purely restrictive procedure in which a small upper stomach pouch is created

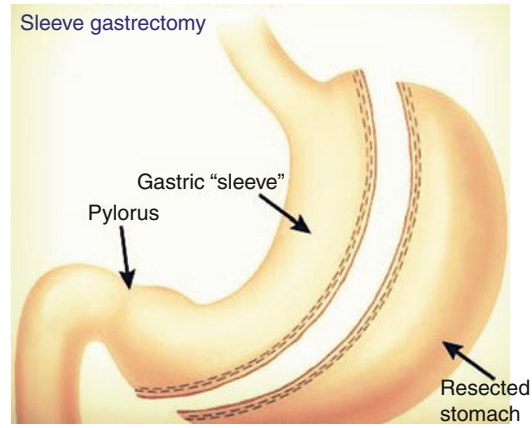

Fig. 5.5 With sleeve gastrectomy, a tubular stomach is created; after that, the majority of the greater curvature of the stomach is removed

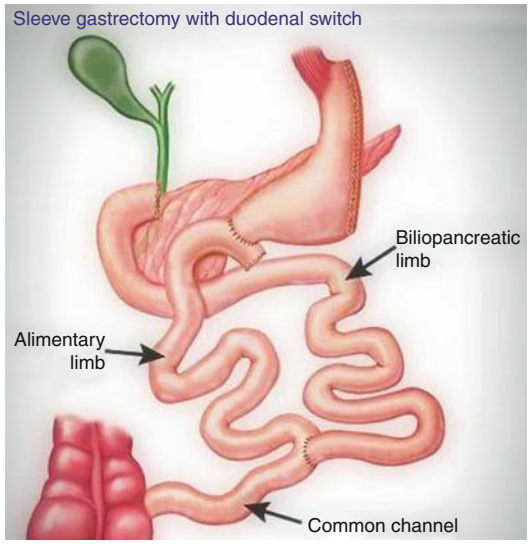

Fig. 5.6 The biliopancreatic diversion with duodenal switch is a partial sleeve gastrectomy with creation of a Roux limb

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6 Timing and Protocols of Endoscopic Follow-Up in Operated Patients After Small Bowel Surgery

Emanuele Rondonotti and Marco Pennazio

6.1 Introduction

Intestinal anastomoses are commonly performed surgical procedures. Among them, those involving the small bowel account for an important proportion of both elective and emergency performed anastomoses [1].

The papers concerning small bowel anastomoses are mostly focused on technical issues (i.e., comparison of sutured vs stapled anastomosis) [2, 3] or on short-term complications (i.e., surgical site infection or leakage) [4, 5], while data about the possible long-term complications or long-term clinical outcomes (i.e., local recurrence of primary disease) are scarce.

This may be due to the unavailability, at least until a few years ago, of diagnostic tools allowing a direct and complete visualization of the small bowel mucosa. In fact, whereas scientific societies issued guidelines about the endoscopic surveillance of anastomoses between the small bowel and colon or stomach [6, 7], clear-cut indications about the endoscopic surveillance of small bowel anastomoses over time are lacking.

Nevertheless, the strategy for diagnosis and treatment of small bowel diseases has dramatically changed in the last 10 years. Up to that time, the endoscopic evaluation of the small bowel was performed by means of invasive (i.e., intraoperative enteroscopy) or inefficient (i.e., push enteroscopy) techniques. Since 2001, the introduction in clinical practice of capsule endoscopy (CE) and device-assisted enteroscopy (DAE) contributed to set up new standards for the evaluation of the small bowel.

In this chapter we will review the available evidence concerning the use of CE and DAE in patients with small bowel anastomoses, speculating their possible role in long-term surveillance programs in this subgroup of patients.

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6.2 Available Tools for Endoscopic Surveillance of Small Bowel Anastomosis: Pros and Cons

6.2.1 Capsule Endoscopy

The major advantage of CE is its low invasiveness: it is well tolerated by patients, easy to perform, does not require hospitalization, and can be performed with minimal/no preparation. In addition, CE has a high diagnostic yield, higher than that of other diagnostic modalities, in identifying small bowel mucosal lesions [8, 9].

All these features make CE an ideal test for surveillance programs, in which the same procedure should be repeated over time. However, CE has a low specificity in differentiating the nature

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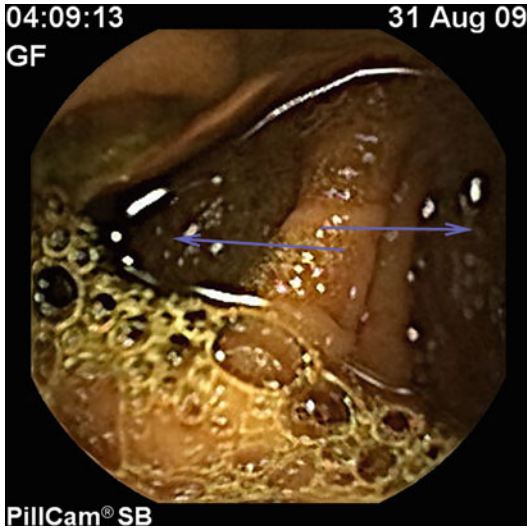

Fig. 6.1 Small bowel anastomosis at CE: *arrows* indicate the presence of a double lumen, a finding consistent with a small bowel anastomosis provide that a diverticulum has been excluded

of small bowel lesions. This limitation may have a particular relevance in case of small bowel anastomosis, where, without taking biopsies, it may be difficult to distinguish between postsurgical complications and recurrence of the primary disease (Fig. 6.1).

Another possible limitation of CE in this setting is related to the delayed capsule transit, which prevents, in operated patients, the complete evaluation of the small bowel. In the study by De Palma [10], where CE was performed in previously operated patients, the rate of complete evaluation of the small intestine was lower (about 70 %) than usually expected. The authors advocated the altered motility, resulting from the small bowel resection, as possible cause of the slow capsule transit.

Interestingly, in this study, all the ten enrolled patients excreted the capsule naturally; nevertheless, the surgically altered anatomy is a well-known risk factor for capsule retention, particularly in case of side-to-side anastomoses [11] in which the capsule can enter blind loops. In the study of De Palma [10], all patients were therefore screened, before undergoing CE by means of the small bowel follow-through to exclude critical stenosis. Subsequent studies have proposed to use, in patients with surgical anastomoses at risk for capsule retention, the patency capsule as "screening test" [12]. Although some studies [13] reported that the patency capsule can cause acute obstruction, the majority of available data [12, 14–16] especially in cases in which the Agile® patency capsule [17] was ingested, seem to suggest that this test is both safe, even in case of tight stenosis, and effective in selecting patients in whom CE could be performed safely.

6.2.2 Device-Assisted Enteroscopy

With the increased detection rate of small bowel lesions, by means of purely diagnostic procedures such as CE or radiological examinations, innovations in overtube-assisted deep enteroscopy have been crucial. Although some studies report that DAE is helpful in the diagnostic process (sometimes it is able to identify neoplastic lesions missed by other techniques) [18, 19], the main advantage of this procedure over CE is represented by its therapeutic and operative capabilities. DAE allows delivering therapies (i.e., hemostasis), but more importantly, in patients with small bowel anastomoses, to take biopsies, to place tattoos, and to perform balloon dilations.

In a recently published paper [20], the authors reported that all cases of small bowel neoplasm were histologically diagnosed on the of ground biopsies obtained during DAE and, interestingly, the tattoo placed during the procedure made the laparoscopic approach feasible in about 80 % of them.

Recent studies have also suggested a possible role for DAE in the endoscopic balloon dilation of small bowel strictures mostly in patients with Crohn's disease or ischemic enteritis [21, 22]. In these patients, where the dilation was usually performed for disease-related stenosis, the technical success rate and the complication rate range between 80–100 % and 0–6 %, respectively [23]. Nevertheless, data about long-term outcome are lacking as well as those concerning results of postsurgical strictures dilation.

As far as limitations of DAE are concerned, this procedure is invasive, challenging, and time-consuming and requires trained endoscopists and, often, deep sedation or general anesthesia with intubation. Moreover, even when guided by other diagnostic procedures (i.e., CE or radiologic techniques), DAE can fail in reaching the small bowel finding. This often requires a new examination performed through the opposite route to access the small bowel [24]. The rate of entire small bowel examination, even when performed by DBE, which, although controversial results exist, seems to be the DAE with the highest small bowel completion rate [25, 26] is on average 40–50 % [23], with a wide range between the various published studies. Last but not least, although the complication rate of DAE appears to be low; severe complications (such as pancreatitis and bowel perforation) occur in about 1 % of all diagnostic procedures, whereas the complication rate of therapeutic procedures is reported to be higher, up to 4–5 % [27, 28]. Focusing the attention on operated patients, some authors reported an increased risk of perforation in patients with recently performed anastomosis [29]. On the other hand, the abdominal adhesions, which can arise after small bowel resection, can make DAE difficult to perform, less successful in exploring the small bowel, and more risky for the patients [27].

6.3 Endoscopic Surveillance of Small Bowel Anastomoses: Timing and Protocols

6.3.1 Preventing Postsurgical Complications

The most common complication of intestinal anastomosis is the development of ulcers [30]. Anastomotic ulcers may occur a few months to many years after surgery; in the study by Weinstock and Shatz [31], focused on ileocolonic anastomoses, the mean time frame between surgery and detection of ulcer was 5.1 years. Reaction to foreign body (Fig. 6.2) has been postulated as the main cause for the ulceration [32];

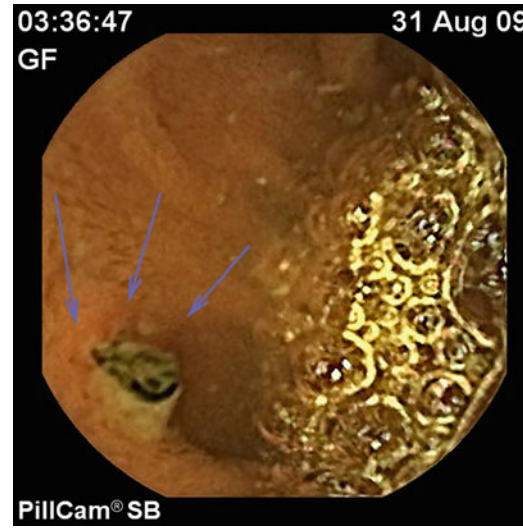

Fig. 6.2 Retained postsurgical suture at CE; *arrows* indicate the suture stitch

however, the majority of patients who have their anastomosis either with hand-sewn sutures or stapled do not develop ulcers. The local ischemia, secondary to scar formation, as well as abnormal motility and local intussusceptions, has also been advocated as mechanisms contributing to ulcer formation [30]. Although it has been postulated that some conditions (i.e., radiation therapy) can facilitate anastomotic ulceration, this complication appears to be unrelated to the clinical indication to small bowel resection and somewhat unpredictable. Therefore, although both CE (Fig. 6.3) and DAE are able to recognize the presence of small bowel anastomotic ulcers, the routine endoscopic surveillance of small bowel anastomoses, aimed at preventing this complication, is not recommended.

Conversely, at least from a theoretical point of view, there may be an indication to the endoscopic surveillance of small bowel anastomosis for those diseases with the potential for local recurrence, at the site of the anastomosis, such as Crohn's disease or small bowel tumors.

6.3.2 Crohn's Disease

Crohn's disease (CD) most commonly affects the ileocolonic region involving the small bowel up

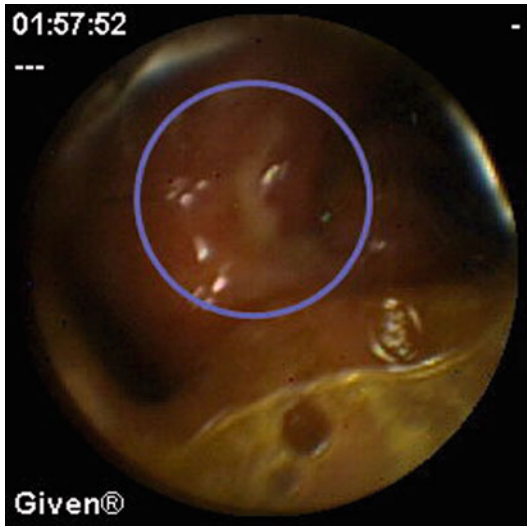

Fig. 6.3 Small bowel anastomotic ulcer at CE (inside the *blue circle* the ulcer covered by fibrin)

to 80 % of cases, while in about 30 % of patients, the disease is limited to the SB alone [33–35]. Therefore, in case of complication and/or failure of medical therapy, a significant proportion of patients with CD receive surgical interventions, and particularly ileocolonic resections, during their lifetime.

After ileal or ileocolonic resection, most patients have a postsurgical CD recurrence in the neoileum (endoscopic recurrence is indeed observed in almost 73 % of CD patients at 1 year and in 90 % at 3 years after curative resection) [36–38]. This recurrence follows a sequence of endoscopic lesions in the anastomotic and pre-anastomotic regions, followed by the development of clinical symptoms. The presence of extensive lesions in the neoileum area, identified through ileocolonoscopy in the months following surgery, predicts a rapid evolution to recurrent symptoms and eventual complications [39]. There are patient- and disease-related risk factors for postoperative recurrence: fistulizing disease, ileocolonic location, and a smoking habit increase the risk of recurrence [40–42]. Thus, these patients usually receive immunosuppressive therapy immediately after surgery. However, patients with a low risk of recurrence, such as nonsmokers and those with fibrostenotic disease, do not usually receive prophylactic treatment to prevent the development of new lesions. In such patients, clinical practice guidelines recommend that they undergo an ileocolonoscopy, grading the severity of lesions according to the Rutgeerts' score, 6–12 months after resection [43, 44]. In this setting, the feasibility, the diagnostic performances, and the safety of CE have been explored.

Some studies reported CE diagnostic performances similar to that of ileocolonoscopy in recognizing lesions located at the site of anastomosis (sensitivity and specificity of CE 50–80 % and 94–100 %, respectively) [43, 45–47]. In addition, in these studies, CE was able to depict in a relevant proportion of patients, about 60 % [45, 47], inflammatory changes in the small bowel proximal to the anastomosis, although the clinical relevance of such lesions remains to be determined. Nevertheless, in these studies, about 10 % of patients developed, over time, anastomotic strictures and they could not undergo CE because of being tested positive to a patency capsule test [46].

In patients with CD, as far as the small intestine resections are concerned, strictureplasty is often performed. This way to restore the intestinal continuity allows avoiding extensive resections and consequently the risk of short bowel, but on the other hand, it creates large dilated loops with altered motility, potentially causing capsule retention [48].

Therefore, trying to translate the data collected with CE on the evaluation of ileocolonic anastomoses to small bowel anastomoses, and taking into account possible risks (capsule retention) and the low recurrence rate (lower than that observed in ileocolonic anastomoses) [49], it seems that a surveillance program, with CE, for evaluating the small bowel anastomoses in patients with CD cannot be proposed at the present time.

In this setting one should ask whether it is worthwhile to perform DAE for evaluating the small bowel. Theoretically, in these patients, the DAE could provide the same information of CE without the risk of capsule retention (Fig. 6.4). On the other hand, we have to take into account that DAE may be difficult to perform in patients with previously abdominal operations and an increased risk of perforation

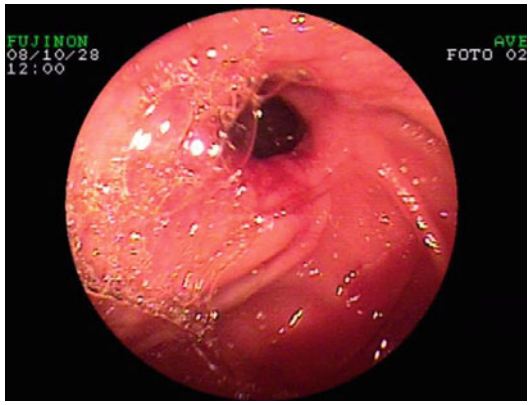

Fig. 6.4 Small bowel anastomotic stricture at DAE in a patient with Crohn's disease

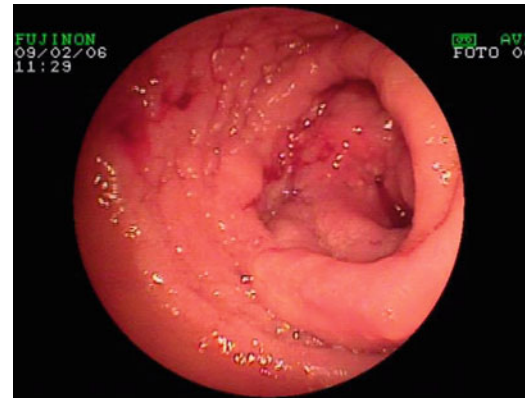

Fig. 6.5 Anastomotic recurrence of non-Hodgkin lymphoma identified at DAE

has been reported in case of severe inflammation of the small bowel wall and recently performed anastomoses [27].

Unfortunately, to the best of our knowledge, there are no studies that have specifically addressed this type of assessment and this may represent an area for future research [50].

Endoscopic balloon dilation of small bowel strictures by DAE has the potential to obviate surgery in carefully selected patients [35, 51]. One study [52] showed that, an anastomotic stricture is an independent marker of the symptom-free outcome after enteroscopic balloon dilations. This emphasizes that, even with the limitations above mentioned, DAE has the potential to improve outcome of patients who previously underwent small bowel surgery.

6.3.3 Small Bowel Tumors

Small bowel tumors are a small proportion of gastrointestinal neoplasms; accounting for 1–3 % of all primary gastrointestinal tumors [53]. Nevertheless, recent studies suggest that the incidence of these diseases is increasing [53, 54]. Among malignant tumors, about 30–50 % are adenocarcinomas, 25–30 % are carcinoids, and 15–20 % are lymphomas [54]. As long as for some subtypes of small bowel lymphomas (i.e., follicular lymphoma) at the early stage, chemotherapy has been proposed as the primary curative therapy [55, 56], in the majority of cases, the surgical intervention, with en bloc resection, remains the cornerstone for the treatment of small bowel neoplams. Bilimoria et al. [54], collecting over the last 20 years more than 67,800 patients diagnosed with small bowel neoplasm, reported that about 80 % of them received surgical intervention. These data have also been confirmed by a recently published study [57] in which, in 141 patients with small bowel neoplasms, a segmental bowel resection was the most commonly used surgical procedure (about 70 % of cases).

After surgical resection, despite the differences between the various neoplasms, the restaging is usually carried out with imaging modalities (e.g., CT scan and/or FDG PET for lymphoma). There are no data, however, at present about the systematic use of CE or DAE in the follow-up of these patients.

The main limitation of CE in this specific setting, as reported above, is its low specificity (difficulty in distinguishing between surgical outcomes, postsurgical complications, or possible local recurrence of primary disease). This limitation could be easily overcome by DAE, which has also shown, at the time of the diagnosis, a diagnostic yield that, in some cases (i.e., lymphomas) (Figs. 6.5 and 6.6), was higher than that of other diagnostic methods (i.e., radiological) commonly used in the process of staging and restaging [58, 59].

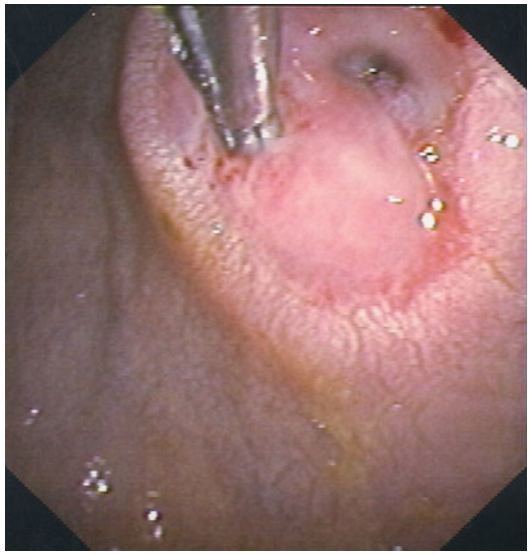

Fig. 6.6 Biopsy by DAE on a small bowel anastomotic stricture in a patient with recurrence of non-Hodgkin lymphoma

Conclusions

So far, CE and DAE have been mainly used, in patients with small bowel resections, when complications or recurrence of the primary disease were suspected and imaging techniques resulted negative. Robust evidence about the possible role of these techniques as surveillance tools is lacking at the present time.

On the one hand, CE seems to be an ideal tool for a surveillance program (noninvasive, easy to perform, with high diagnostic yield), while on the other hand, it has some limitations (low specificity, risk of retention), hampering its application in this subset of patients. DAE could overcome CE limitations, allowing to perform biopsies, to place tattoos, and to dilate strictures; nevertheless, it is invasive, challenging, and burdened by possible serious complications.

It is conceivable that, in the near future, in patients who underwent small bowel surgery and deserve surveillance over time (i.e., Crohn's disease patients), a combination of CE (once patency is proven) and DAE would represent the method of choice. These issues warrant future research.

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7 Timing and Protocols of Endoscopic Follow-Up in Operated Patients After Colorectal Surgery

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7.1 Introduction

Endoscopic follow-up (FU) after *colorectal surgery* remains controversial, and it is addressed mainly to patients operated on for *colorectal cancer* (CRC). CRC is the third most common cancer in the US, where this type of cancer was diagnosed in 140,000 individuals during 2012 [1]. Similarly, in Europe, CRC is the second most frequent cancer, with 376,400 incident cases diagnosed in 2004 [2]. Approximately two-thirds of patients with CRC undergo curative surgery, and every year 230,000 Western patients are entered into follow-up [3].

Endoscopic FU has the objective to detect both early recurrences and metachronous colorectal adenomas and/or cancer in order to increase survival among CRC survivors [4]. In fact, endoscopic FU does not improve survival from recurrent colon cancer, while it is useful in the detection of luminal recurrences in patients with rectal cancer who underwent either endoscopic or surgical resection, because of high recurrence rates [4–8]. The most significant potential benefit of endoscopic FU is the prevention of metachronous cancer, by means of

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identification and removal of metachronous adenomas, or the detection of such cancers at an early, curable stage, with a reduction of risk of death among CRC survivors [4, 5, 9].

In recent years, several organizations have published guidelines and subsequent updates with their recommendations for endoscopic surveillance of patients after CRC surgery [4, 7, 8, 10–14]. Despite these published guidelines, there is both overuse and underuse of endoscopic surveillance, and many physicians often refer their patients for endoscopic surveillance procedures that are not indicated [15–19]. This testifies a certain lack of familiarity with the recommended FU protocols, and many institutions continue to have their own surveillance regimens [20].

There are several questions that need to be answered regarding the *appropriateness* of endoscopic FU, its *timing*, its *duration*, and its *cost-effectiveness*. This chapter will summarize recent literature, with the purpose to examine the role of endoscopic FU for the surveillance of CRC survivors in the current era of specialized care.

7.2 Is Endoscopic Follow-Up After Colorectal Surgery Appropriate?

After curative resection of CRC, it is common clinical practice to follow the patients according to standardized FU programs which include several tests to screen for *local recurrences*, *distant metastases*, and *metachronous neoplasia* [21]. FU is considered crucial to improve survival of CRC survivors detecting lesions suitable for radical surgery [3]. This raises the question about appropriateness of endoscopic FU, which is an important component of the current recommended surveillance regimens [4, 7, 8, 10–14]. Candidates for endoscopic FU are those patients with stage I, II, or III CRC or patients with stage IV CRC who have undergone surgery with curative intention [4, 8, 10–12, 22].

Endoscopic FU should allow diagnosis of early anastomotic recurrences and metachronous adenomas and/or cancers in patients operated on for CRC [23]. In regard to the detection of early recurrence, a distinction should be made between rectal and colon cancer based on different rates of local recurrences reported for these two types of cancer [24, 25]. Anastomotic recurrences occur in 2–4 % of operated patients with colon cancer, and they are usually associated with metastatic intra-abdominal or pelvic disease [20, 24–27]. Therefore, endoscopic surveillance of the colonic anastomosis does not have any survival benefit for the patients, and colonoscopy should not be performed for this purpose [4, 12]. On the other hand, there is a rationale for endoscopic surveillance after surgery for rectal cancer, because local recurrences occur in 2–30 % of patients, and they are usually detectable within 30 months from surgery [7, 24]. Recently, the rate of recurrence after surgery for rectal cancer has been significantly lowered by the combination of total mesorectal excision and neoadjuvant chemoradiation [28]. However, this practice is limited to tertiary centers and the rate of local recurrences in rectal cancers survivors is still elevated worldwide. Therefore, endoscopic FU of colorectal anastomosis is recommended for patients operated on for rectal cancer [4, 12]. According to the recent guidelines, those patients operated on for *rectal cancer*, who did not receive neoadjuvant chemoradiation and who did not undergo mesorectal excision, should be periodically followed by means of *sigmoidoscopy* [7]. The latter might be associated with *endoscopic ultrasound* (EUS), which has shown to be accurate for the diagnosis of local recurrence at a resectable stage [29]. The major limitation of EUS is its poor specificity due to postoperative and/or postradiation mucosal inflammation. This can be overcome by the use of transrectal EUS-guided biopsy, which brought the detection rate for anastomotic recurrence from 79 to 100 % in a recent study [30]. Thus, EUS can be useful in diagnosing an extra-luminal tumor recurrence, which cannot be detected by routine endoscopic surveillance; however, its impact on patient's long-term survival is unknown [7].

After CRC surgery, the major indication for endoscopic FU remains the detection of metachronous adenomas and/or cancer [4, 7, 8, 10–14]. If colonoscopic clearing is performed at the time of CRC diagnosis, any lesion found at endoscopic FU is metachronous, although it is possible that some

adenomas and even early CRC are synchronous lesions which were missed during the perioperative endoscopy. Patients operated on for CRC are at high risk for metachronous adenomas, whose incidence ranges from 8 to 46 % during the average FU of 3 years, with a cumulative 3-year incidence rate of 31 % [31]. The risk of metachronous adenomas and/or CRC is higher in patients who had synchronous adenomas at the time of surgery [31–34]. Indeed, among clinical and endoscopic risk factors, the presence of advanced synchronous adenomas is the strongest predictor for future development of advanced metachronous adenomas and/or cancer [32]. These data support the recommendation for an appropriate clearing colonoscopy before or immediately after CRC surgery, since approximately 50–60 % of patients have *synchronous adenomas* and *synchronous CRC* is diagnosed in 2–7 % of cases at the time of perioperative colonoscopy [4, 7–14, 31–34]. Therefore, if synchronous CRC has been ruled out, all subsequently identified CRCs are metachronous. The latter have a cumulative incidence of 1.5 % at 5 years, and many of these cancers are found within the first 2 years after surgery, with an incidence rate of 0.7 % in this time frame [35]. It has been reported that 157 colonoscopies are needed to diagnose one metachronous cancer during endoscopic FU, after CRC surgery [4, 11]. This rate is cost-effective when considering that the majority of metachronous cancers are asymptomatic, stage Dukes A or B lesions, and are resectable for cure in 80 % of cases [4, 11, 12, 34–36].

The data available from published studies and systematic reviews for endoscopic surveillance after CRC resection indicate a minor improvement of *survival rates* with endoscopic FU, which is considered appropriate and cost-effective for the detection of metachronous advanced adenomas and/or CRC and recurrent rectal cancer (Table 7.1) [4, 5, 7–14, 35–37].

Table 7.1 Objectives of endoscopic follow-up after surgery for colorectal cancer

Colon cancer	Rectal cancer
Detection and removal of metachronous adenomas	Detection and removal of metachronous adenomas
Diagnosis of early metachronous cancer	Diagnosis of early metachronous cancer
	Diagnosis of anastomotic and/or endoluminal recurrences[a]

Modified form Refs. [4] and [12]
[a]Only patients who did not undergo neoadjuvant chemoradiation and mesorectal resection at time of surgery

7.3 How Frequent Should Endoscopic Follow-Up Be?

Endoscopic FU is an established procedure in the surveillance protocols for patients operated on for CRC. However, despite the published *guidelines,* there is a high variability in the use of endoscopic surveillance following CRC surgery [15–19, 38–41]. Some studies have reported a suboptimal endoscopic FU, which has been related to patient characteristics like older age, presence of comorbidity, different ethnicity, and advanced stage of CRC [40–42]. Other studies have shown that many physicians have little familiarity with the published guidelines, with subsequent overuse or underuse of endoscopic FU [15–17, 19]. Besides the variable patterns of surveillance, the alarming data is that approximately 30 % of CRC survivors do not undergo any endoscopic FU within 3 years from surgery [41].

There is a certain variability about the *timing* of endoscopic FU after CRC surgery among the most recent published guidelines, which all recommend performing the first *surveillance colonoscopy* 1 year after surgery (Table 7.2) [4, 7, 12–14]. This recommendation originates from several studies that reported a high frequency of both metachronous advanced adenomas and cancer within the first 2 years after CRC surgery [4, 9, 31–35, 43, 44]. Moreover, the observation that local recurrences of rectal cancer occur within 30 months from surgery supports the need of intensive endoscopic FU of the anastomosis, starting at 6 months after rectal cancer surgery [7, 24, 44]. Recent studies have confirmed that the best interval between the first colonoscopy and CRC surgery is 1 year, provided that appropriate clearing of the colon has been achieved in the perioperative period [45–47].

While the time of the first endoscopic FU has been clearly established, there is still uncertainty

Table 7.2 Summary of the latest guidelines for surveillance colonoscopy among CRC survivors

Recommending agency	Timing of first colonoscopy	Subsequent colonoscopies
American Cancer Society	1 year after surgery or 1 year after postoperative clearing colonoscopy	at 4 and 9 years after surgery; then every 5 years
American Society of Gastrointestinal Endoscopy	1 year after surgery or 1 year after postoperative clearing colonoscopy	at 3 and 5 years after surgery; then every 5 years
European Society of Gastrointestinal Endoscopy	1 year after surgery or 1 year after postoperative clearing colonoscopy	at 3 years after surgery; then every 5 years

American Cancer Society = Refs. [4] and [12]; American Society of Gastrointestinal Endoscopy = Ref. [7]; European Society of Gastrointestinal Endoscopy = Ref. [13]
These recommendations assume that follow-up colonoscopy is normal. If adenomas are detected, the interval of follow-up can be varied according to the pathological diagnosis of the adenoma
Additional endoscopic follow-up is recommended for those patients with prior rectal cancer who did not undergo neo-adjuvant therapy and mesorectal excision at the time of surgery, according to the following schedule: flexible sigmoidoscopy ± EUS every 3–6 months for 2–3 years

about the appropriate interval between subsequent colonoscopies for CRC survivors. Initial reports suggested that intensive endoscopic FU was beneficial for CRC survivors, improving their *overall survival* rate [48–50]. However, the results of several studies have shown that intensive endoscopic FU with frequent surveillance colonoscopies does not give a clear clinical benefit to CRC survivors, and therefore a reduction in frequency of the endoscopic FU after CRC surgery is appropriate [25, 51–55]. These observations support the recommendation of the current guidelines which suggest either surveillance colonoscopies at 3 and 5 years after the first normal endoscopic FU at 1 year from surgery or an interval of 3 and then 5 years after subsequent normal surveillance colonoscopies, following the first examination performed 1 year after surgical resection of CRC [4, 7, 12–14] (Table 7.2).

Recently, it has been proposed that endoscopic FU should be tailored for CRC survivors according to factors associated with an increased risk for metachronous cancer and/or local recurrence [56]. Some *risk factors* are related to the patient like older age, obesity, cigarette smoking, and alcohol intake, while others are linked to CRC like its distal location, microsatellite instability, and the presence of synchronous lesions [31–33, 57–59]. The only significant risk factor for metachronous advanced adenomas and/or cancer is the presence of synchronous adenomas at the time of perioperative colonoscopy [31–33, 57, 58]. According to these data, patients who undergo curative resection for CRC and have no synchronous neoplasms or have synchronous tubular *adenomas* without *advanced features* (Table 7.3) are at lower risk of developing metachronous adenomas and/or cancer [32, 57, 58]. For these patients a less intensive colonoscopic surveillance program may be appropriate, with a surveillance colonoscopy every 5 years, after the first normal endoscopic FU [4, 12, 52]. On the contrary, the presence of advanced synchronous adenomas at the time of perioperative colonoscopy carries a high risk of subsequent advanced metachronous neoplasia during the endoscopic FU, which therefore should be more frequent [32, 57]. These patients should undergo surveillance colonoscopy at 3 and 5 years after the first normal endoscopic FU, provided that no *high-risk* metachronous *adenomas* are diagnosed [7]. If this is the case, CRC survivors should undergo subsequent FU colonoscopy 1 year after the diagnosis of advanced adenoma, while the diagnosis of *low-risk* metachronous *adenomas* is indication for a 3-year repeat colonoscopy [9, 12, 53, 60]. Therefore, the findings at the time of surveillance colonoscopies will further tailor the endoscopic FU, modifying it according to the presence or the

Table 7.3 Features of colorectal adenomas

Low-risk adenomas	High-risk adenomas
No more than three adenomas	Multiple adenomas (≥3)
Size < 1 cm	Size > 1 cm
Tubular histology	Villous or tubulovillous histology
Low-grade dysplasia	High-grade dysplasia

Modified form Ref. [13]

absence of metachronous adenomas and to their features [9, 12, 14, 32, 55].

Patients with prior rectal cancer should undergo a tailored endoscopic FU, which is based on the type of surgery and the administration of neoadjuvant chemoradiation. Postoperative surveillance sigmoidoscopy is not recommended in patients treated with neoadjuvant chemoradiation and mesorectal excision, given the decreased likelihood of local cancer recurrence [7]. These patients should undergo standard endoscopic FU. On the contrary, an intensive endoscopic FU with sigmoidoscopy ± EUS every 3–6 months, for the first 3 years after surgery, is highly recommended for patients with rectal cancer who have undergone surgery without mesorectal excision and neoadjuvant chemoradiation [7, 60]. This intensive endoscopic FU helps to identify resectable local recurrences; however, it has not been shown to improve patient's survival, and its only rationale is the high rate of local recurrences within the first 2–3 years from rectal surgery [4, 7, 24, 61]. Finally, a tailored approach is mandatory for patients with inherited syndromes of CRC. Hereditary non Polyposis Colorectal Cancer (HNPCC) patients diagnosed with CRC should undergo proctocolectomy, because of the high risk of metachronous cancer, which is 25 % after segmental colectomy and 8% after total colectomy with ileorectal anastomosis [62–64]. However, many HNPCC patients still undergo either segmental colectomy or total colectomy with ileorectal anastomosis, and therefore they require yearly surveillance colonoscopy or rectoscopy to remove premalignant adenomas [62–64]. Similarly, patients with Familial Adenomatous Polyposis (FAP) require strict endoscopic FU of the *rectal stump* or the *ileal pouch* [62, 65, 66]. Rectal cancer has been reported in 17 % of FAP patients with ileorectal anastomosis and in 8 % of cases with an ileal pouch [65]. These data confirm the recommendation that FAP patients should undergo intensive endoscopic FU, which forecast a *proctosigmoidoscopy* every 6–12 months, according to the number of adenomas detected [62, 65, 66].

7.4 How Long Should Endoscopic Follow-Up Last?

According to the natural history of CRC, FU should be discontinued 5 years after surgery [67]. However, the published guidelines recommend long-term endoscopic surveillance of CRC survivors because they have a lifelong risk of developing metachronous CRC [4, 7, 8, 10–14, 34, 68–73]. A retrospective study reported that metachronous CRCs occur in approximately 30 % of patients 5 years after the resection of the primary CRC [34]. The authors of another retrospective study calculated that the *cumulative risk* of metachronous CRCs ranges from 2 %, for 5 years CRC survivors, to 7 % for those patients who are alive 20 years after colorectal surgery [73]. Therefore, the risk of developing metachronous CRCs seems to increase continuously over time, after surgical resection of the primary CRC. Metachronous CRCs occur from 1 to 25 years after surgery among various studies, and this data justifies a lifelong endoscopic FU [34, 68–73]. The latter may explain the high rate of resectable metachronous CRCs which are diagnosed at an early stage, as compared to the general population [72, 73]. However, endoscopic FU does not prevent the occurrence of metachronous cancers in CRC survivors, probably because patients with a history of CRC cancer may differ biologically from patients with adenomatous polyps and are at higher risk for metachronous cancer [69]. This hypothesis is supported by the observation that the incidence rate of metachronous cancer in

CRC survivors is 6.8 times higher than that observed among patients in the National Polyp Study Group [69]. Another possible explanation is a suboptimal *adenoma detection rate* during surveillance colonoscopy, due to several factors which are mainly related to the quality of *bowel preparation*, the cooperation of the patients during the exam, and the skills of the endoscopist [74]. All these factors reflect the imperfect nature of endoscopic FU and its possible failure to always accurately examine the entire colon at the time of a surveillance colonoscopy.

Provided that long-term endoscopic FU is mandatory and must be continued after the first 5 years of surveillance, CRC survivors should undergo a *colonoscopy* every 5 years, if the exam is normal, until the benefit is outweighed by comorbidity [14]. Indeed, the potential benefit of the endoscopic FU should be weighed against the potential risks of diagnostic and operative colonoscopy. Given bleeding and perforation risks of 2.0 and 0.38 %, respectively, and a 5-year cumulative prevalence of non-advanced adenomas of 56.6 %, it has been estimated that 4 % of the CRC survivors will suffer from a major *complication* after 3 subsequent surveillance colonoscopies [75, 76]. This complication rate should be weighed against the substantially reduced potential survival benefit granted to elderly CRC survivors from removal of metachronous adenomas [77]. *Elderly* patients often have significant concomitant illnesses which increase the risk of death. These competing causes of death can overwhelm any benefit of endoscopic FU for CRC survivors older than 65 years of age [78]. Therefore, discontinuation of endoscopic FU should be considered in elderly CRC survivors and/or in presence of *comorbidities* according to the physician's judgment [4, 7, 12, 13].

7.5 Is Endoscopic Follow-Up Cost-Effective?

The potential benefits of endoscopic FU after surgical resection of CRC include improved *overall survival*, better monitoring of *outcomes*, identification of other treatable colorectal lesions diagnosed during surveillance, and greater psychological support of the patients [5, 9, 78, 79]. These benefits must be carefully weighed against the potential negative physical, financial, and psychological consequences of postoperative surveillance of CRC survivors; moreover, *cost/benefit ratio* of the FU should be sufficiently favorable to justify its routine use [80].

According to an estimate of the British National Health System, endoscopic FU included in a postoperative surveillance regimen lasting 5 years is not cost-effective because of its uncertain benefit [14]. On the other hand, two recent retrospective studies reported that CRC survivors who undergo endoscopic FU appear to have improved survival, providing the strongest evidence to date of the effectiveness of endoscopic surveillance for CRC survivors [5, 9]. As previously stated, the number of colonoscopies needed to detect a metachronous cancer in CRC survivors, irrespectively of the time of diagnosis, is 157, with a relatively high cost of endoscopic FU [4, 12]. However, the possibility of diagnosing metachronous CRCs leads to significant improvement in life expectancy of CRC survivors, and this compensates for the relatively high costs of endoscopic FU [35]. Similarly, using a decision model analysis, it has been demonstrated that performing colonoscopy 1 year after colorectal surgery for CRC is a cost-effective option [35]. Therefore, endoscopic FU seems to be a highly cost-effective strategy in terms of metachronous CRCs detection and cancer-specific death prevention.

Conclusion

Endoscopic FU is a crucial component of *postoperative surveillance* of patients operated on for CRC. It has been shown to be *cost-effective* because it is capable of improving survival of *CRC survivors* at a relatively affordable economic and social cost. Despite the published guidelines, its timing is still uncertain and most likely the best strategy is to tailor endoscopic FU, according to the find-

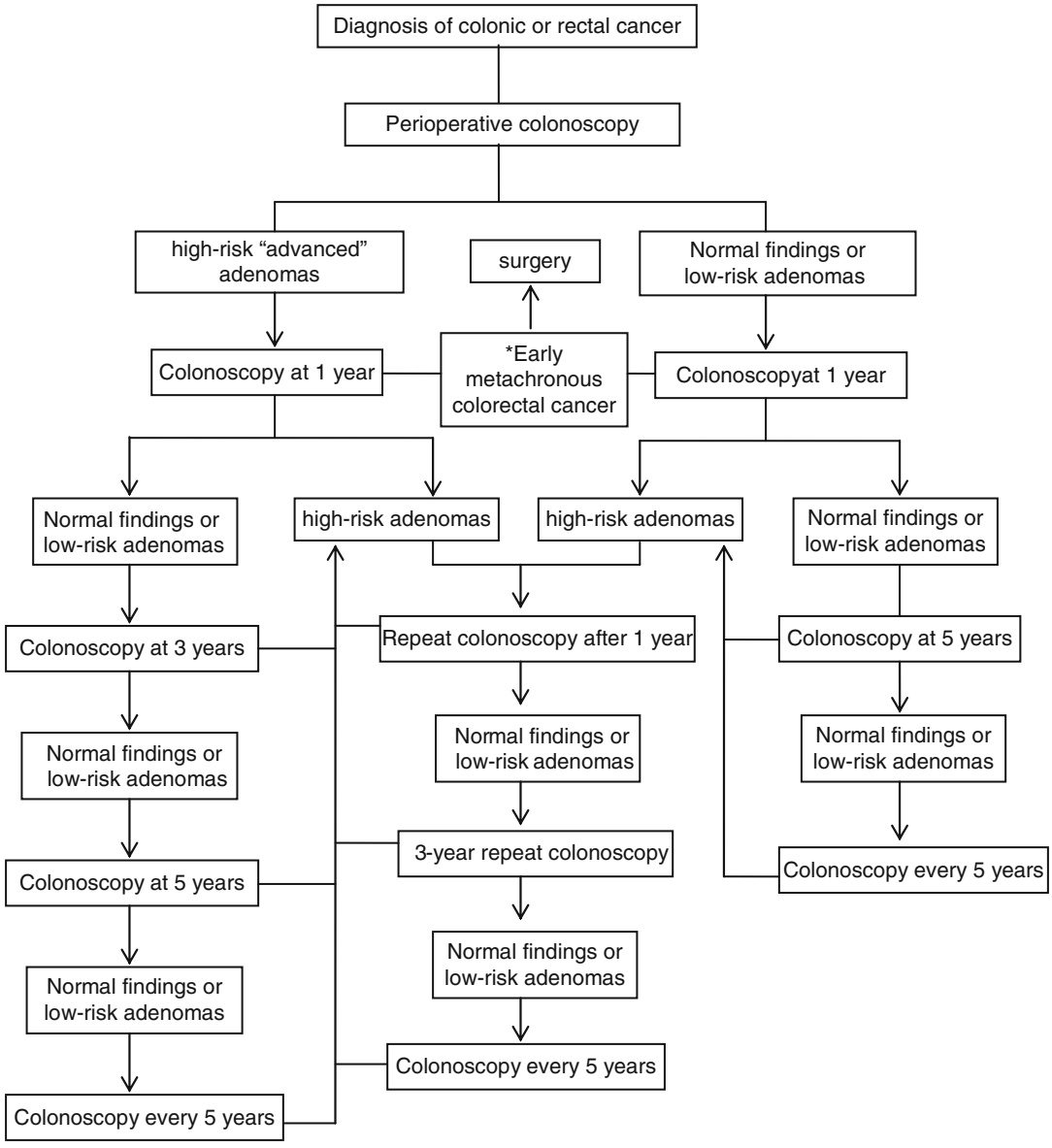

Fig. 7.1 Proposed algorithm for a tailored endoscopic follow-up of CRC survivors. *The diagnosis of early metachronous cancer is indication for surgery at any time during endoscopic follow-up. HNPCC patients who undergo segmental colectomy require yearly surveillance colonoscopy. Endoscopic FU will be continued until the benefit is outweighed by comorbidity

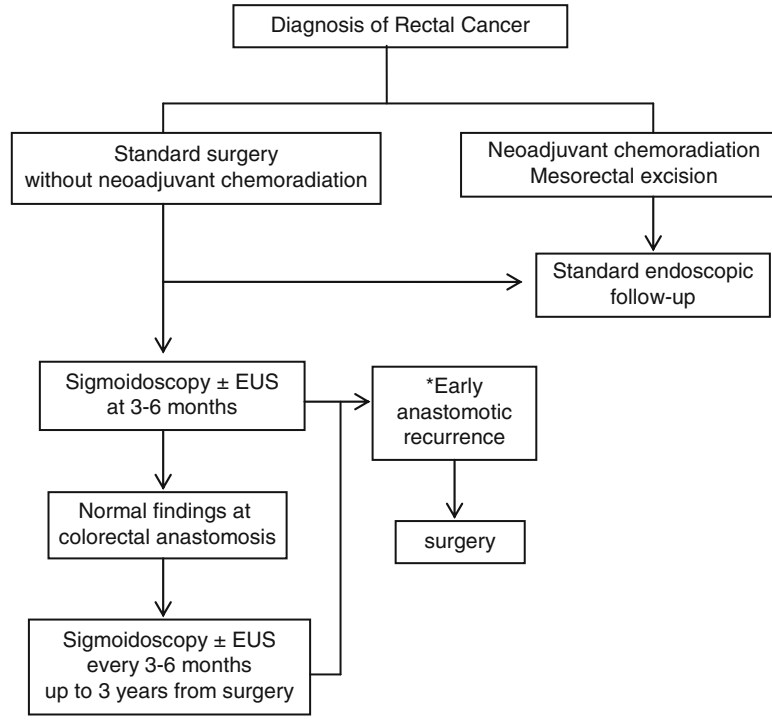

Fig. 7.2 Proposed algorithm for additional tailored endoscopic follow-up of CRC survivors after rectal surgery. *The diagnosis of early anastomotic recurrence is indication for surgery at any time during endoscopic follow-up. HNPCC patients who have undergone total colectomy with ileorectal anastomosis require yearly surveillance proctoscopy. Operated FAP patients require strict endoscopic FU of the rectal stump or the ileal pouch. FAP patients should undergo proctosigmoidoscopy every 6–12 months, based on the number of adenomas detected during the exam

ings of both perioperative colonoscopy and surveillance endoscopies (Figs. 7.1 and 7.2).

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8 Intraoperative Endoscopy in the Evaluation of Digestive Anastomoses

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8.1 Introduction

Most GI tract surgical interventions require anastomotic procedures which are associated with complications such as leakage, bleeding, impaired transit, or strictures. Since the 1970s, intraoperative endoscopy was applied as a diagnostic tool during colorectal surgery to help the surgeon locating the exact area of interest [1–3]. Afterwards, intraoperative endoscopy has been utilized for evaluation of patency and integrity of GI tract anastomoses during the surgical procedure [4, 5]. Since endoscopic intraoperative anastomotic testing allows direct visualization of anastomosis, complication rates can be reduced by the use of this technique.

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8.2 Intraoperative Endoscopy in Upper GI Tract Surgery

8.2.1 Gastric Bypass

Morbid obesity is a global epidemic. As the demand for bariatric surgery increases, endoscopy is being increasingly used both intra- and postoperatively.

In 1994, Wittgrove et al. [6] introduced laparoscopic Roux-en-Y gastric bypass (LRYGBP). Anastomotic leakage is the most serious early postoperative complication following LRYGBP. Leakage can occur at the gastrojejunal anastomosis, at the gastric pouch, or at the jejunojejunal anastomosis. The commonest site for a leak after a LRYGBP is the gastrojejunal anastomosis (GJA) site with reported incidences from 0 to 5.2 % [7–10].

The detection of early postoperative leaks traditionally was based on upper GI series. Intraoperative assessment of the GJA, however, in a study performed in 245 patients (Madan et al.) showed that an upper GI series has a sensitivity of 75 % and a positive predictive value of 67 % in the detection of anastomotic leaks [11].

The main advantage of intraoperative endoscopy is that it can be used not only to detect leaks but also to treat them in the operating room. Moreover, intraoperative endoscopy can also ensure that the anastomosis isn't too tight. To treat leaks from the GJA and from the gastric pouch, application of fibrin sealant, bovine pericardial strips, and omental patches has been used with variable success [12–14].

Fernandez et al. [15] analyzed more than 3.000 patients undergoing gastric bypass surgery and identified GJA leakage as an independent risk factor associated with postoperative mortality besides weight, hypertension and the type of bypass operation.

A number of techniques have emerged over the years to eliminate anastomotic or staple-line disruption. In the past, postoperative leaks were detected intraoperatively for GJA by simple visualization of the anastomosis by the surgeon. Later on, air insufflation under saline or methylene blue instillation was used, but more recently various groups have used intraoperative endoscopic examination of the anastomosis.

Methylene blue can be instilled through a nasogastric tube or even through an upper GI endoscope, with the patient in the anti-Trendelenburg position [16]. The nasogastric tube is positioned in the gastric pouch and the jejunum is occluded. However, the technique is demanding and retesting is problematic as the tissue remains stained after the first evaluation.

Ramanathan et al. [17] compared endoscopy to the methylene blue test and found the low pressure infusion of methylene blue to be less sensitive to leak detection than air insufflation by endoscopy. This study showed that a 10 % incidence of leaks was reduced to 3.8 % owing to suture strengthening after intraoperative gastroscopy (IOG).

Champion et al. [10] demonstrated that postoperative leakage can be reduced from 3.8 to 0.36 % with the aid of IOG.

With the advent of intraoperative endoscopy, many surgeons raised a concern that the insufflation caused by the endoscope may damage the anastomosis. There is also a concern raised that insufflation of air during IOG may produce more false-positive air leak test. Mohos et al. [18] showed that the pressure leading to damage of the staple line in the animal model is more than three times higher than the maximal pressure measured in humans during IOG. However, the recent use of CO_2 insufflation instead of air will probably solve these problems.

Intraoperative endoscopy has been shown to reduce postoperative morbidity. One study has reported a 0 % postoperative anastomotic leakage rate in more than 250 patients using IOG [8]. In 340 patients who underwent LRYGB, Sekhar et al. [12] found no postoperative leaks because 56 intraoperative leaks were detected and corrected by IOG. In a study assessing 400 patients undergoing LRGYB, Alaedeen et al. demonstrated that IOG reduced postoperative leak rates from 4 to 0.5 % and mortality from 1 to 0 % [19].

GI bleeding is another important complication after gastric bypass surgery. The incidence can vary from 0.5 % for open procedures to 4.4 % for the laparoscopic approach. Intraluminal bleeding can occur during intervention from any of the staple lines and can be missed unless an IOG is carried out [6, 10].

– Technique for IOG During Laparoscopic Gastric Bypass

The upper esophageal sphincter is intubated under vision. Occasionally a jaw thrust may be of help during the introduction of the endoscope. The proximal pouch is initially inspected, and then the endoscope is gently guided through the anastomosis into the Roux limb. A bowel clamp is placed on the intestinal limb distal to the GJA. The table is leveled and operative field containing the anastomoses is filled with sterile normal saline to cover the proximal pouch and anastomosis. The area is then irrigated until it is cleared from blood and operative debris. The gastroscope is then withdrawn into the proximal pouch, and the anastomosis reinspected with continuous insufflation. Before withdrawal the air that has been introduced is aspirated completely. In case of persistent air leak, the endoscope is left in situ till the repair of gastrojejunostomy suture line. The procedure is repeated.

What can go wrong during an intra–operative endoscopy is shown below:

1. *An intraoperative gastroscopy has to be carried out with due care especially during intubation of the esophagus. Intubation must be carried out under vision to avoid pharyngeal tears.*
2. *In gastric bypass surgery, the proximal gastric pouch should be examined carefully to prevent pouch tear, and this can be done by ensuring that the gastroscope controls are in the unlocked position.*
3. *It is mandatory to carefully perform endoscopic maneuvers and air insufflation in order to avoid an important complication that can occur during IOG well described in some cases report: air embolism can occurred in patients of all ages in association with an interruption in the mucosal barrier* [20, 21].

8.2.2 Other Gastric Interventions

Besides LRYGB, vertical banded gastroplasty, sleeve gastrectomy, laparoscopic adjustable gastric bands, and placement of gastric pacemakers can also be assisted with intraoperative endoscopy to minimize early complications [10].

Usefulness of IOG during sleeve gastrectomy for obesity was demonstrated by Frezza et al. in 2008. They used a 29 F endoscope instead of bougies in order to caliber the anastomosis width and to help in the sleeve gastrectomy procedure [22].

No report has been published about the use of intraoperative endoscopy during videolaparoscopic GIST removal. At the New S. Agostino-Estense Hospital in Baggiovara-Modena (Italy), we elected to routinely perform IOG during laparoscopic removal of gastric GIST located in the gastric body or fundus wall (Fig. 8.1). In our experience (10 cases), after adoption of IOG leakages and early hemorrhages were not registered. The only adverse event that we registered was entrapment of the endoscope in the stapler valves that was immediately resolved without further complication.

Finally, IOG has also been proved useful in patients undergoing total gastrectomy for gastric cancer [23, 24].

8.3 Intraoperative Endoscopy in Colorectal Surgery

Anastomotic complications such as leakage and bleeding still represent the most serious complications of laparoscopic colorectal surgery. Intraoperative colonoscopy allows detection of the bleeding source and of leaks. Surgeons have tried testing the anastomosis, especially in the distal colon and rectum by using rectal probes filled with air [25–27] or saline [28–30] or by using methylene blue enema [31]. Adopting intraoperative endoscopy, the pelvis is filled with saline and air is insufflated in the rectum using a sigmoidoscope. The presence of air bubbles indicates anastomotic leaks which can be repaired without delay. In a recent study carried out in 60 patients, intraoperative air testing of colorectal anastomosis proved to be an effective method for prevention of anastomotic dehiscence, incidence being 50 % lower in comparison with the control group [32]. A more novel and recent application of intraoperative endoscopy to evaluate the adequacy of GI anastomoses is based on narrow band imaging (NBI). As vascularization is the primary factor determining anastomotic viability, NBI could prove useful to ascertain tissue vascularity after the anastomotic procedure [33].

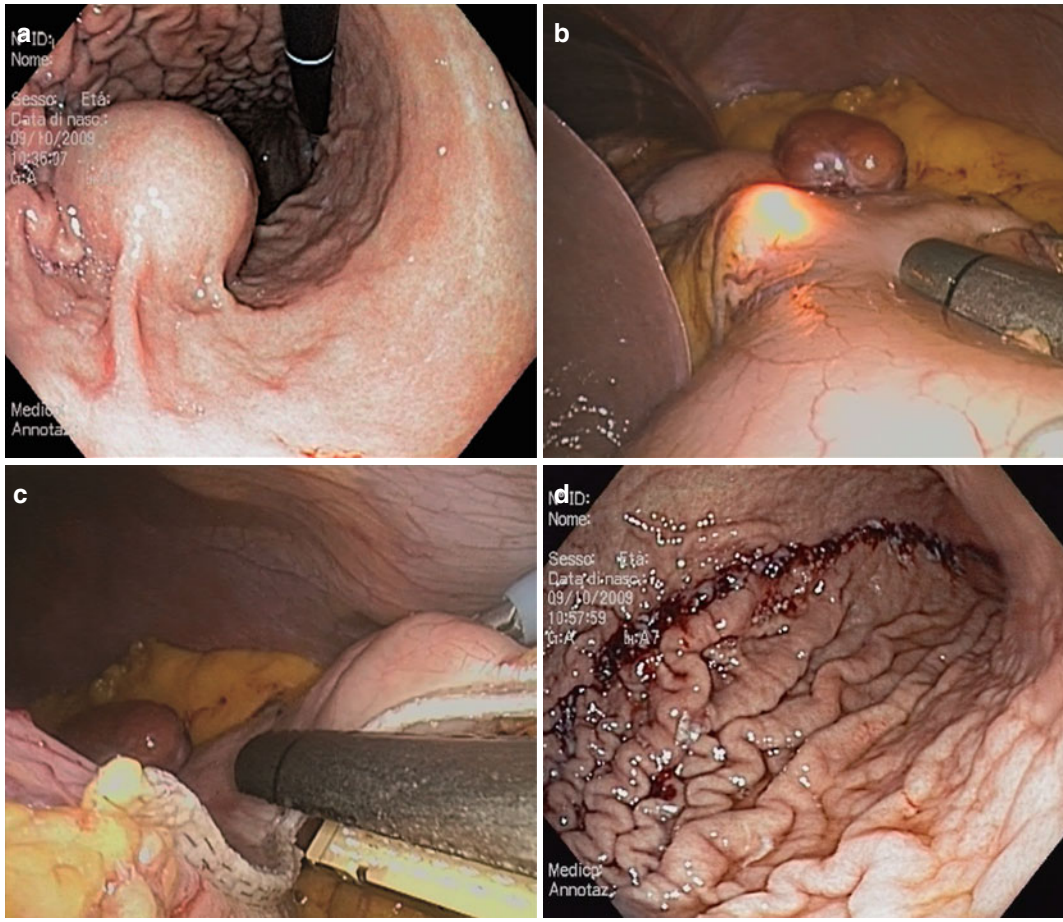

Fig. 8.1 Endoscopic assisted of video-laparoscopic sleeve gastrectomy for GIST removal. Endoscopic view of gastric GIST (located on the anterior wall of the fundus) obtained during intraoperative upper GI endoscopy performed to help the surgeon (**a**). Laparoscopic view during abdominal access showing the gastroscope into the gastric lumen in order to assess the surgical anastomosis during sleeve gastrectomy (**b**). Laparoscopic stapler performing cutting along the large curvature of the stomach (**c**). Step-by-step endoscopic control surgical anastomotic/staple line resulting after laparoscopic sleeve gastrectomy (**d**)

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Contribution of Endo-ultrasonography

9

Vincenzo Napolitano, Maria C. Bondanese, and Manuela Avellino

9.1 Introduction

The potential role of endo-ultrasonography in the follow-up of gastrointestinal anastomoses mainly concerns the diagnosis of *local recurrences* after surgical resection of esophageal, gastric, or rectal cancer.

Despite the introduction of new modalities of treatment (multimodal therapy) and the improvement of surgical techniques, local recurrences still represent a significant problem, though their incidence ranges widely depending on many factors such as the initial stage of the disease, hospital case load, and surgeons' procedure volume.

At least for rectal cancer, some patients with local recurrence can undergo a reoperation with a curative intent but only on the condition of making a diagnosis as early as possible. Most of the local recurrences are perianastomotic with no or very late mucosal involvement, so the lesion is not accessible for an endoscopic biopsy procedure.

Endo-ultrasonography can overcome the diagnostic limits of endoscopy permitting the evaluation of both the gastrointestinal wall and the adjacent organs.

Before discussing the diagnostic yield of EUS in the follow-up of gastrointestinal anastomoses, it is useful to briefly describe the instruments and technical principles of endo-ultrasonography.

9.2 Technical Aspects of Endo-ultrasonography

Different types of instruments are currently available to perform endo-ultrasonography. There are flexible and rigid instruments. The latter, which are blind ultrasound probes, can only be used for *transrectal ultrasonography* (*TRUS*).

Flexible instruments (echoendoscopes) have been conceived for *endoscopic ultrasound* (*EUS*), an imaging technique that combines both endoscopy and ultrasound in one. There are radial echoendoscopes which provide a 360° image scanning plane perpendicular to the long axis of the instrument and linear echoendoscopes which provide a scanning plane which is parallel to the long axis of the scope. These types of instruments allow real-time visualization of a needle introduced in the operative channel,

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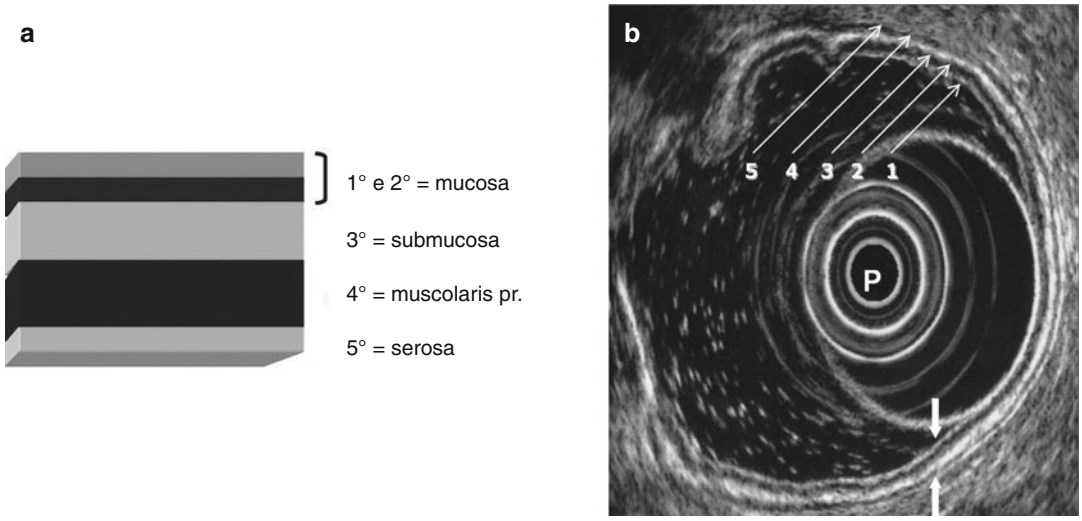

Fig. 9.1 Correspondence between endo-ultrasonographic (**a**) and anatomical (**b**) layers of the GI wall (*white arrows*). *P* probe

making possible an EUS-guided fine needle aspiration (FNA) or a FNA biopsy (FNAB) procedure. Endo-ultrasonography can also be performed by the so- called miniprobes which consist of a long, thin cable with a rotating mechanical transducer at its tip. Miniprobes can be easily introduced along the working channel of a standard endoscope and placed near the target lesion under endoscopic control. These instruments are specifically indicated for the evaluation of the superficial GI cancers but can also be used in the presence of a stricture that cannot be passed with a dedicated instrument.

As for flexible echoendoscopes, there are both radial and linear rigid transrectal probes. Ultrasound probes with multiplane transducers are also available.

In this chapter, the terms endo-ultrasonography and endoscopic ultrasound, with the abbreviation EUS, with regard to the upper gastrointestinal tract will be used indifferently. For the rectum, the term transrectal ultrasonography, with the abbreviation TRUS, will be mainly used because rigid blind probes have been employed in the majority of the studies.

All the instruments for endo-ultrasonography have a common property: the short distance between the ultrasonic sources, placed into the GI lumen and the structures which have to be evaluated. This condition makes it possible to employ frequencies that are higher than those of transabdominal US and produce a significant increase of the resolution of images. Above all endo-ultrasonography is capable of providing a precise visualization of the digestive tract wall. Usually EUS imaging of GI consists of a five-layered echostructure. In vitro studies have demonstrated that there is a good correspondence between the ultrasonographic and the anatomical layers (Fig. 9.1); therefore, it is possible through endo-ultrasonography to precisely define how deeply a tumor infiltrates the gastrointestinal wall (T parameter) and to obtain an EUS staging which is directly comparable to the pathologic one.

Endo-ultrasonography is also able to provide high-resolution images of the organs and structures which are adjacent to the GI wall. Therefore, EUS can adequately evaluate locoregional lymph nodes (N parameter). A size larger than 10 mm; a round shape, well-demarcated boundaries; and echo-poor, homogeneous texture represent EUS criteria suggestive of lymph node involvement (Fig. 9.2). Malignancy is almost certain only when all of the abovementioned features are recognized at the same time. Diagnostic yield of EUS can be significantly improved by performing a FNAB under EUS guidance.

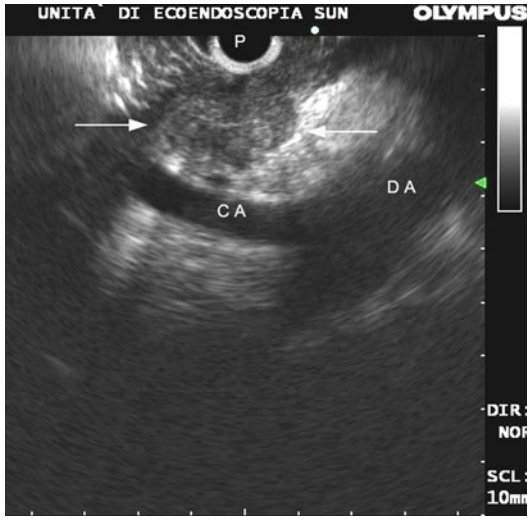

Fig. 9.2 Malignant lymph node (between *arrows*). All typical endosonographic features are shown (size larger than 10 mm, round shape, well-demarcated boundaries and echo-poor, homogeneous texture). *P* probe, *CA* celiac artery, *DA* descending aorta

9.3 Endo-ultrasonography for the Diagnosis of Anastomotic Recurrences: Early Results

Preoperative *locoregional staging* of the gastrointestinal tract cancers was one of first and most successful applications of EUS. Therefore, since the late 1980s, endo-ultrasonography has also been proposed for the diagnosis of anastomotic recurrences after surgical resection of gastrointestinal tumors.

In 1989, Lightdale et al. [1] first described the use of radial EUS after radical surgery for esophageal or gastric cancer in 40 patients with a clinical suspicion of local recurrence. EUS correctly identified recurrent malignancy in 23 out of 24 patients in whom a local recurrence was then proven, showing an overall sensitivity of 95 % and a specificity of 80 %. In six cases EUS was the only technique that diagnosed the recurrence.

In 1986 Hildebrand et al. [2] published the first study on rectal cancer. They reported a local recurrence in 22 patients who had undergone surgical resection, within a 3-year observation period. Transrectal ultrasound (TRUS) identified all the lesions (sensitivity 100 %) and was the only method that allowed for the diagnosis in nine cases (41 %). Also in a series by Beynon et al. [3], TRUS detected all 22 recurrences which occurred in a group of patients treated by radical surgery. However, in 19 of the 22 patients, the recurrence was also identified by digital examination or proctoscopy, so that only in 3 of the 22 patients (13.6 %), the diagnosis was based exclusively on ultrasonography.

The abovementioned results confirmed EUS as a very promising technique for the early diagnosis of anastomotic recurrences but were not sufficient to establish its *clinical impact* and to justify the inclusion of endo-ultrasonography in *follow-up protocols* for the surveillance of patients who had undergone surgical resection of gastrointestinal tract cancer.

9.4 Criteria for Endo-ultrasonographic Diagnosis of Tumor Recurrence

Endo-ultrasonographic imaging of gastrointestinal anastomoses can vary depending on several factors.

One of the most important is the interval between the surgical operation and the EUS examination. The longer the time is, the lesser the postoperative changes at the level of the anastomosis are. EUS imaging also depends on the surgical technique which has been employed in performing the anastomosis. The effects of local surgical complications can also considerably affect EUS imaging of anastomosis. So it is very important to know if anastomotic leakage, abscess, or fistula had occurred in the early postoperative period (Fig. 9.3).

Usually, EUS imaging of a gastrointestinal anastomosis, if evaluated within the first 6 months following surgical resection, shows a significant thickening of the wall, with *circumferential hypertrophy* of the third and the fourth layer (submucosa and muscularis propria, respectively) related to postoperative changes (Fig. 9.4). Hypertrophy of the submucosa generally

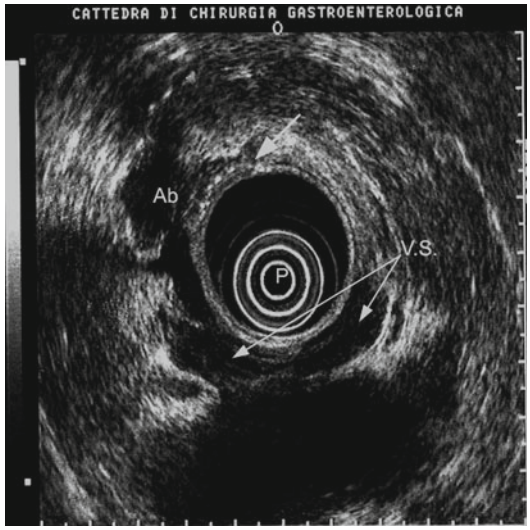

Fig. 9.3 Perirectal abscess (*Ab*) following a leakage of the anastomosis (*white arrow*). EUS appearance is an echo-poor lesion which can mimic a tumor recurrence. *P* probe, *VS* vesiculae seminales

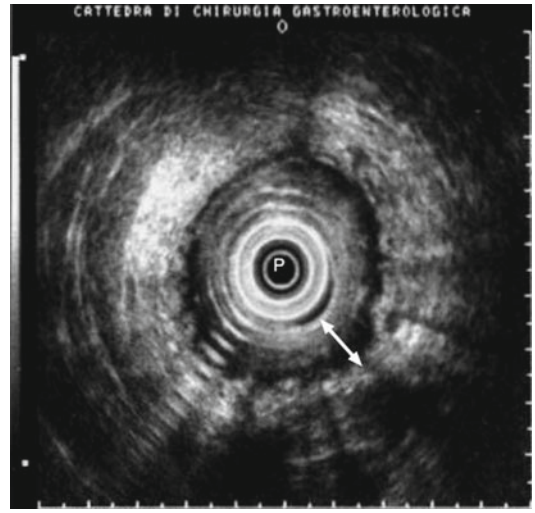

Fig. 9.5 Rectal anastomosis of a patient who had undergone radiotherapy. Note the thickening of the wall (*white arrow*) and the irregularity of the outer margin which is well demarcated from the surrounding tissues. *P* probe

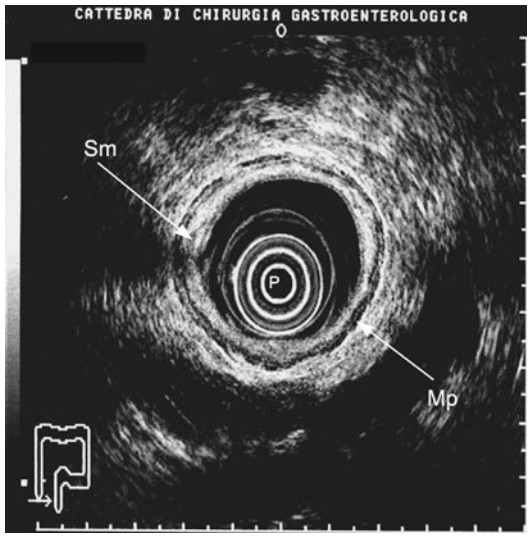

Fig. 9.4 A colorectal anastomosis evaluated within the first 6 months after surgical resection. Note the hypertrophy of the submucosa (*Sm*). *Mp* muscularis propria

disappears in a short time, whereas the circumferential thickness of the Mp. may last for even several years [4]. A previous radiotherapy [5] or manual anastomosis [6] can cause a persistent broadening of the wall. Sometimes typical five-layer wall structure is no longer recognized, and it is replaced by a mixed echoic tissue, sometimes with a "pseudo lamellar" appearance. Especially in the case of rectal anastomosis, the outer margin of the wall is often irregularly shaped along the whole circumference, but it is always demarcated from the surrounding tissues (Fig. 9.5) [7].

Once postoperative changes have disappeared, it can be difficult to even identify the site of the anastomosis [8]. A mechanical anastomosis is almost always visible because of the staples which appear as a circumferential line of small, bright echoes without a shadow [9] (Fig. 9.6).

The so-called central recurrences**,** which appear as a focal echo-poor inhomogeneous thickening originating at the site of the anastomosis (Fig. 9.7), are quite rare, mainly developing as a consequence of an inadequate surgical resection of the primary tumor and a microscopic tumor infiltration of the surgical margins. Apart from technical errors, these types of recurrences can also occur depending on the location of the primary tumor, for instance, in the case of low rectal cancers treated by preserving sphincters surgical resections or in the case of cancers of the cardia involving the distal part of the esophagus treated with a gastrectomy plus distal esophagectomy by a transhiatal approach.

In truth, most of the anastomotic recurrences have an extra-luminal development or are located out of the wall, so they could be better defined as

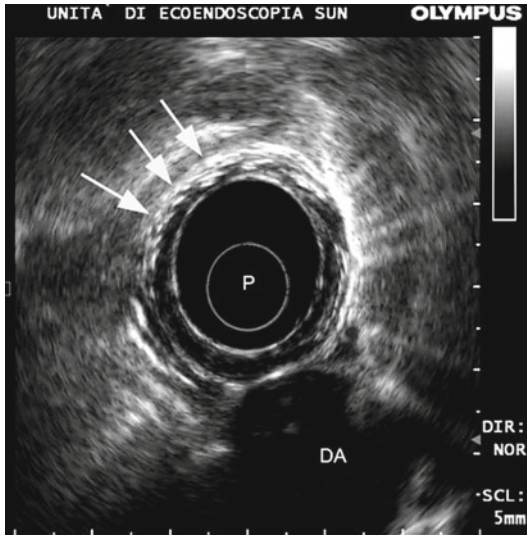

Fig. 9.6 Mechanical esophageal anastomosis. The staples produce a circumferential line of small bright echoes without a shadow (*white arrows*). *P* probe, *DA* descending aorta

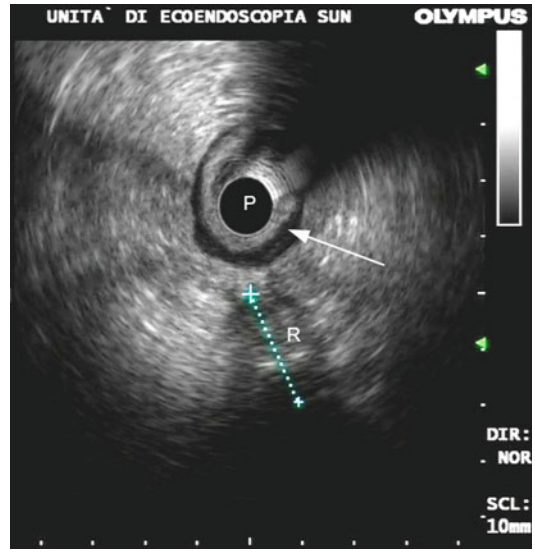

Fig. 9.8 A pelvic recurrence (*R*) originating out of the rectal wall (*arrow*). *P* probe

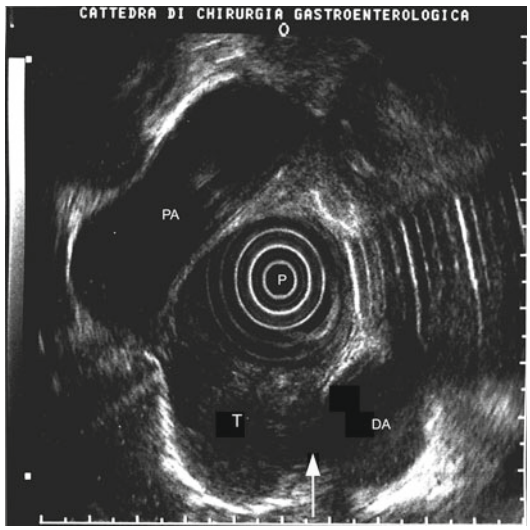

Fig. 9.7 A "central" recurrence (*T*) at the site of esophageal anastomosis. Note the adherence (*arrow*) with the wall of the descending aorta (*DA*). *PA* pulmonary artery

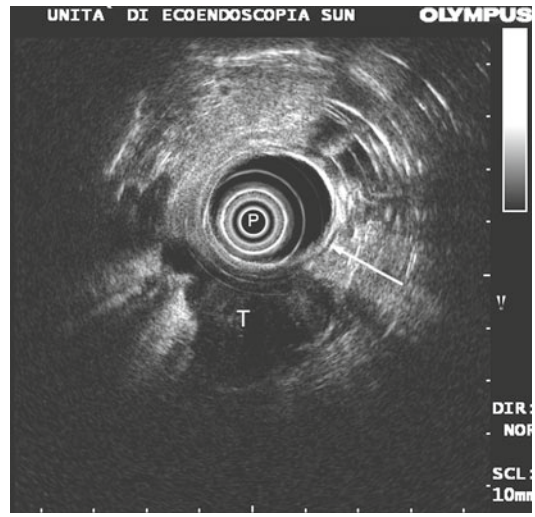

Fig. 9.9 A local recurrence after surgical resection of rectal cancer. Note the irregularly shaped echo-poor mass (*T*) involving from outside the rectal wall (*arrow*). *P* probe

"locoregional recurrences." With regard to rectal cancer, up to 80 % of the tumor recurrences develop in the perianastomotic area or in the pelvic space (Fig. 9.8) [10].

A local recurrence usually appears at the endo-ultrasonographic evaluation as an irregularly shaped *echo-poor mass* with a heterogeneous texture involving from outside the gastrointestinal wall (Fig. 9.9). However, less typical findings may also be found. De Witt et al. [11] reported that 16 out of 21 tumor recurrences (76 %) were hypoechoic at EUS, but remnants were hyperechoic or had a mixed echo texture. The presence of lesions with echo-free areas usually suggests the diagnosis of postoperative seroma or hematoma, but it is not infrequent to find perirectal recurrence with large fluid components (Fig. 9.10).

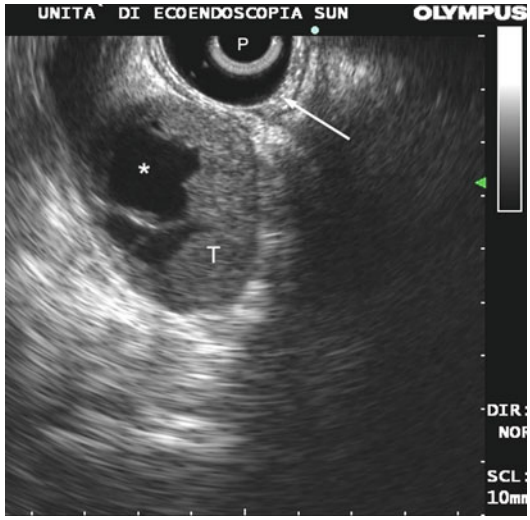

Fig. 9.10 Local recurrence of rectal cancer (*T*) with a fluid component (*) located close to the rectal wall at the level of the anastomosis (*arrow*). *P* probe

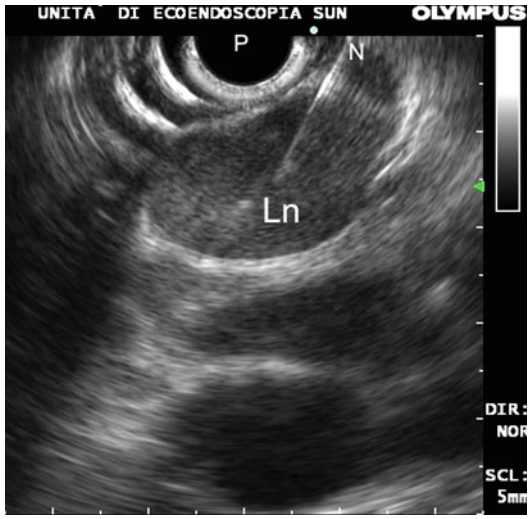

Fig. 9.11 EUS-guided FNA of a mediastinal lymph node (*Ln*) highly suspicious of esophageal cancer recurrence. *N* needle, *P* probe

Due to these difficulties, diagnostic accuracy of endo-ultrasonography based on the imaging alone is not as high as expected, ranging at about 70 %, according to published data. A misdiagnosis, especially when endo-ultrasonography is the only technique which detects the lesion, can very negatively affect both the management and the outcome of the treatment. Nevertheless diagnostic yield can be greatly improved by performing a FNAB under endo-ultrasonographic guidance (Fig. 9.11). Cytohistological examination of the collected material can allow the pathologist to provide a definitive diagnosis.

The clinical impact of an endo-ultrasonographic-based surveillance will be further discussed in the following paragraphs.

9.5 Follow-Up of the Anastomoses After Surgical Resection of Esophageal or Gastric Cancer

Very few studies have specifically investigated the value of EUS for the diagnosis of recurrent esophageal or gastric malignancy after radical surgical resection. One of the most important still remains the prospective study published by Fockens et al. in 1997 [12], with the aim to assess the effectiveness of EUS in detecting tumor recurrence in symptom-free patients. All the 43 patients who were enrolled had undergone resection of the esophagus and gastric cardia with reconstruction by means of gastric pull-up with a cervical anastomosis. The authors scheduled EUS examination every 6 months during the first 2 years after surgery, considering that the majority of tumor recurrences are likely to develop within this interval of time.

The first planned EUS examination failed in 13 patients (30 %) because of the inability to pass a cervical anastomosis too narrow for the echoendoscope, which had an external diameter of 13 mm. Currently, due to the availability of new instruments, such as *miniprobes*, the presence of an *anastomotic stricture* is no longer an obstacle for EUS examination.

During the follow-up period, a total number of 16 patients showed EUS features suspicious of a tumor recurrence which was then histologically proven in 12 patients (75 %). In 3 patients the suspicion of recurrence was based only on the presence of free fluid in the mediastinum. In 2 of these patients, no recurrence developed, so the sole finding of free fluid around the gastric pull-up did not result in being a predictive factor. On the contrary, the finding of one or more suspicious lymph nodes was associated to a proven tumor recurrence in 7 out of 8 patients, with a positive predictive value of 88 %. Finally, all of

the 5 patients with a *focal wall thickening* or a mass adjacent to the gastric pull-up really had a tumor recurrence; in this way, positive predictive value of EUS for recurrent disease was 100 % in this group of patients.

It needs to be underlined that follow-up protocol allowed an EUS diagnosis in a preclinical stage only in 8 out of the 12 patients with a proven recurrence disease (67 %). On the contrary, 4 patients became symptomatic during the interval of time between two subsequent scheduled EUS examinations.

Another point which needs to be discussed is the clinical impact of an EUS-based follow-up protocol. Local tumor recurrences following surgical resection for esophageal cancer can rarely be treated by a reoperation. However, an early diagnosis should at least aim at an aggressive chemoradiotherapy in order to prolong the survival of patients. Actually Fockens et al. reported that 9 of the 12 patients with a biopsy-proven recurrent disease (75 %) died within a few months of the EUS diagnosis (range 1–9), though the recurrence had been detected before any clinical evidence in 8 patients.

Similar results have been reported by others. Muller et al. [7] investigated the role of an EUS-based surveillance in 37 patients who had undergone surgical resection for esophageal or gastric cancer. EUS showed a sensitivity of 92 % and a specificity of 84 % for the early diagnosis of local tumor recurrence. Nevertheless, none of the 11 patients with recurrent disease could benefit from a reoperation, and aggressive radio-chemotherapy did not produce any substantial improvement of survival.

On the basis of the abovementioned results, it is possible to conclude that a follow-up protocol including endo-ultrasonography in patients who had undergone surgical treatment of a primary esophageal or gastric carcinoma has a very limited clinical impact and, therefore, it is not justified.

Currently EUS has to be considered as a second-line investigation, aimed at obtaining a cytological confirmation which is often required before starting chemoradiotherapy. In this respect FNA under EUS guidance has proved to be the best available technique, improving the accuracy for the diagnosis of local recurrence up to 95 % [11].

9.6 The Follow-Up of Anastomoses After Surgery of the Rectum

The incidence of local recurrence in patients who have undergone surgical resection of rectal cancer with curative intent still ranges from 2.6 to 32 % [13]. It has already been underlined that so-called "central" recurrences are very rare, and their possible causes have been discussed too. It is well known that most recurrences arise in the perianastomotic area or in the pelvic space. They may originate from residual cancer cells in the mesorectum in the case of incomplete excision or may develop as a microscopic tumor spreading beyond the circumferential margin also in patients treated by a *total mesorectal excision* [14, 15].

Different from esophageal or gastric cancer, some patients with local recurrences following the treatment of a rectal cancer can benefit from a *reoperation* with a curative intent. However, it has to be again underlined that the outcome of the patients is strongly related to a very early detection of the recurrence [16]. As the matter of fact, the possibility of a reoperation dramatically decreases in the case of a late diagnosis. Several studies have shown that endo-ultrasonography is a reliable method for the early detection of a local rectal recurrent disease with a diagnostic accuracy ranging from 69 to 85 % [17–19].

The most important limit of EUS diagnosis based on imaging alone concerns the difficulties in distinguishing malignant from reactive tissue, particularly if the endo-ultrasonographic findings are not typical [5, 6, 9]. It has been suggested to perform serial examination in doubtful cases to monitor the evolution of the presumed recurrence. Besides the negative impact on the compliance of the patients, such behavior can also produce a diagnostic delay which would compromise the treatment if the suspicious lesion proved to be a recurrence.

Problems of differential diagnosis can be overcome by an *EUS-guided FNAB* which is the sole method to obtain a tissue acquisition when the suspicious lesion is located outside the GI wall (Fig. 9.12). FNAB can be performed using a linear array flexible echoendoscope or a dedicated rigid blind probe. The latter instruments

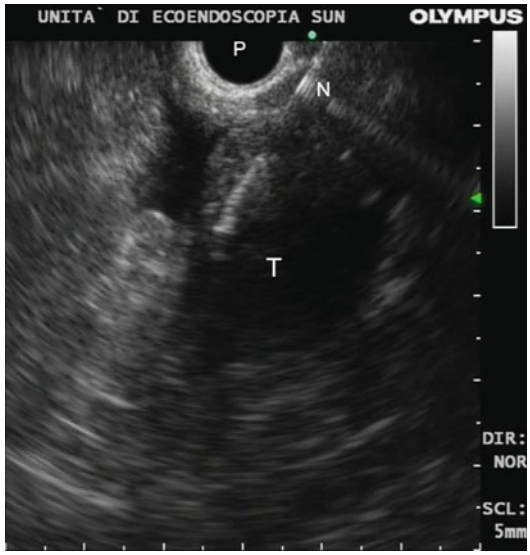

Fig. 9.12 EUS-guided FNA of an extra-luminal tumor recurrence (*T*) after surgical resection of rectal cancer. *N* needle, *P* probe

have been used in the majority of the published series concerning FNAB for diagnosis of rectal recurrences. Using a rigid ultrasound probe, tissue sampling is generally carried out by a spring-loaded core biopsy needle, which allows for the obtainment of histological specimens. On the contrary, standard needles used with flexible echoendoscopes only allow a fine needle aspiration procedure, although a new type of needle with a small core trap at its tip is now also available.

Transrectal US-guided FNA is a relatively simple and safe procedure with a rate of complications ranging from 0.5 to 2 % [20]. Nevertheless perirectal, even severe infections may occur, albeit rarely. Therefore, an antibiotic prophylaxis should be mandatory before performing the procedure, especially when a cystic component is found. FNAB significantly improves diagnostic yield of transrectal US. Its accuracy is estimated to range from 87 to 100 % [18, 19]. Additional information provided by FNA is able to modify therapeutic strategy in 25–35 of the cases [18, 19].

However, once again the question concerns the real usefulness of a follow-up program including both proctoscopy and transrectal US.

In 2004 Hernandez de Anda et al. published a study on transrectal US follow-up in 275 patients with invasive rectal cancer treated by curative-intent local excision or radical surgery [9]. FU protocol consisted in an anal digital examination, proctoscopy, and transrectal US every 4 months for the first 3 years after surgery and every 6 months for the subsequent 2 years. In the local excision group, most recurrences (81 %) were diagnosed during scheduled examinations in asymptomatic patients. However, only 30 % of recurrences were detected by TRUS alone. The proportion of salvage surgery was similar in patients whose recurrence was diagnosed by transrectal US or by other techniques (respectively, 80 % vs 86 %). In the radical surgery group, the proportion of recurrences diagnosed in patients still asymptomatic was 42 %, and the lesion was only detected by transrectal US in 33 % of the cases. As expected, the proportion of salvage surgery in the patients with recurrences enrolled in the follow-up protocol was higher compared to a control group without follow-up, but the difference was not significant. Not even the results of this large study were able to assess the impact of an endo-ultrasonographic follow-up on the survival of the patients with local recurrences after surgical resection of rectal cancer.

According to the guidelines for posttreatment follow-up of patients with colorectal cancer of the American Society of Colon and Rectal Surgeons published in 2004 [21], *periodic anastomotic evaluation* is recommended for patients who have undergone resection/anastomosis or local excision of rectal cancer (level of evidence III, grade of evidence B). Authors, however, underlined that the role of endo-ultrasonography in this field would need further confirmation with larger multi-institutional clinical trials. So far these trials are not yet available.

Maybe, especially in patients with *AJCC II or III disease*, a follow-up protocol including endo-ultrasonography would be justified, because of the higher risk of local recurrence, but neither the interval nor the total duration of the follow-up has been defined yet.

At present, the programs for the postoperative follow-up of patients with GI cancers contemplate

multi-slice CT as the first-line exam and *PET* as the second-line tool. PET is the most sensitive method currently available, but its specificity is not completely satisfactory. Thus, endo-ultrasonography, associated with FNAB, can play a fundamental role in obtaining a definite diagnosis of malignancy, which is very often required before planning a therapeutic strategy.

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10 Augmented Endoscopy Imaging in the Study of Digestive Anastomosis: Does It Really Work and How?

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10.1 Augmented Endoscopy Imaging

10.1.1 Magnifying Chromoendoscopy

0.4 % indigo carmine (IC) dye is used to accentuate the outline and surface pattern of the lesions. It does not stain the lesion, but remains only in the depressed area and makes a clear contrast between the higher and lower parts of the lesion (contrast method). The pit pattern proposed by Kudo is evaluated by magnifying view [1]. The orifices of the colonic crypts are described as "pits," and the specific arrangement of the pits is described as "pit pattern." Pit pattern is useful to predict the histological structure of colorectal lesions. It is divided into five groups: type I, II, III, IV, and V.

Type I pit pattern is seen in normal mucosa. It consists of roundish pits with a regular distribution. Type II pit pattern is found in the majority of the lesions classified as nonneoplastic at histology. It is larger than the normal pits and asteroid or star shaped. The distribution of the pit is regular. Type III pit pattern is divided into two categories, III_S and III_L. III_S pit pattern is composed of tubular or roundish pits smaller than the normal ones ("S" stands for "small" or "short"). It is seen mainly in depressed lesion and tends to be early cancers. III_L pit pattern is composed of tubular or roundish pits larger than normal ones ("L" stands for "long" or "large"). It is seen mainly in adenoma. Type IV pit pattern is a branched or gyrus-like pattern and is also seen mainly in adenoma. Type V pit pattern is divided into V_I and V_N. V_I pit pattern (the "I" stands for "irregular") has pits which are irregular in shape, size, and arrangement. V_N pit pattern shows an absence of pit pattern (the "N" stands for "nonstructural"). V_N pit pattern is seen in deep submucosal invasive cancer and in advanced cancer. V_I pit pattern is mainly seen in adenoma with high-grade dysplasia, intramucosal cancer, and superficial submucosal invasive cancer. However, sometimes it is seen in deep submucosal invasive cancer.

A clinical classification which modified Kudo's classification was described by Fujii with the aim to discriminate between m-sm1 (intramucosal cancer and superficial submucosal invasive cancer) and sm2 (deep submucosal cancer) or beyond [2]. In this classification, type V_I pit pattern is divided into two categories, V_I noninvasive pattern and V_I invasive pattern. Noninvasive pattern composed of regular crypts with or without demarcated area or irregular pits without a demarcated area. This pattern

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indicates adenoma, intramucosal cancer, and submucosal superficial cancers, so endoscopic resection are appropriate. Invasive pattern is composed of irregular and distorted crypts in a demarcated area. This pattern indicates deep submucosal invasive cancers, so surgical resection is appropriate. When high-magnification observation with IC is not enough for determining pit pattern, 0.05 % crystal violet is applied as a staining method. A prospective study revealed the sensitivity, specificity, and diagnostic accuracy of the invasive pattern to differentiate m-sm1 cancers (intramucosal cancer and slight submucosal invasive cancer) from deep submucosal cancers to be 85.6, 99.4, and 98.8 %, respectively [3].

10.1.2 Narrow Band Imaging (NBI)

Narrow band imaging (NBI) uses a narrowed wavelength light source to optimize hemoglobin light absorption. By this system, contrast in the microvascular architecture on the surface of the lesions is improved. The microcapillary vessels become elongated and enlarged in the process of changing from premalignant to malignant lesions.

Sano et al. proposed a classification of microcapillary vessels of colorectal lesions [4]. In the Sano's classification, the microvascular architecture (capillary pattern: CP) is divided into three categories (CP type I, II, and III). CP type I is indicating normal mucosa or hyperplastic polyps. In this type, the microcapillary vessels are invisible or only faintly visible on magnifying NBI colonoscopy. CP type II is seen in adenomatous lesions. Meshed capillary vessels arranged in a honeycomb pattern around the mucosal glands are clearly visible because these capillaries are elongated and enlarged. CP type III lesions are defined as showing an irregular unstructured pattern in meshed microvascular architecture and show at least one of the following characteristics: irregular size complicated branching and/or disrupted irregular winding when compared with small-caliber capillaries observed in adenomatous polyps. CP type III is divided into two types, IIIA and IIIB. CP type IIIA lesions clearly show visible microvascular architecture and high microvessel density with a lack of uniformity, branching, curtailed irregularly, and blind endings. CP type IIIB lesions show a clearly visible demarcation between normal and cancerous mucosa on the surface based on the presence of a nearly avascular or loose microvascular area.

NBI is effective to distinguish neoplastic and nonneoplastic lesion. A prospective study revealed the overall diagnostic accuracy, sensitivity, and specificity of CP pattern for the differential diagnosis between neoplastic and nonneoplastic colorectal polyps smaller than 10 mm to be 95.3, 96.4, and 92.3 %, respectively [5].

There is no definite evidence about the usefulness of CP pattern for assessing depth of invasion of early colorectal cancers. Ikematsu et al. reported that the sensitivity, specificity, and diagnostic accuracy of CP type IIIA and IIIB for differentiating intramucosal or slight submucosal invasion from deep submucosal invasion were 84.8, 88.7, and 87.7 %, respectively [6].

NBI is also used for evaluating upper gastrointestinal neoplasms. Muto et al. conducted a prospective, randomized controlled trial to compare the real-time detection rates of superficial cancer in the head and neck region and esophagus between white light imaging (WLI) and NBI [7]. The sensitivity, specificity, and accuracy of NBI for diagnosis of superficial cancer in the head and neck region were 100, 78.6, and 86.7 %, respectively. Those for diagnosis of superficial cancer in the esophagus were 97.2, 31.3, and 88.6 %, respectively. The sensitivity and accuracy were significantly higher using NBI than WLI in both lesions.

For gastric lesions, NBI is also useful. Ezoe et al. A multicenter, prospective, randomized controlled trial was conducted to assess and compare the real-time diagnostic yield of conventional white light imaging (C-WLI) for depressed gastric mucosal cancers with that of magnifying narrow band imaging (M-NBI) [8]. The combination of M-NBI with C-WLI identified

small, depressed gastric mucosal cancers with 96.6 % accuracy, 95.0 % sensitivity, and 96.8 % specificity.

10.1.3 Endocytoscopy

Endocytoscopy is a recently developed emerging endoscopic system. It involves a contact light microscopy system integrated into the distal tip of a conventional colonoscope. The ultramagnifying view of endocytoscopy enables on-site observation not only of structural atypia but also of cytological atypia. Mori et al. recently conducted a prospective randomized noninferiority trial to assess the potential of endocytoscopy for the diagnosis of colorectal neoplasms. The diagnostic accuracy of endocytoscopy for identifying neoplastic lesions was 94.1 % with a sensitivity of 97.6 % and a specificity of 100 % [9].

10.2 The Usefulness of Augmented Endoscopy in the Study of Digestive Anastomoses

Digestive anastomotic sites are often exposed to several mechanical stimuli such as food or stool or chemical stimuli such as gastric juice or bile. Therefore, erosions or hyperplastic changes often occur on there. On the other hand, neoplastic lesions, both benign and malignant, sometimes occur on the anastomotic site. In the cases which the previous surgery was performed for a nonneoplastic disease, the neoplastic lesion on the anastomotic site occurs incidentally or partly due to the increased stimulus after surgery. In the cases which the previous surgery was due to a neoplastic lesion, anastomotic recurrence, metachronous cancer, and previously overlooked neoplasm are considered as the causes of anastomotic neoplasm. Anastomotic recurrence after curative surgery of colorectal cancer is thought to be due to several causes: implantation of viable cancer cells in the suture line, instability of the mucosa at the anastomotic site, positive resection margin, and lymphovascular invasion [10].

The Japanese guidelines for the treatment of colorectal cancer report a local luminal recurrence rate of 0.4 % for colorectal cancer [11]. When distinguish the colon and rectum, the recurrence rate was significantly higher in rectum than colon (0.8 % vs 0.3 %, $p=0.0052$). Sakamoto et al. also reported the local luminal recurrence rate of colorectal cancer to be 0.7 % [12]. Compared with these date, anastomotic recurrences occur in 5–10 % of patients in the Western countries [13]. The majority are recurrent rectal rather than colon cancers [14].

The augmented endoscopy should be useful to distinguish the anastomotic recurrence from benign erosion or hyperplastic change. The ability for differential diagnosis of NBI for neoplastic and nonneoplastic lesions is mentioned above.

Patients with colorectal cancers have high risk of metachronous colorectal cancers. Metachronous colorectal cancers develop in 1.5–3 % of patients in the first 3–5 years after surgery [15]. Of these "metachronous" lesions, some lesions which were detected early may represent synchronous cancers that were overlooked initially [13]. Therefore, development of overlooked synchronous cancers or metachronous cancers may be occurred on the anastomotic site after surgery of colorectal cancer. Detailed observation with magnifying endoscopy not only in postoperative phase but also in preoperative phase is important to reduce the anastomotic neoplasm.

10.3 A Case of Intramucosal Colon Cancer on the Anastomotic Site After Surgery for Colon Cancer

A 75-year-old male underwent a colonoscopy in another hospital. A circumferential severe stenosis was detected in the transverse colon. The scope could not pass through. He underwent partial colectomy. Histologically, the

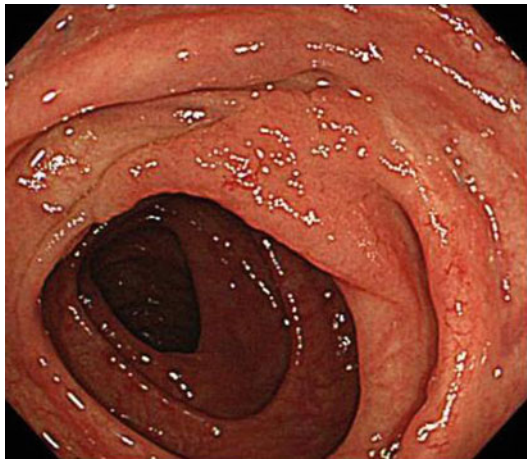

Fig. 10.1 Conventional view: a flat elevated lesion was seen on the anastomotic site in the transverse colon

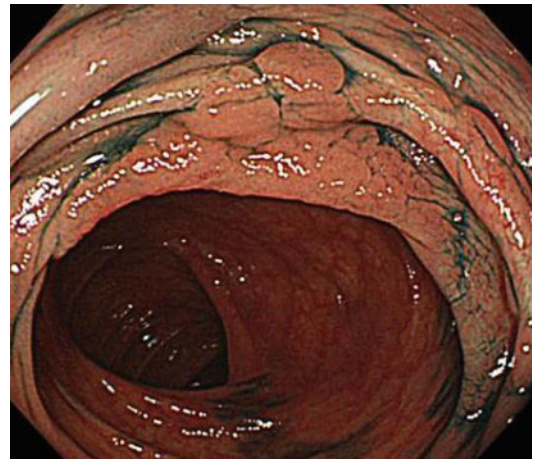

Fig. 10.3 Chromoendoscopy using indigo carmine dye spraying. The outline of the tumor was accentuated

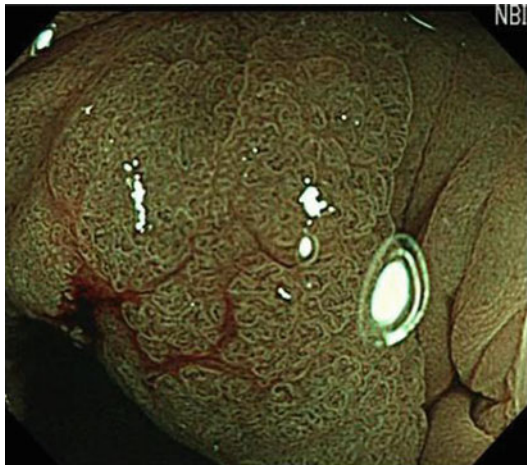

Fig. 10.2 NBI with magnifying colonoscopy revealed slightly dilated capillary vessels (type IIIA in Sano's classification of capillary pattern)

lesion was identified as a tubular adenocarcinoma. The depth of invasion was subserosa. There were several lymph node metastases. No distant metastasis was detected. The pathological stage of the lesion was IIIa (pSS, pN1, H0, P0, M0) according to the General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum, and Anus [16]. He received adjuvant chemotherapy (oral administration of TS-1, Taiho Pharmaceutical CO., LTD, Tokyo, 100 mg/body/day on day 1–28, withdrawal day 29–42). He underwent surveillance total colonoscopy in previous hospital 8 months after the surgery. A laterally spreading tumor was detected in the distal side of the anastomotic site. He was referred to our hospital for the endoscopic treatment. We performed total colonoscopy again and found two lesions. One was the lesion that was detected in previous hospital. The other was anastomotic recurrent lesion that was not detected in previous hospital. The detailed findings of the recurrent lesion were as follows. In conventional view, a flat elevated lesion was seen on the anastomotic site in the transverse colon (Fig. 10.1). NBI with magnifying colonoscopy revealed slightly dilated capillary vessels (Fig. 10.2). We evaluated this finding as type IIIA in Sano's classification of capillary pattern. Chromoendoscopy using indigo carmine dye spraying accentuated the pseudopodiac outline of the tumor (Fig. 10.3). With magnification, pits were irregular in shape, size, and arrangement (Fig. 10.4). We estimated this pit pattern as V_I noninvasive pattern. In deflation view, the lesion seemed to be relatively soft. Endoscopic diagnosis was a recurrent colon cancer, 40 mm in size, located on the anastomotic site in the transverse colon. The macroscopic type was 0-IIa,

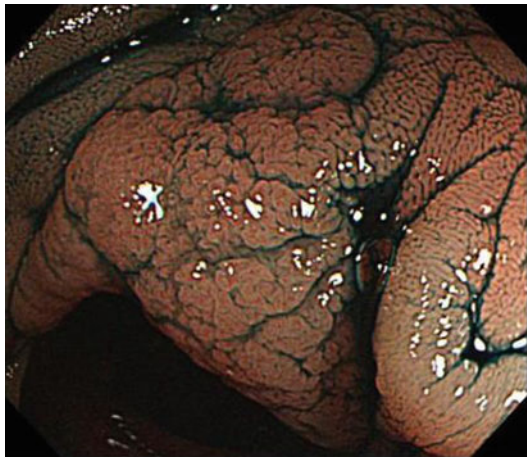

Fig. 10.4 Chromoendoscopy with magnification. Pits were irregular in shape, size, and arrangement (V_I noninvasive pattern)

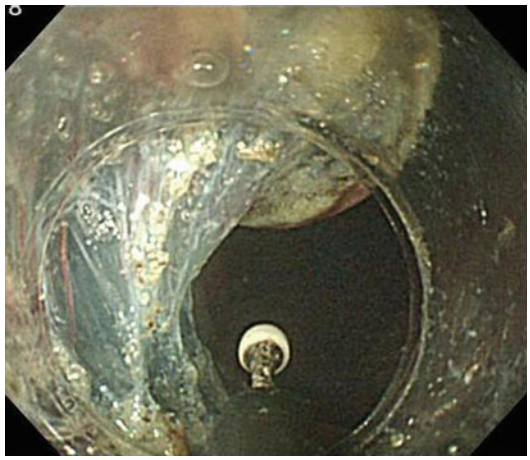

Fig. 10.5 Endoscopic submucosal dissection (ESD)

laterally spreading tumor, nongranular type [17]. Estimated depth was mucosal layer. We performed endoscopic submucosal dissection (ESD) for this lesion [18] (Fig. 10.5). We used a bipolar needle knife (Jet B-knife, Xeon Medical Co, Tokyo, Japan), an insulation-tipped knife

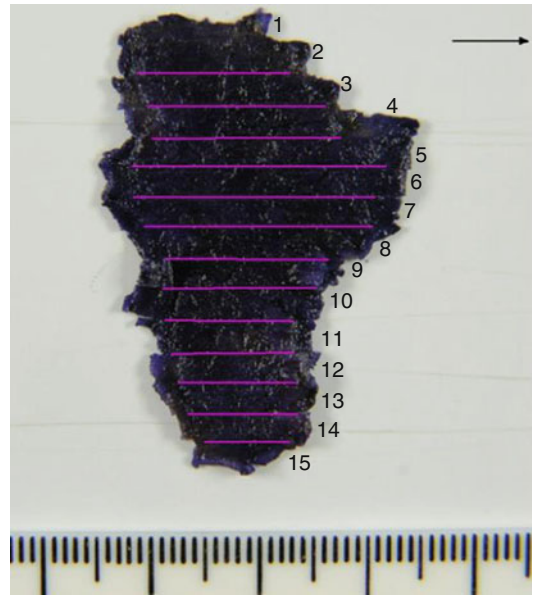

Fig. 10.6 Mapping of the resected specimen. The area showed by *pink color lines* revealed intramucosal cancer

(IT knife nano, Olympus), and attachment hood (Short type ST hood, Fuji Film, Tokyo, Japan). En bloc resection was done. Histologically, the lesion was identified as a tubular adenocarcinoma, well differentiated (Fig. 10.6). The size of the tumor was 34 × 23 mm. The depth of invasion was mucosal layer (Fig. 10.7). No lymphovascular invasion was seen. Horizontal and vertical margin were free from cancer cells. We performed surveillance colonoscopy 1 year and 1.5 year after the ESD. No recurrence was detected.

In this case, the previous doctor could not perform total colonoscopy before surgery due to severe stenosis. The lesion on the anastomotic site therefore should be a synchronous lesion. Surveillance colonoscopy should be performed with special attention to synchronous and metachronous colorectal cancers after this kind of surgery.

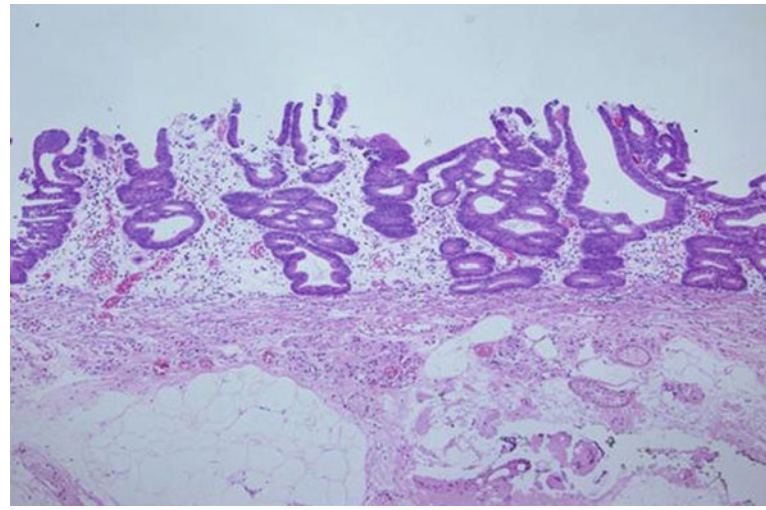

Fig. 10.7 Tubular adenocarcinoma, well differentiated

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Part II

Therapeutic Procedures of Anastomotic Complications

11 Physiopathology and Treatment of Anastomotic Ulcer: An Emerging Pathology?

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Anastomotic ulcer is a benign lesion which may potentially occur on the surgical resection margin of intestinal wall in both upper and lower tract. Although anastomotic ulcer development is an infrequent event, a quite high incidence has been reported following operations in the upper gastrointestinal tract, while both duodenal stump-ileal anastomosis [1] and ileocolon anastomotic ulcers are very rare, especially in adult patients. Indeed, a systematic review collected only seven cases of ileocolon anastomotic ulcer in adults reported in literature [2], and only few cases were described thereafter [3]. A case we observed is provided in Fig. 11.1. Therefore, we mainly focused the present review on marginal ulcer occurring in the gastrojejunal anastomosis.

11.1 Epidemiology

Currently, anastomotic ulcers in the upper gastrointestinal tract are mainly reported following bariatric surgery, which is increasingly performed in developed countries due to the increased prevalence of obesity [4]. In detail, several studies assessed the occurrence of anastomotic ulcers in patients who underwent laparoscopic Roux-en-Y gastric bypass (RYGB) [5–30]. As reported in Table 11.1, the incidence of such a lesion widely ranged from 0.35 % to as many as 15.8 %. Different factors may be invoked to explain these hugely divergent estimations, including the length of follow-up (from few months to several years), operator experience (learning curve), surgical technique performed (hand-sewn or stapler anastomosis), and surgical devices (absorbable or not absorbable suture, different staplers) used. By considering only data of the five studies with a large (>500 pts) sample size and long (>1 year) follow-up, the incidence of marginal ulcer was ranging from 1.7 to 7.2 %

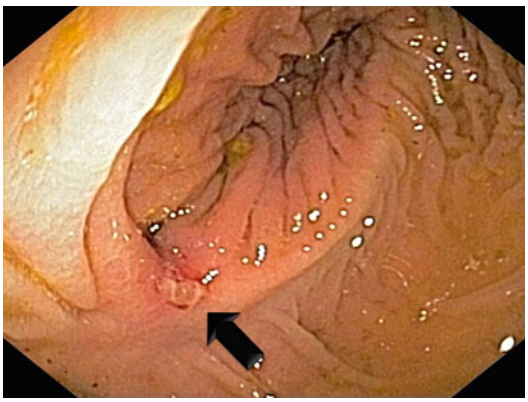

Fig. 11.1 A marginal ulcer (*arrow*) in the ileocolon anastomosis was observed at 5-year follow-up in an asymptomatic 74-year-old female with a previous right hemicolectomy. Histological assessment excluded cancer recurrence

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Table 11.1 Overall incidence of gastrointestinal anastomotic ulcer following bariatric surgery

Author [Ref.]	Year	Country	Patients	Follow-up	Cases (%)
Sapala [5]	1998	USA	173	3 years	1 (0.6)
Capella [6]	1999	USA	810	8 years	53 (6.5)
Schauer [7]	2000	USA	275	9.4 months	2 (0.7)
Higa [8]	2000	USA	1,040	NA	14 (1.4)
Sugerman [9]	2004	USA	80	5 years	10 (12.5)
Lujan [10]	2005	Spain	350	1–36 months	12 (3.4)
Sacks [11]	2006	USA	3,285	12 months	57 (1.7)
Dallal [12]	2006	USA	201	NA	7 (3.5)
Wilson [13]	2006	USA	1,001	NA	81 (8.1)
Yang [14]	2006	Taiwan	636	NA	22 (3.5)
Gumbs [15]	2006	USA	347	3 years	16 (4)
Ramsussen [16]	2007	USA	260	10 months	19 (7.3)
Suggs [17]	2007	USA	438	14 months	23 (5.3)
Han [18]	2007	USA	835	1–3 years	29 (3.5)
Papasavas [19]	2008	USA	422	12.4 months	16 (3.4)
Cariani [20]	2008	Italy	287	6–36 months	1 (0.35)
Lee [21]	2009	USA	76	NA	12 (15.8)
Ruiz- de-Adana [22]	2008	Spain	250	NA	4 (1.6)
Vasquez [23]	2009	USA	315	3 months	33 (10.5)
Csendes [24]	2009	Chile	315	17 months	2 (0.6)
Ramirez [25]	2010	USA	287	2 years	14 (4.5)
Garrido [26]	2010	Brazil	118	2 months	9 (7.6)
Suter [27]	2010	Switzerland	1,128	ND	9 (0.8)
Bendewald [28]	2011	USA	835	14 months	60 (7.2)
Rawlins [29]	2012	USA	228	2 years	5 (2.2)
Callery [30]	2012	USA	1,073	14 months	25 (2.3)

NA not available

(Table 11.1), with 224 cases on 6,838 patients corresponding to a cumulative mean of 3.3 %. However, this value should be considered as an underestimation of anastomotic ulcer rate, since a scheduled upper endoscopy in all patients was not performed in the vast majority of these studies. Indeed, patients underwent upper endoscopy only when gastrointestinal symptoms and/or ulcer complications occurred, while the marginal ulcer rate has been calculated on the entire sample size. For instance, only 226 (23 %) of 1,001 RYGB patients underwent upper endoscopy due to symptoms, and a marginal ulcer was detected in as many as 81 (36 %) cases [13]. Indeed, it has been found that as many as 28 % of marginal ulcers were detected in asymptomatic RYGB patients when an endoscopic control was performed in all patients irrespectively of presence of symptoms [24].

11.2 Clinical Presentation

Following RYGB surgery, all the ulcers virtually develop on the gastrojejunal anastomosis, while ulcers on the jejunojejunostomy are rarely detected. In these patients, marginal ulcers may develop either in the early (few days) postoperative period or at long-term (several years) follow-up. However, the vast majority (95 %) of anastomotic ulcer develops within 12 months [13]. In a prospective study on 441 RYGB patients, the scheduled upper endoscopy in all patients showed a 5.7 and 0.3 % incidence of marginal ulcer at 1 month and 13 months, respectively [24].

From a clinical point of view, the anastomotic ulcer may remain totally asymptomatic or cause significant morbidity, which may result

Table 11.2 Incidence of anastomotic ulcer complication following bariatric surgery

Author [Ref.]	Year	Country	Patients	Follow-up	Cases (%)	Type
Higa [8]	2000	USA	1,040	ND	2 (0.2)	2P
Lujan [10]	2005	Spain	350	1–36 months	3 (0.8)	1B + 1P + 1S
Sacks [11]	2006	USA	3,285	12 months	11 (0.03)	7B + 3P + 1S
Dallal [12]	2006	USA	201	ND	4 (2)	3B + 1P
Ramsussen [16]	2007	USA	260	10 months	4 (1.5)	4B
Ruiz-de-Adana [22]	2008	Spain	250	ND	3 (1.2)	2B + 1P
Suter [27]	2010	Switzerland	1,128	ND	1 (0.009)	1B
Vanek [33]	2006	USA	144	20 months	4 (2.8 %)	4B
Kalaiselvan [34][a]	2012	UK	1,213	8 years	10 (0.82 %)	10P
Wendling [35][a]	2012	USA	1,760	9 years	15 (0.85 %)	15P

B bleeding, *P* perforation, *S* stenosis. Data refer to ulcer complications. Bleeding, perforation, and stenosis cases not clearly related to an anastomotic ulcer were not included

[a]These studies a priori selected patients with anastomotic perforation

in multiple hospital admissions. Nausea, severe epigastric pain, abdominal pain, and iron deficiency anemia may be common complaints in patients with marginal ulcers [4]. The onset of overt bleeding, dysphagia, and vomiting should alert for a potential ulcer complication, suggesting a prompt endoscopy for both diagnosis and treatment [31, 32]. In selected cases, a reoperation is needed to resolve the anastomotic ulcer complication.

Anastomotic ulcer complications include bleeding, perforation, and stenosis. The incidence of these complications following bariatric surgery observed in different studies is reported in Table 11.2 [33–35]. Although the incidence widely varies among different series, an overall complication rate of near 1 % was reported in the majority of studies. Analogously to peptic ulcer disease, marginal ulcer bleeding seems to be the most frequent complication followed by perforation, while an anastomotic stenosis clearly related to a marginal ulceration has been rarely described. By considering data of the selected studies (Table 11.2), bleeding from a marginal ulcer was cumulatively observed in 18 out 5,474 patients enrolled in 7 studies, accounting for a 3.3 % incidence. A marginal ulcer at the gastrojejunal anastomosis is the more common cause of late gastrointestinal hemorrhage following RYGB, while early postoperative hemorrhage usually originates from the staple lines [11].

11.3 Physiopathology

The mechanisms underlying the development of marginal ulceration have not been completely elucidated, and the physiopathology is likely multifactorial [16, 36]. During the immediate postsurgical period, factors like ischemia caused by the sutures, foreign body reaction to the presence of synthesis material, and anastomotic tension may play a role [13]. It has been suggested that minimal staple-line dehiscence with small gastrogastric fistula formation can also contribute to the development of marginal ulcers, although data are controversial [6]. Other contributory factors include gastric pouch size, orientation, and residual gastric acid production [13].

Although different risk factors have been suggested as potential cause of anastomotic ulcer development, data are not conclusive. *Helicobacter pylori* infection, use of nonsteroidal anti-inflammatory drugs (NSAIDs), lacking of preventive therapy with a proton pump inhibitor (PPI), and smoking habit are the most complained culprits. The potential role of either different sutures (absorbable or permanent) or different staplers (linear or circular) used has been also evaluated in some studies.

A study specifically investigated the risk factors involved in the anastomotic ulcer development following RYGB which occurred in 19 (7 %) out of 260 patients with a mean follow-up

of 12 months [16]. The study found that, at univariate analysis, only the seroprevalence for *H. pylori* infection was significantly higher in patients who developed the marginal ulcer as compared to those who did not (23 % vs 12 %; $p = 0.02$). A reduced incidence of marginal ulcers was observed in a group of patients who tested positive for *H. pylori* and were treated before RYGB as compared with a group of patients not tested for the infection (2.4 % vs 6.8 %; $P = 0.02$) [29]. Similarly, *H. pylori*-negative patients had a lower incidence of postoperative marginal ulcers compared with a group of untreated *H. pylori-positive* patients (19 % vs 48 %; $P = 0.01$) [37]. In addition, it has been found that patients with preoperatively *H. pylori* had a threefold higher incidence of postoperative GI bleeding or ulcer (18 % vs 6 %), although the difference was not statistically significant due to the low sample size [33]. On the contrary, several studies failed to demonstrate that the preoperatively test and treat strategy for *H. pylori* infection would affect marginal ulcer incidence in RYGB patients [19, 29, 38–40]. However, some pitfalls may have hampered the accurateness of these studies. For instance, *H. pylori* infection was assessed only by serology, which is not accurate to diagnose an ongoing infection. In detail, no study evaluated whether *H. pylori* bacteria were actually present in the small gastric pouch which remain following RYGB. It is counterintuitive that an active infection in this particular niche is prerequisite for a potential role on marginal ulcer development. However, different studies failed to find *H. pylori* bacteria in gastric pouch mucosa of anastomotic ulcer patients previously treated for the infection [20, 26]. Therefore, further well-designed studies are needed in such a field.

Although a very small (20–30 ml) gastric pouch remains following RYGB, parietal cells in the remnant gastric mucosa are able to produce gastric acid which may play a role in the anastomotic ulcer onset. Indeed, peptic digestion of the unprotected jejunal mucosa leads to marginal ulceration. Therefore, a preventive therapy reducing gastric acidity is generally performed. However, in some studies a proton pump inhibitor therapy was started the day after surgery and maintained for only 1 month to prevent the development of marginal ulceration [27]. In other series, a less effective postoperative H2-blocker therapy was administered for a longer period (3–6 months) [16, 19]. In a study [35], as many as 10 (55 %) of 18 patients who developed marginal ulcer were not taking PPI therapy. It has been also found that lacking of PPI therapy was associated with marginal ulcer perforation [34]. Studies aimed to identify the correct dose and duration of gastric acid inhibition therapy in RYGB patients are needed.

NSAIDs, including low-dose antiplatelets drugs used for cardiovascular prevention, are associated with an increased risk of gastroduodenal ulcers, erosions, and bleeding [41]. Therefore, NSAID therapy has been considered as a factor also involved in marginal ulcer development in RYGB patients, but data are conflicting. Indeed, the prevalence of NSAID therapy in the anastomotic ulcer patients was widely ranging from 0 % [26], 10 % [25], 11 % [16] 7–16 % [19], 16 % [12], and 28 % [35]. Moreover, in a large series, the majority of patients who developed marginal ulceration were taking NSAIDs despite written and verbal precautions [8]. In addition, over-the-counter use of NSAIDs in some patients could be not excluded. Of note, NSAIDs use has been also associated with anastomotic ulcer perforation [8, 34].

Tobacco use has been associated with marginal ulcer development. Smoking and nicotine elevate levels of gastric ulcerogens and inhibit nitric oxide synthesis, which leads to a reduction in angiogenesis in the gastric mucosa causing ischemia [13]. The potential role of smoking on anastomotic ulcer development and ulcer perforation has been suggested in different studies [12, 20, 40]. A multivariate analysis performed on data of 81 marginal ulcer cases detected on 226 RYGB patients showed that both smoking (OR = 30.6, 95 % CI: 6.4–146) and NSAID use (OR = 11.5, 95 % CI: 4.8–28) significantly increase risk of marginal ulcers following surgery, while PPI therapy was protective (OR = 0.33, 95 % CI 0.11–0.97) [13]. Alcohol consumption, open and laparoscopic surgery, age, gender, and

surgeon experience were not significant predictive factors, while *H. pylori* infection was not taken into account in this study.

Different studies evaluated the role of surgical-related procedures on marginal ulcer onset. The use of absorbable suture was found to significantly reduce anastomotic ulcer onset as compared to permanent suture, the incidence being 1.3 % vs 2.6 % [11], 2.4 % vs 13.4 % [23], and 0 % vs 1.6 % [6]. However, others found no difference between the sutures used (7 % vs 8 %) [16]. A study found that marginal ulcer incidence tended to be lower by using reinforced stapler with bovine pericardium strips as compared with standard stapler (2.9 % vs 6 %; $P=0.06$) [25], while no improvement emerged with collagen matrix staple-line reinforcement [29]. Other studies found no difference between the use of 21-mm and 25-mm stapler [17], as well as among hand-sewn, linear-stapled, and 25-mm circular-stapled anastomosis [28].

The orientation of the gastric pouch also has been hypothesized to play a role in acid secretion and marginal ulceration development, and the formation of a small gastric pouch with a lower acid production seems to reduce the incidence of marginal ulcer [42]. Moreover, by excluding parietal cells from the gastric pouch, creating a smaller reservoir, and building the gastrojejunostomy using the greater rather than the lesser curvature, the anastomotic ulcer incidence was as low as 0.6 % [5]. Finally, incidence of marginal ulcer was significantly lower following vertical banded gastroplasty as compared to RYGB (12/60 vs 10/22; $P=0.027$) [14].

11.4 Therapy

The first attempt to minimize the marginal ulcer development should be its prevention by improving the surgical techniques. The use of absorbable suture and building a very small gastric pouch through the greater curvature are considered surgical adaptations able to reduce anastomotic ulcer development [5, 11]. In addition, a therapy aimed to reduce gastric acid secretion is advisable as postoperative prophylaxis. Such a preventive therapy has been found to be effective [16], but it was not always performed [44]. However, the appropriate drug, dosage, and duration of such a preventive therapy have not been established.

When a marginal ulcer develops, a therapy is required to both heal the lesion and to prevent potential ulcer complications. Medical therapy mainly consists of antisecretory therapy with PPIs. Differently from peptic ulcers, these lesions tend to require a prolonged therapy, usually for 3–4 months [5], and repeat endoscopy is recommended to confirm ulcer resolution. Such a therapy is generally effective in healing marginal ulcers [16, 43, 44]. In some studies, sucralfate suspension has been added to PPI therapy, although there are not robust evidence on its efficacy. In addition, potential causative factors—such as NSAID use, the presence of a remnant of suture at the ulcer base, and smoking—should be removed [11]. In detail, long-term cessation of tobacco use could be useful, since some evidences would suggest that resuming smoking is associated with marginal ulcer recurrence and complications [12, 20]. Unfortunately, some marginal ulcers may occur despite the absence of *H. pylori* infection and NSAIDs use, and a preventive PPI therapy was performed [26]. In selected refractory cases a reoperation is needed [45].

11.5 Experimental Therapies

Some experimental therapeutic approaches have been tested as a potential therapy for anastomotic ulcer prevention and healing [46]. Platelet-derived factors (VEGF, TGF-β factor, platelet factor-4) have been found to be able to promote tissue growth, new angiogenesis, and ulcer healing. In rat model, oral administration of platelet-rich plasma significantly accelerated healing of acetic acid-induced gastric ulcer [47], suggesting a potential role of platelet factors also in anastomotic ulcer healing. The use of becaplermin gel—a recombinant human PDGF-BB—on the anastomotic line just after completion of the colon anastomosis reversed the detrimental effects of ischemia and promoted anastomotic healing in an experimental model [48]. In a pig

model, a suture-free glued small bowel anastomosis using a fibrin-covered collagen fleece achieved an improved healing without onset of a deep ulcer at the anastomotic line which occurred at conventional sutured anastomosis [49]. Similarly, the subserosal injection with recombinant human granulocyte–macrophage colony-stimulating factor in the perianastomotic area improved the healing of ischemic colon anastomoses in rats [50]. Leptin potentiates endothelial cell proliferation and increases collagen synthesis, and its potential role in improving anastomosis healing when administered intraperitoneally in rats has been suggested [51]. Finally, a recent experimental study in rats showed a halved incidence of ischemia-induced colonic anastomotic ulcer by local injection of adipose-tissue-derived stem cells as compared to controls [52]. Although interesting, data of these studies need to be verified in humans. In addition, the efficacy of such potential therapeutic approaches has been mainly investigated on colonic anastomoses, and consequently, these results may not be directly applied to gastrojejunal anastomosis where gastric acid plays an adjunctive detrimental role.

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12 Endoscopic Treatment of Anastomotic Recurrences in Oncologic Patients

Antonella De Ceglie, Andrea Parodi, and Massimo Conio

12.1 Upper Gastrointestinal Tract

Locally recurrent upper gastrointestinal (GI) cancer is a common problem after surgical resection.

Dysphagia, nausea, and vomiting after esophageal or gastric resection for cancer are observed in 20 % of patients due to malignant local recurrence, with or without distant metastasis [1].

Most of these recurrent tumors are unsuitable for further radical and even palliative surgery due to the advanced stage of the disease and the poor condition of patients. Surgery has a significant morbidity and mortality rate and requires prolonged hospital stay, and the successful control of symptoms is achieved in about one half of these patients [2–6].

Most patients who develop a local recurrence after surgery have undergone previous chemotherapy and/or radiotherapy. Often, further treatments are usually not possible due to the poor general condition of these patients.

Palliation is the only choice that can be offered, improving the quality of life in patients with a short life expectancy [7].

Upper GI tract patency can be obtained by using a self-expandable metal stent (SEMS) or by other methods such as laser ablation, argon plasma coagulation (APC), photodynamic therapy (PDT), endoscopic alcohol injection, or brachytherapy [8–10].

12.1.1 SEMS for Recurrent Malignant Obstruction in Upper GI Anastomoses

Although most previous studies focused on stent insertion for inoperable malignant upper GI obstructions, only limited experiences of stent placement for neoplastic anastomotic recurrence after esophagectomy and gastrectomy are available (Table 12.1) [4, 5, 7, 11–24].

In these patients, stent placement may be more difficult due to anatomic alteration resulting from surgery, and sometimes functional results are disappointing [17, 18].

An accurate endoscopic and radiologic evaluation is mandatory before stent placement in order to know the type of surgical procedure performed.

The lack of symptomatic improvement after stent insertion may be due to multiple bowel strictures or ileus as a result of peritoneal seeding [4, 17, 18].

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Table 12.1 Published experience on stents in patients with neoplastic anastomotic recurrence after esophagectomy and gastrectomy

Author	Year	Study origin	Study design	N. Pts	Side recurrence	Stent type	TS %	CS %	Major complications stent related %	Mortality stent related %
De Palma et al. [11]	1998	Italy	PS	16	Esophagogastric A. Esophagojejunal A.	Plastic stent Ultraflex stent Microvasive stent Watertown stent Mass stent	81.2	100	23	6.2
Yates et al. [13]	1998	USA	PS	11	Gastroduodenal A. Gastrojejunal A. Duodenum Jejunum	Wallstent (*biliary and tracheobronchial*) Endocoil Ultraflex stent	91	82	0	0
Lee et al. [14]	2001	Korea	RS	11	Gastrojejunal A. Gastroduodenal A.	Duodenum Jejunum A. Song stent	87	82	0	0
Siersemaet al. [15]	2001	The Netherlands	RS	31	Cervical esophagogastric A. Esophagojejunal A.	Covered Gianturco Z stent Partially covered Flamingo Wallstent Partially covered Ultraflex stent	90.3	100	19.3	0
Jeong et al. [4]	2004	Korea	RS	25	Gastrojejunal A. Esophagojejunal A.	Choo stent Niti-S stent Song stent	96	100	20	0
O'Connor et al. [12]	2004	Ireland	CR	2	Gastrojejunal A.	Wallstent	100	100	0	0
Solt et al. [24]	2004	Hungary	CR	2	Gastrojejunal A. Esophagojejunal A.	Boubella FerX-ELLA	100	100	0	0
Naso et al. [21]	2005	Italy	CR	3	Esophagojejunal A.	Esophacoil	100	100	0	0
Perez-Roldan et al. [16]	2006	Spain	CR	3	Esophagoenteral A.	Ultraflex stent	100	100	0	0
Song et al. [5]	2007	South Korea	RS	20	Gastrojejunal A. Esophagojejunal A.	Niti-S stent covered Niti-S stent uncovered	100	80 uncovered 100 covered	0	0
Yang et al. [19]	2007	South Korea	RS	16	Gastroduodenal A.	FC retrievable stent Covered dual stent	81	100	19	0

Kim et al. [23]	2007	South Korea	RS	32	Esophagojejunal A.	FC retrievable stent Covered dual stent	94	91	31.2	0
Song et al. [18]	2007	South Korea	RS	39	Gastrojejunal A.	Song FC stent FC retrievable stent Bare nitinol stent Dual stent	100	90	25.6	5.1
Cho et al. [20]	2009	South Korea	RS	20	Esophagojejunal A Gastroduodenal A. Gastrojejunal A.	Niti-S stent Choo stent	100	70	30	0
Kim et al. [17]	2009	South Korea	RS	47	Esophagojejunal A. Gastrojejunal A.	Niti-S stent (*covered/uncovered*) Choo stent (*covered/uncovered*)	95.7	87.2	27.6	0
Tong et al. [7]	2010	China	PR	35	Esophagojejunal A. Esophageal remnant GOO Extrinsic compression ERF	Ultraflex stent Choo stent Niti-S stent	97.6	100	14	0
Kim et al. [22]	2011	South Korea	RS	35 *39 stent*	Esophagojejunal A. Gastroduodenal A. Gastrojejunal A.	Choo esophageal stent Hanaro esophageal stent Niti-S esophageal, pyloric/duodenal stent Wallstent colonic stent WallFlex duodenal stent	92 of 39	90 of 39	44 of 39	0

N number, *Pts* patients, *TS* technical success, *CS* clinical success, *PS* prospective study, *A* anastomosis, *RS* retrospective study, *CR* case report, *FC* fully covered, *GOO* gastric outlet obstruction, *ERF* esophagorespiratory fistula

Multiple strictures occur in 11 % of cases, and stent placement for two successive synchronous strictures is exceptional [13].

SEMS insertion may be performed both by endoscopically guided and by fluoroscopically guided methods. Similar high technical success (TS) and clinical success (CS) rates have been reported (92 and 90 % TS and CS, respectively, in endoscopic approach vs TS at 94–100 % and CS at 90–96 % in fluoroscopic approach) [4, 5, 22, 23].

However, the advantages of the endoscopic method in patients with distal gastrectomy are the ease of accessing the stricture site and the avoidance of looping the delivery system through the dilated gastric lumen due to the stiffness of the endoscope [20].

The friction between the working channel of the endoscope and the long delivery system may result in a difficult stent insertion when the endoscope is in an angulated position [22, 25]. Balloon dilatation can be exceptionally performed when the tightness of strictures does not allow the introduction of the delivery system; excessive dilatation should be avoided to prevent stent migration [24].

A stent at least 2–4 cm longer than the stricture should be chosen to allow for a 1–2 cm extension beyond the proximal as well as distal tumor margins [15].

Generally, in patients treated with SEMS, dysphagia is relieved in approximately 90 % of cases, and these patients undergo significantly fewer procedures, thus spending fewer days in the hospital [26, 27].

Stent placement has several advantages over surgery: it is a less-invasive procedure is preferred both by the patient and surgeon because of its lower morbidity, shorter procedural time and hospital stay, as well as faster recovery of gut function [17, 18, 28].

This is important for patients whose life expectancy is of 4–6 months, or less.

The overall survival rate for stent-treated patients has been reported to be similar to that for patients undergoing surgery, whose hospitalization is three times longer and costs are three times greater [29].

The recurrent rate of stenosis in patients with SEMS placed for anastomotic malignant obstruction ranges from 8 to 46 % after an interval of 2–21 weeks. It is generally due to tumor in-overgrowth [5, 30].

Some studies report that early occlusion of SEMS (within 4 weeks after their implantation) occurs more frequently in patients with the stent at the anastomotic level, than in those treated for unresectable cancer, but the causes are unknown [5, 6, 31].

Chemotherapy could decrease the tumor ingrowth and overgrowth; however, chemotherapy after stent placement is likely to shrink the tumor, increasing stent migration, if a covered SEMS has been used [5, 19, 32].

Stent migration rates range from 4.2 to 27.8 %; a pooled analysis of 21 studies reports that migration rate was 2.7 and 16 % for uncovered and covered stents, respectively [33].

An appropriate choice among the marketed SEMS according to the type of surgery performed may reduce the migration rate of stents placed in malignant recurrences [17].

A retrospective study reported that a double coaxial stent had a longer patency and lower migration rate than an uncovered stent in anastomotic recurrence [5].

At present, several types of SEMS are available, varying by type of alloy, configuration, degree of shortening after their release, lengths and diameters, presence, type, and extent of covering, delivery system, expandable force, presence or absence of anti-reflux valve, and removability.

Most SEMS are made of nitinol, an alloy of nickel and titanium, whose peculiarity is superelasticity and shape memory.

The covering is either polyurethane, silicone, or polytetrafluoroethylene (PTFE). Their flexibility, the small diameter of the delivery system, and the large availability of models allow the treatment of any type of malignant obstruction [26, 34].

There are no data to date demonstrating significant differences in outcomes or complications among SEMS types. Therefore, the choice of specific SEMS is often based on the endoscopist's

experience, although the initial stent selection has a significant impact on the clinical outcome in patients with inoperable malignancy [35].

Use of a self-expandable plastic stent (Polyflex® stent, *Boston Scientific*, *Natick*, *MA*, *USA*) is not recommended in GI anastomotic malignant recurrence. The major disadvantage of the current version of plastic stents is the large diameter and stiffness of the stent delivery system when compared with metal stents. Therefore, plastic stents cannot be released in patients with angulated strictures as in anastomotic ones.

SEMS may be placed hardly in some cases, especially in the presence of narrow bowel loops. In such situations, SEMS cannot fully expand, and they may migrate or cause perforation due to excessive stretching of gut wall, determined by the device. New D-Weave Niti-S colonic stent (*TaeWoong Medical Co*., *Seoul*, *South Korea*) has characteristics that may reduce the risk of such complications. It is a self-expandable nitinol stent, whose particular configuration confers some interesting properties to the device, such as compliant flexibility, high expansible force, and negligible foreshortening, in order to reduce the risk of migration, perforation, and inadequate expansion [36].

SEMS for malignant anastomotic obstruction after:

- *Esophagectomy*

  For patients with a gastric tube interposition after esophagectomy, recurrent tumor growth occurs at the level of cervical anastomosis [37].

  Endoscopic placement of a stent for lesions within a few centimeters of the upper esophageal sphincter (UES) is challenging. Complications such as migration, perforation, and tracheal compression can occur. The opening of the upper flared end of a regular esophageal SEMS is often incomplete and causes an intolerable foreign body sensation, leading to an inadequate swallowing capacity [15, 38, 39].

  The use of SEMS with a diameter <18 mm could minimize patient intolerance and stent-related complications [15, 39].

  The risk of distal migration of the stent is high as the length of the anastomotic stricture is short, preventing an adequate adhesion. In fact, even placing a 6-cm stent, most of it is free into the stomach.

  Siersema et al. inserted 4 covered Gianturco Z stents, (body diameter/flared ends: 18–25 mm) and 6 partially covered Ultraflex stents (body/flared ends diameter: 18–23 mm) in 10 patients with a recurrent tumor located in the proximal part of the gastric tube interposition. They obtained technical success rate of 90 %, improvement of dysphagia of at least 1 grade, and complications and recurrent dysphagia due to tumor overgrowth in 30 and 20 % of patients, respectively [15].

  In selected cases, as in the one mentioned above, anatomic morphology may prevent the use of SEMS. The only palliative option we use is thermal ablation with APC or neodymium: yttrium–aluminum–garnet (Nd:YAG) laser.

  Small diameters SEMS (12, 14, 16 mm the body; 14, 16, 18 mm the upper flared end) may be used in patients with neoplastic recurrence occurring after chemo/radiation treatment and surgery, for laryngeal cancer.

  Montgomery salivary bypass tube (MSBT) (*Boston Medical Products*, *Westborough*, *USA*) may also be used as a palliative measure in this subgroup of patients.

  MSBT is a silicone prosthesis with a flared upper end. It is available in 7 sizes, ranging 8–20 mm. The length of the stent is 191 mm.

  It can be placed trough the stricture using a Savary-Gilliard dilator. The stent is released with a finger, inserted deep in the throat, when the dilator is partially retracted. This maneuver allows the mobilization of the MSBT. The final adjustment is made pushing gently the stent with the Savary and, in the end, with the tip of the scope.

  However, its upper flared end has a large diameter, and it should be adapted according to the modified anatomic morphology, by cutting it with scissors before its introduction [40–42].

  The onset of an esophagorespiratory fistula (ERF) is an ominous complication that can occur both in patients with esophageal cancer

Fig. 12.1 New BETA™ Stent (Courtesy of TaeWoong Medical Co., Korea)

and also in those who underwent previous surgery. ERF can be successfully sealed by using of covered SEMS. Late erosion into the trachea may be a stent placement complication; however, it should be kept in mind that these patients have a short life expectancy (usually less than 3 months) [43].

- *Esophageal Resection*
  After lower third esophageal resection, the placement of a stent across the esophagogastric anastomosis has an increased chance of migration because of the relatively more spacious stomach into which the distal end of the SEMS projects freely [35].
  The use of a large bore covered stent has been suggested in order to avoid both ingrowth and migration [7, 44].
  Flexible stents are preferred for angulated strictures to prevent that the ends of the prosthesis from assuming an eccentric position into the lumen leading to pressure necrosis, ulceration, bleeding, perforation, and esophagoaortic fistula [25].
  In these cases, the new conformable stents by TaeWoong (*BETA™ Stent*, *TaeWoong Medical Co*., *Korea*) might represent a useful solution. This is a prototype of a conformable SEMS able to fit into angulated or tortuous strictures, thus avoiding the risk of pressure necrosis. Fully covered design allows reposition or removal of the device. Two additional covered mesh (double layer) should prevent migration. However, studies are ongoing in order to evaluate their safety and efficacy (Fig. 12.1).
- *Gastrectomy*
  Kim et al. reported a high technical and clinical success rates (94 and 91 %, respectively) in 32 patients with malignant stricture following total gastrectomy with esophagojejunostomy using fully covered stents (*TaeWoong*, *Ilsan*, *Korea*, and *dual stent S&G Biotech*, *Seongnam*, *Korea*) placed under fluoroscopic guidance [23].
  The covering is associated with a lower risk of stent-related ulcerations and no tumor in growth; although the migration rates are generally high for covered stents, the migration rates of covered stents in malignant strictures at the site of an esophagojejunostomy are lower than those in malignant primary gastroduodenal strictures (9 % vs 21–28 %) [23, 30, 45]. Uncovered stents are more suitable for insertion in the afferent loop after gastrojejunostomy and loop esophagojejunostomy or at gastroduodenostomy in Billroth-I reconstruction; covered stents could create a pressure on the ampulla of Vater causing biliary obstruction [13, 17].
  Kim J et al. in their retrospective analysis of the endoscopic placement of SEMS in 35 patients with malignant recurrence after total or subtotal gastrectomy (15 with total gastrectomy, 8 with subtotal gastrectomy and Billroth-I reconstructions, 12 with subtotal gastrectomy and Billroth-II reconstruction) reported TS and CS in 92 and 90 %, respectively, with no significant differences between the stent types (covered vs uncovered).
  Complications were similar in the gastrectomy group and in the subtotal gastrectomy group; the median patency duration did not differ between covered and uncovered stents (10.7 and 11.4 weeks, respectively, $p = 0.515$) [22].
  However, only a few cases with a small number of patients are reported on stent placement for recurrent malignant obstruction after gastrojejunostomy.
  In our experience, in patients with local recurrence after esophagojejunal anastomosis, we use partially covered enteral stents to bypass the angulated portion of the jejunum below the stenosis, if a peritoneal seeding is present (Fig. 12.2).
  As first step we release at the level of the anastomosis a fully covered double layer SEMS to avoid distal migration. After 24–48 h, we insert, if needed, an enteral stent overlapping

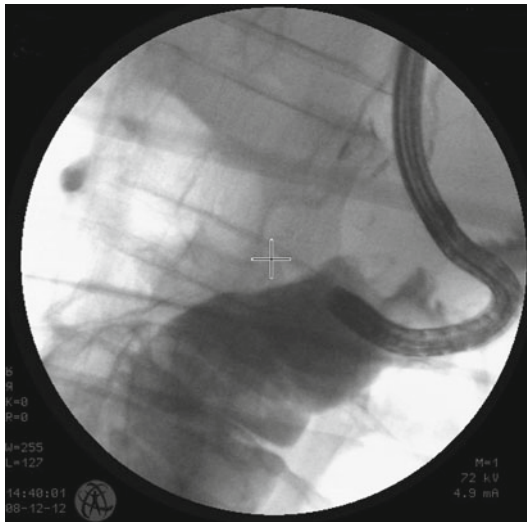

Fig. 12.2 Pediatric gastroscope is inserted through the esophageal SEMS (fully covered double layer Niti-S 28×20×100 mm, Courtesy of TaeWoong Medical Co., Korea) until reaching the narrowed and stenotic jejunal loop

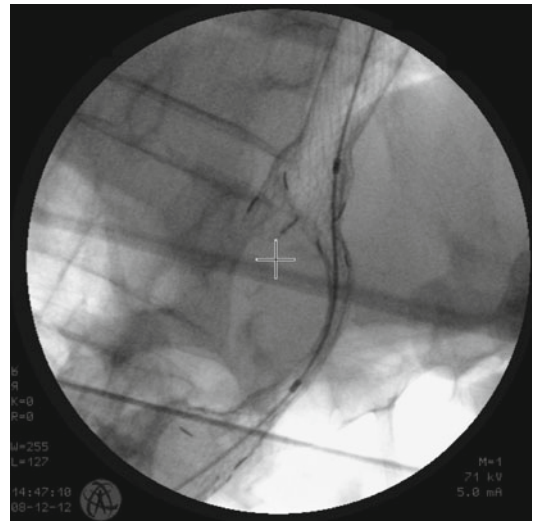

Fig. 12.4 Enteral SEMS (partially covered ComVi Enteral Colonic Stent 20×80 mm, Courtesy of TaeWoong Medical Co., Korea) is introduced over the guidewire through the esophageal SEMS, up to completely bypass the jejunal stenosis

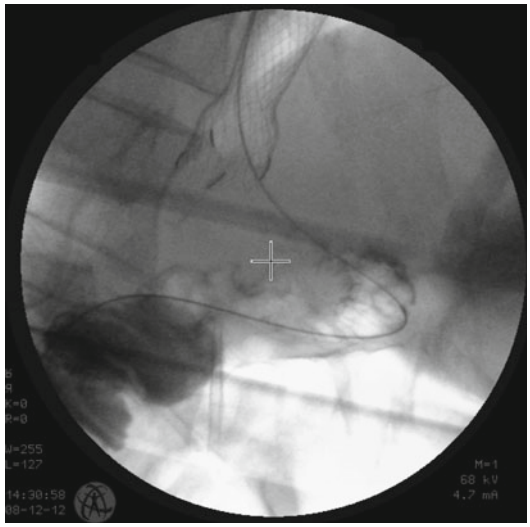

Fig. 12.3 The guidewire is positioned beyond the stenotic jejunal loop, under X-ray control

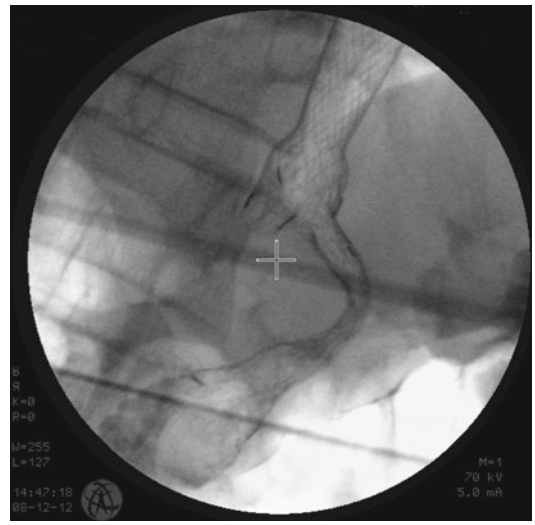

Fig. 12.5 Enteral SEMS correctly released crossing the jejunal stenosis. The proximal end of enteral SEMS is positioned inside the distal part of esophageal SEMS

the distal portion of the esophageal one (Figs. 12.3, 12.4, and 12.5).

This approach allows the patients to swallow a semiliquid diet.

Knowledge of the type of surgical anastomosis and determination of the pattern of tumor recurrence are important for successful stent placement.

Sometimes neoplasia occludes the afferent loop or the efferent loop (or both), and distinguishing them may be difficult even under combined endoscopic and fluoroscopic control.

When two stents are required, one in the afferent and one in the efferent loops, because both

involved by the neoplasia, the upper end of the stent in the efferent loop should be placed above the upper end of the stent in the afferent loop; otherwise, the passage of food into the efferent loop would be hindered. Technically, it is preferable to place a stent delivery system simultaneously in afferent and efferent loops, before stent deployment; otherwise, the deployed stent in one loop might occlude the anastomosis, hampering the insertion of the guidewire through the other loop to place the second stent. If a jejunojejunostomy distal to the obstruction is present, the placement of only one stent in the afferent or efferent loop should be sufficient [18].

12.2 Lower Gastrointestinal Tract

Disease recurrence after apparently curative surgery for colorectal cancer (CRC) represents a significant problem in 15–25 % of patients.

More than 50 % of the patients will have local recurrence only, without distant metastasis, and this typically occurs within the first 2 years after primary surgery [46–50].

The local recurrence rate of colon cancer is thought to be lower than that of rectal cancer (0.8–1.4 % vs 7.8 % vs 7.8–13 %) [51–53].

Although the 5-year survival rate of patients who had curative reoperation has been reported to be 47.7 % compared with the 10.3 % of those who have no curative operation, about 53 % of patients are not surgical candidates because the lesion of anastomotic recurrence is already widespread at the time of endoscopic diagnosis [50, 54].

Approximately 80 % of the local recurrences are perianastomotic or involve the pelvic area [55].

From a clinical point of view, bowel obstruction is uncommon and usually indicates advanced disease. These patients are mainly referred for endoscopic palliative treatment aimed at controlling bleeding, and this is carried out by using a thermal technique (APC, Nd:YAG laser). In most cases, when patients survive for several months and the local disease progresses causing obstructive symptoms, it is recommended to place a covered SEMS.

SEMS alleviate obstructive-related symptoms and avoid stoma formation. Moreover, the pressure of the stent on the lesion may also control bleeding. The possibility of placing a partially covered SEMS can be considered for the prevention of migration.

12.2.1 SEMS for Recurrent Malignant Obstruction in Lower GI Anastomoses

To our knowledge, only one study reports about the use of SEMS in the management of colonic obstruction due to a malignant anastomotic stricture [56].

However, successful palliation of primary obstructing CRC by stenting can be achieved in 85–100 % of patients, with some stents remaining patent and in place for more than 1 year [57, 58].

SEMS specifically designed for colonic use are available in mid-body diameters of up to 25 mm, although any type of SEMS can be used within the colon [59].

Many of the colonic SEMS are available outside the USA; currently, the Food and Drug Administration (FDA) in the USA has approved three stents for use in the large bowel, all of them uncovered because of the high migration rate associated with covered SEMS [59, 60].

Most SEMS are constrained on delivery catheters and can be placed through the scope or under fluoroscopic control only. The latter method is limited to the left colon, whereas, as for primitive CRC, stents may be placed endoscopically in the right colon anastomotic recurrence [26, 37].

A variety of adverse events can occur after stent placement, including perforation, stent migration, bleeding, stent malpositioning, and the occlusion of the stent by stool [26].

Stents placed low in the rectum may produce tenesmus and fecal incontinence, although one study reported that placement of SEMS within 5 cm of the anal verge was tolerable in most patients [61].

12.2.2 Non-stent Treatments

12.2.2.1 Upper GI Tract

All endoscopic therapies for palliation of malignant primitive or recurrent cancer, except stenting, require multiple sessions to maintain luminal patency with negative impact on patient quality of life. For this reason they have been progressively abandoned [62].

Therapy with Nd:YAG laser is expensive and not available in many centers [63].

Complications as perforation, bleeding, and tracheoesophageal fistula have been reported in 4–20 % of patients [64].

At present laser therapy is not used, except for those patients with proximal esophageal lesions in whom stenting is not feasible [65].

An alternative to laser therapy is APC (argon plasma coagulator). Using APC in obstructive esophageal cancer, recanalization has been reported in 89 % of patients and perforation in 1–8 % of cases [66, 67].

Photodynamic therapy is a nonthermal photochemical process of tumor ablation, technically easy to perform, with reported palliation of dysphagia in about 90 % of patients and a dysphagia-free interval ranging from 70 to 85 % [68, 69].

Comparing PDT with laser therapy, rates perforation reported are 1 % vs 7 % and time of palliation failure was 34 days vs 42 days, respectively.

PDT is a relatively expensive treatment modality, and side effects include esophageal stricture, Candida esophagitis, pleural effusion, and skin photosensitivity [65].

Brachytherapy may relieve dysphagia in patients unfit for surgery. Randomized trials comparing stenting with brachytherapy show that both have been proven effective with few complications and similar cost [70, 71].

However, dysphagia score improved more rapidly after stent placement than after brachytherapy, but long-term relief of dysphagia was better after brachytherapy.

The choice between stent placement and brachytherapy as palliative treatment of dysphagia might be done depending on the patient's life expectancy: SEMS are indicated for patients with a short life expectancy, who require a rapid relief of dysphagia, while brachytherapy should be considered in patients with longer survival.

12.2.2.2 Lower GI Tract

Endoscopic techniques other than stents for palliation of recurrent anastomotic colorectal cancer are as follows: laser ablation and APC. Photodynamic therapy is not recommended due its side effects and the high complication rate [72].

Therapy with Nd:YAG laser is an effective treatment in restoring lumen patency, although the effect is not long lasting; benefits are also observed for palliation of bleeding and mucous discharge [59].

However, palliation becomes less effective as patients survive longer, dropping from 80–90 % initially to only 52 % at 6 months and 42 % at 12 months [73].

Disadvantages include the need for expensive equipment and the need to repeat procedures to maintain patency: each treatment session requires a relatively long time to complete ranging from 30 to 90 min with two to six sessions [74].

Serious complications (bleeding, perforation, severe pain, and formation of fistula and abscess) occur in 10–15 % of patients [75].

APC has the same technically limitations as laser therapy.

As all these treatments require periodic reiteration, they are not used anymore and have been supplanted by SEMS placement [72].

Conclusion

In patients with unresectable anastomotic malignant recurrence, SEMS represent a major breakthrough as they can rapidly restore recanalization of the gastrointestinal tract, may control bleeding, and avoid the reiteration of endoscopic procedures. In patients with colorectal malignancies, they prevent the need of a surgical stoma, improving the quality of life of these patients. The wide range of available SEMS requires an expert knowledge by the endoscopist in order to make the appropriate choice to obtain the best results

and minimize the onset of complications. The new conformable SEMS seems to offer a good opportunity in patients with angulated strictures, especially after total gastrectomy.

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13 Therapeutic Endoscopy for the Treatment of Benign Anastomotic Strictures

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13.1 Introduction

Anastomotic stricture-postulated pathogenesis includes surgical technique, inflammation, fibrosis and scar connected to metallic clips, suture threads and sealed leakage, lesion site, marginal ulcers, anastomotic dehiscence, intrasurgical hemorrhage, abscess, ischemia, obesity, adjuvant radiotherapy, and colostomy [1]. The incidence of *anastomotic strictures* is difficult to discern and differs considerably among published studies (2–30 %); the rate of anastomotic strictures has increased in recent years as a result of bariatric surgery development and circular stapler use, particularly when small-caliber circular stapling devices are used (25–28 mm). A symptomatic stricture is identified by the association of specific clinical signs and symptoms and well-defined radiological and/or endoscopic images. Not all stenoses are clinically evident in fact *colonic anastomotic strictures* cause symptoms in only 2–5 % of cases (when anastomosis diameter is less than 9 mm) [2]. The mean time between colonic surgery and the first symptoms related to anastomotic stenosis is about 7 months (range 1–9), while the mean time between the operation and the first endoscopic treatment is about 10 months [3]. Benign strictures can be subdivided into simple or complex, and anastomotic stenoses can normally be included in the second group. Simple strictures are short, focal, and straight and, in most cases, allow the passage of a normal diameter endoscope, whereas complex strictures are usually longer than 20 mm, irregular, angulated, with a severely narrowed diameter that is not crossable by an instrument. This classification is very useful because the former strictures are easily treatable endoscopically, generally requiring 1–3 dilations for symptom resolution and recurring in up to 30–40 % of cases; the latter, on the contrary, are much more difficult to treat, requiring multiple dilation sessions (from 3 to 8), and are associated with higher recurrence rates [2]. Refractory or recurrent anastomotic strictures are characterized by an inability to successfully resolve the anatomic problem after 5 dilation sessions at 2-week intervals (refractory) or by an inability to maintain a satisfactory luminal diameter for 4 weeks once the target diameter has been achieved (recurrent) [3]. Criteria for predicting the lack of *effectiveness of endoscopic treatment* include a short time interval between surgical intervention and appearance of the stenosis and a small initial size of the stenosis; fibrous scarring at the anastomosis is probably complete only about 3 months after surgery, which explains the tendency toward stricture formation after a dilation executed during the previous 90 days [4].

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13.2 Anastomotic Strictures: Treatment

Treatment of anastomotic strictures is indicated whenever there is an associated clinically significant functional impairment or a need to access beyond the stenosis for diagnostic or therapeutic purposes. Surgical treatment is associated with technical difficulties and complications and does not completely eliminate the risk/possibility of restenosis; *endoscopic treatment* should therefore be considered the first choice of therapy [5]. Surgery may be considered necessary only when repeated endoscopic treatments have proven unsuccessful (up to 30 %) and in cases of cancer recurrence (repeated failed endoscopic attempts may be a sign of cancer recurrence). A variety of endoscopic techniques have been proposed: mechanical or balloon dilators, electroincision or Nd:YAG laser/argon plasma coagulation (APC) stricturotomy associated or not with balloon dilation, temporary placement of self-expandable metal (SEMS) or plastic (SEPS) stents, and definitive insertion of biodegradable stents (BD) [5–7]. Endoscopic treatment is effective and safe and, when unsuccessful, does not preclude the possibility of further surgery [5]. *Balloon dilation*, with its high success rate (80–90 %; short-term results are better than long-term results: 3 weeks, 87.2 % vs 3 months, 66.6 %), low complication rate, and good tolerability, is currently the recommended treatment and the most widely used method in the literature [5]. Unfortunately, about 30–40 % of anastomotic strictures recur during long-term follow-up, requiring repeated dilations. Such events, depending on stricture features, are associated with a significant impairment in the patients' quality of life, a higher procedural risk, and considerable long-term treatment costs [8, 9]. The management of refractory and recurrent fibrotic tight strictures is challenging, and temporary endoscopic placement of *fully covered stents* has been proposed as an alternative to surgical revision [10]. The use of uncovered SEMS is associated with hyperplastic tissue proliferation with fixation and difficulty, or entire impossibility, of removal, and with the appearance of long-term complications (recurrent strictures, bleeding, fistula, death); these devices are therefore not recommended or FDA approved for anastomotic strictures and should be avoided in these lesions [11]. Fully covered removable metallic or plastic stents and BD stents represent a new therapeutic approach that has led to a reduction in endoscopic sessions and stenotic relapses; however, it is also associated with a high risk of migration because the covering prevents tissue embedment [12]. Before stent placement and in cases of stent failure, intralesional *corticosteroid injection*, *electrocautery incision*, and *APC* should be tried as a last measure before considering surgical reintervention [12].

13.3 Endoscopic Dilation

Endoscopic dilators are the first treatment option in cases of simple stenoses and can be subdivided into *mechanical* (bougie) or *balloon-type dilators*. Mechanical dilators include bougies filled with mercury or tungsten (e.g., Hurst and Maloney dilators; Medovations, Milwaukee, Germantown, WI), metal olive dilators (Eder–Puestow; KeyMed, UK), and guidewire-assisted polyvinyl bougies (e.g., Savary-Gilliard, Wilson-Cook Medical, Winston-Salem, NC, and American Dilation System, C. R. Bard, Inc., Billerica, Mass); pneumatic dilators, "through the scope" (TTS; CRE, Hercules) or "over the wire" (OTW; Rigiflex, achalasia balloons), are available with or without a guidewire and can be inflated with water or, in the case of fluoroscopy use, contrast medium. Mechanical dilator and achalasia balloon characteristics enable them to be used exclusively when the anastomosis is near the mouth or anus. Savary-Gilliard and, in particular, TTS balloons are the most widely used dilators. Mechanical and pneumatic dilators have different mechanisms of action; the former exert both a longitudinal and radial force on the anastomotic stricture, while the latter deliver only a radial force that increases as the balloon diameter increases [8]. The choice of initial dilator size and maximal diameter per session is made on the basis of stenosis characteristics. During the same procedure the stricture is dilated with

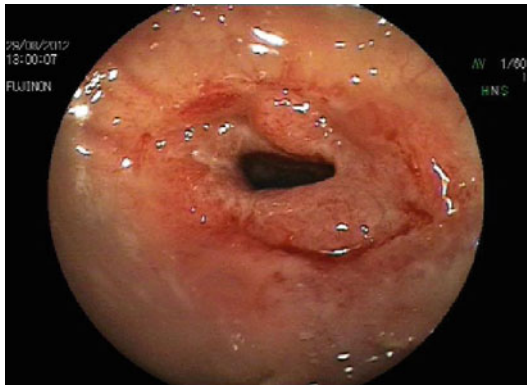

Fig. 13.1 Colonic anastomotic stricture: endoscopic aspect

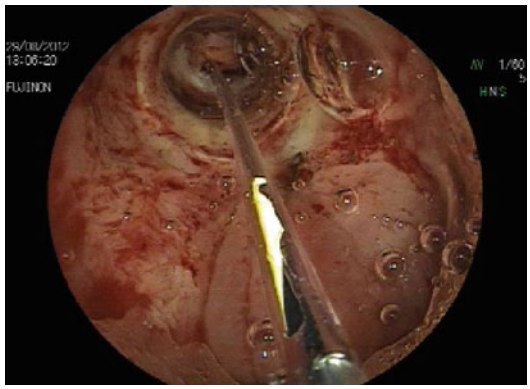

Fig. 13.2 Colonic anastomotic stricture: endoscopic dilation with TTS balloon

progressively larger dilators (6–20 mm) until a diameter deemed safe by the endoscopist is reached (a dilation of up to 12 mm is generally considered optimal in the esophagus and small bowel, while that of the colon is 18 mm or more). In very small strictures (5 mm or less), a less aggressive approach is preferred, the first dilation usually reaching a maximum diameter of 10–12 mm. In an attempt to reduce the risk of complications, the initial dilator diameter must be 1–2 mm larger than the stenosis, and it may be advisable to use no more than two dilators of successively larger diameters than the first device in the same session [8] (Figs. 13.1, 13.2, and 13.3). Inspection of the anastomosis after treatment is useful to confirm an enlargement of the lumen, to evaluate adequate hemostasis, and to exclude

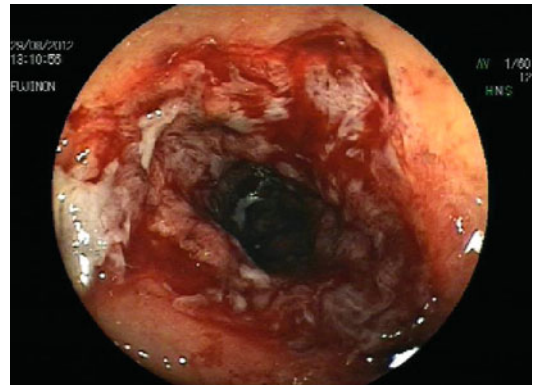

Fig. 13.3 Colonic anastomotic stricture: endoscopic aspect after dilation

ulcerations distal to the anastomosis. Endoscopic dilation is usually effective, and complete symptom relief ranges from 71 to 97.6 %, but dilatative efficacy decreases from short to long term (in esophagus this parameter varies from 90 to 83 % passing from 1 to 12 months and factors indicative of long-term persistence of good results are stricture shortness (length < 12 mm) and cranial position) [4]. Subsequent endoscopic treatments should only be performed in the event of symptom recurrence, with a mean time between dilation sessions of about 2 weeks. The mean number of endoscopic dilations for anastomotic strictures varies from 1 to more than 3 and depends on stenosis features and on the therapeutic strategy followed [8]. Dilation alone is probably not the best endoscopic approach to use in patients with early stricture formation after surgery, more effective treatments being steroid injection during the first dilation or stenting; however, further evaluation of these strategies is needed in randomized studies.

13.4 Stenting

Stenting therapy usually represents the last attempt before surgery in cases of refractory stenosis and is therefore the recommended treatment after 5 or 6 ineffective dilation sessions. Absolute contraindications are esophageal strictures located less than 2 cm from the superior esophageal sphincter and rectal strictures located

less than 5 cm from the anal sphincter [13]. Stent types include *partially covered SEMS and fully covered SEMS and* fully covered *SEPS* and *BD stents*. In *benign diseases* stents are not intended to be permanent and safe removal is an essential feature [14]. The technical success rate of stent placement ranges from 85 to 100 % [14, 15]. Dilation prior to stenting should be avoided (high risk of perforation), and it is not recommended to cross the stent with the endoscope at the end of the procedure (high risk of device dislocation). Endoscopic follow-up after stent placement is not well defined: some authors perform endoscopy after 4–6 weeks or earlier if complications occur, while others propose surveillance with endoscopy or radiology every 2 weeks, with stent removal in the event of stricture [14, 15]. The optimal duration of this treatment has not yet been established, and recommendations are based on data from small case series. Some authors report that 4–8 weeks after placement is the optimal time for removal [16]; during extraction reactive tissue in- and overgrowth can determine major and minor adverse events which subsequently require surgery [17]. Metal stents, long stenting duration, large-diameter devices, and high-expansion force are all associated with high rates of reactive tissue; this problem is infrequent with BD stents, and thus the development of new covered BD stents could further lower the rate of tissue ingrowth [18, 19]. Stent migration is mainly related to device features but is also linked to stenosis peculiarities, and short anastomotic strictures are stent migration-promoting factors. Attempts to prevent stent migration by clipping the device to the intestinal wall have shown poor results; in the large bowel, covered stents almost uniformly migrate even when fixation techniques are used, and so no dedicated covered colonic stents are currently commercially available in the USA [13]. Dilation or placement of a new stent after device explantation is sometimes necessary (up to 21 % in some studies); in cases of ineffective endoscopic treatment surgery is required (up to 50 % in some case series) [14]. Stent placement provides immediate symptom relief and may obviate the need for surgery in selected patients, but data on long-term patency and safety of this technique are lacking [14].

Metal stents. The main limitation of SEMS is tissue neoformation that causes recurrent symptoms in >15 % of patients, a high rate of complications, such as perforation and obstruction, and precludes easy stent removal; although hyperplastic tissue reaction is lower with covered stents, it has also been reported to occur with these devices [14]. With regard to *tissue reaction*, partially covered SEMS show low migration (overall 12 %), can be difficult and traumatic to remove, and should be avoided because of the high risk of *complications* (recurrent stricture formation and mucosal damage, bleeding, or perforation after removal); conversely, fully covered SEMS are easy to remove but have a higher migration rate than the former. SEMS are thus not recommended or approved for *benign strictures* by the US Food and Drug Administration [15]. Some recent studies have examined new coated or temperature-sensitive nitinol stents which show encouraging technical and clinical results and are easy to remove [16].

Plastic stents. SEPS were recently introduced to reduce the risk of hyperplastic tissue growth associated with metal stents. They are effective and safe compared to the metal devices and can be easily removed, but migration occurs more frequently, often when the stricture improves [18]. Polyflex stent (Boston Scientific Corp., Natick, Massachusetts, USA), a self-expanding plastic polyester silicone-coated stent, is particularly effective because the radial expansive force is similar to that of SEMS and the silicone coating resists tissue ingrowth and hyperplasia [18]. The Polyflex esophageal stent is currently the only FDA-approved retrievable stent marketed in the USA. Esophageal stenosis such as that found in refractory benign strictures is one of the FDA-approved indications for Polyflex stents [18]. SEPS stenting time is not well defined: although some authors consider 6 weeks as the optimal duration (X), a longer period probably results in a higher success rate in cases of refractory strictures. It has therefore been hypothesized that the optimal stenting time depends on stricture features. The role of SEPS is still widely debated

because of conflicting results from various studies, with success rates ranging from 0 to 94 % and an unexpected high rate of complications described in some cases series but not in others (in the majority of studies SEPS appear to be relatively safe) [20].

Biodegradable stents. BD stents would appear to eliminate the risk of mucosal hyperplastic reaction, have a shorter patency, show low migration, and do not require subsequent removal: the prolonged dilatory effect before absorption and the progressive degradation could represent a favorable solution for refractory anastomotic strictures (stent degradation is about 3–4 months and the radial force remains around initial values for the first 5 weeks, decreases to about 2/3 of the initial force after 7 weeks and further reduces to about 1/2 of the starting force at week 9) [21].

These stents often need an anastomotic stricture pre-dilation of up to 12–20 mm to facilitate the introduction of the delivery system and to ensure adequate device expansion; however, pre-dilation increases the risk of stent migration. Several authors advise endoscopy and fluoroscopy to be repeated at 1-month intervals in order to monitor stent position, patency, and degradation; in some studies clinical and radiographic follow-up is performed 1 week after insertion and again 1 month later, whereas endoscopic evaluation is only performed in the presence of symptoms [7]. Although mucosal hyperplasia after BD stenting can cause reobstruction, this problem responds well to single-balloon dilation and resolves completely after stent degradation [7]. Anastomotic stricture recurrence after complete stent degradation is easily resolved, treatment based on balloon dilation of up to 18–20 mm (usually only one session is needed to obtain an adequate lumen size) or on a new BD stent placement [22]. The main disadvantages of BD stents are that they can only be placed in areas close to the mouth or the anus [23], the devices tendency to migrate if they are not fixed to the wall, and that a second stent after degradation in more long-standing strictures may become necessary. Even if anastomotic stricture long-term patency after BD stents placement is better than after dilation, there is a lack of published series; probably a longer BD stent duration would be associated with a *higher long-term success rate*, and consequently new devices with delayed degradation process could well give a more prolonged benefit. The efficacy of steroid injections in improving the effects of BD stents warrants investigation [24, 25].

13.5 Incisional Therapy, Argon Plasma Coagulation, Intralesional Steroid Injection

There are no standard recommendations for the management of persistent or recurrent strictures resistant to dilation, and thus various techniques have been adopted: incisional therapy and Nd:YAG laser/APC, with or without dilation, intralesional steroid injection combined with dilation, stenting, and finally endoscopic surgery [6]. *Incisional therapy*, performed using a needle knife or polypectomy snare and evaluated in small cases series, is safe and particularly effective in short strictures (<10 mm). In one study it was used in patients previously treated with dilation therapy or not and showed a success rate of 87.5 % after only one session [26]. This treatment has been successfully used together with balloon dilation or APC in uncontrolled studies, showing a good safety profile [6]. A combination of APC and Savary dilation appears to be potentially useful in strictures that do not respond after three sessions of mechanical dilation [26]. In one study on 10 patients, *neodymium: yttrium–aluminum–garnet laser* used in association with balloon dilation determined technical and clinical success without recurrence or complications in 90 % of patients with a median follow-up of 82 months. In various small, uncontrolled studies, some authors treated recurrent anastomotic strictures with steroid injection followed by dilation (*intralesional steroid injections* increase the effect of dilation by reducing collagen formation through the local inhibition of the inflammatory response) [27]; steroid treatment combined with dilation has an uncertain benefit for the initial treatment of benign strictures [27].

13.6 Endoscopic Treatment in Different Anastomotic Sites

13.6.1 Esophagus

Anastomotic strictures after esophageal resection occur in 5–46 % of patients; although there is no universal consensus, an esophageal anastomosis is normally considered stenotic when the diameter is less than 12 mm. Proximal strictures are particularly difficult to treat and are at a *higher risk of complications* [26]. The success rate of dilation therapy ranges from 70 to 90 %, but 40 % of patients require more than 3 dilation sessions; the risk of relapse can be reduced by performing a dilation of 18–20 mm, but a diameter of 12 mm may be sufficient to mitigate dysphagia to solids [26]. Intralesional steroid injections associated with balloon dilations increase the maximum dilation diameter achieved and reduce the severity of symptoms (significant improvement in the dysphagia score: 0.63 ± 0.59 vs 2.42 ± 0.5, $P < 0.001$), the number of dilation sessions required, and the rate of recurrence [27]. The clinical success rate of fully covered *SEMS* is less than 50 % [28, 29]; a recent meta-analysis highlighted an improvement in dysphagia in 46 % of patients with benign strictures after placement of various removable stents, and another pooled analysis with Polyflex stent placement showed a clinical success rate of 52 % [18, 28]. In the literature more than 15 papers have reported promising results for Polyflex stents placed for benign esophageal disorders: technical success 96 % (range 75–100 %), clinical success 89 % (range 69–100 %), and migration 27 % (range 7–57 %) [18]. A number of studies have tempered initial enthusiasm regarding *SEPS* by reporting high stent migration (62.1 %), a low rate of long-term improvement after stent removal (17 %), the need for new stent placement (55 %), and dysphagia relapse (70 %) [18]. A recent review evaluated a total of 10 studies on 130 patients with benign esophageal *strictures* treated with SEPS placement (49 anastomotic strictures, 39 %): technical success 98 %, clinical success 52 %, early migration with fully covered stents 24 %, need for endoscopic reinterventions 21 %, and major complications 9 % [18]. Only a small number of studies have focused on the use of *BD stents*, reporting complete relief from dysphagia in 40–60 % of cases [19]; however, BD stents are "Conformité Européenne" marked, certified to conform to European regulations for the treatment of patients with refractory benign esophageal stricture. One study investigated the efficacy and safety of a BD stent (Ella-BD stent, Ella-CS, s.r.o., Hradec Kralove, Czech Republic) in 21 patients with refractory benign esophageal strictures, showing that this treatment is safe and effective: technical success 100 %, stent migration 9.5 %, recurrent dysphagia caused by stent obstruction secondary to hyperplastic tissue in- and overgrowth 5 %, clinical success after a follow-up of 6 months 45 %, and major complications 0 % [29]. Another recent study evaluated safety and long-term efficacy of the same stent in 28 patients with refractory benign esophageal stricture previously treated with multiple dilations associated or not with nonbiodegradable stenting; total technical success was 93 % and 13 patients were treated with sequential BD stent placement (median 3, range 2–8) showing that sequential stenting, in selected cases, may be a valid option to avoid serial dilations or surgery [30]. In cases of anastomotic strictures located near the upper esophageal sphincter, the use of stents has been associated with an extremely high rate of complications (almost 100 %), suggesting that dilation or incisional therapy may be better alternatives. Some esophageal stenoses are particularly complex making it very difficult to identify the true lumen of the anastomosis; in such cases an endoscopic "rendezvous" technique, i.e., combined antegrade and retrograde dilation, can be applied through a gastrostomy or jejunostomy to reduce the risk of a false route.

13.6.2 Stomach and Small Bowel

Anastomotic strictures associated with bariatric surgery are now the most frequent indications for endoscopic treatment (estimated rate of postoperative stricture formation following gastroplasty is about 2 %, while that for Roux-en-Y gastric

bypass [RYGB] is around 3–27 %) [31]. The most common region of anastomotic stricture is the site of gastrojejunostomy, and the mean time to diagnosis after surgery is generally 3 months [31]. Gastrojejunostomy should have a diameter of 10–12 mm: in case of higher diameter surgical treatment executed is useless, while in case of lesser diameter problems of canalization may arise. Endoscopic stricture control is achieved in 95–100 % of cases; the best endoscopic technique remains to be defined, but pneumatic dilation is the most widely used method, and many endoscopists prefer to use TTS balloons, dilating them to at least 15 mm in the first session in order to decrease the risk of recurrence [32]. As the optimal diameter of the pylorus is approximately 12 mm, balloons with a smaller diameter, e.g., such as 10, 11, or 12 mm, may be sufficient [32]. *Pneumatic dilation* is an effective and safe treatment strategy with a high overall success rate; the number of dilations required to successfully treat a gastrojejunal stricture is unknown, but many reviews have reported that the majority of patients require at least two dilation sessions [32–34]. Balloon dilation can produce desirable results in the short term (symptom improvement following the initial dilation is observed in 58–93 % of patients), but further research is needed to identify the endoscopic treatment modality that results in long-term success [33, 34]. Savary dilation is also effective and safe: 100 % clinical success has been achieved using a maximum diameter of 12.8 mm and performing endoscopies 1–2 weeks after each session, the majority of patients requiring only one (46 %) or two dilations (50 %) and not experiencing complications [35]. *Mechanical dilation* may be useful in case of pneumatic failure; using Savary with size of 15–18 mm in anastomotic strictures treated unsuccessfully with initial pneumatic dilation, clinical success is 100 % and complication rate is low (1.6 %) [33]. Diathermy combined with APC has been used in limited cases with good results (only one treatment session to gain long-term recanalization in 92 % of patients) [26]. The use of stenting in post-RYGB anastomotic strictures is not particularly frequent or useful because of the high stent migration rate (about 60 % of cases) whose occurrence is related to stenosis length and small bowel peristalsis [35]. A study has evaluated the clinical efficacy and safety of balloon dilation and stent placement in 63 patients undergoing treatment for early benign anastomotic strictures after gastric surgery: clinical success was achieved in 89 % of patients after a single-balloon dilation (49 %), multiple-balloon dilations (32 %), and stent placement (8 %), highlighting that pneumatic dilation is safe and effective and that stenting can be effective in selected refractory patients [35]. The development of *double-balloon endoscopy* has rendered possible the endoscopic therapy of anastomoses located in sites which in the past could only be treated by surgeons; various endoscopic treatments are currently possible for the small intestine, and stent placement is also feasible, depending on the lesion site [36, 37]. As the small intestine wall is very thin, great care must be taken during endoscopic therapy to avoid complications such as bleeding and perforation. Although endoscopic balloon dilation may be taken into consideration as the first therapeutic option, a single session is generally not sufficient and symptoms may recur after treatment [38]. Dilation diameter is determined on the basis of stricture size, and the first dilation is usually performed up to a diameter of 12 mm (this diameter allows intake of a low-residue diet); sometimes, with a higher perforation risk, it is possible to dilate up to 15 mm. In cases of a tight stricture, dilation should initially be limited to a small diameter and gradually increased in size in multiple therapeutic sessions [39].

13.6.3 Large Bowel

Colonic postoperative stricture, which usually occurs from 1 to 9 months after surgery in 5.8–30 % of cases, is more common after colorectal anastomosis and in cases of intraperitoneal stapled anastomoses rather than extraperitoneal ones [3]. Stricture occurs more frequently in cases of previous neoplastic resection ($p < 0.05$), and anastomoses of previous oncologic surgery are more difficult to treat than those of benign

resection (TTS balloons, technical success: benign resection 88–92.8 %, oncologic surgery 59–61.5 %) [2, 8]. A colonic anastomosis is generally defined as stenotic when it is not transitable by a 13 mm endoscope [2, 3]. Endoscopic dilation should be considered as the first therapeutic approach as it is immediately effective and repeatable and does not preclude surgery [2, 5]. *Balloon dilation* is the treatment of choice, with clinical success rates ranging from 86 to 97 % (usually 2 or 3 dilations are needed for a good long-term result) [2, 8]. Treatment end point is the easy transit of a standard colonoscope through the stricture after dilation. Ileocolic and colic anastomotic strictures can be dilated up to 15–20 mm without specific risks and sometimes, if the 20 mm diameter is easily reached, it is also possible to use a 30 mm balloon. In active Crohn's disease, long and complex anastomotic strictures with marked inflammation should not be dilated due to a high risk of perforation (11 %). When proximal to the anus, anastomotic strictures can be treated not only with TTS balloons but also with Savary dilators, Eder–Puestow metal olives, and achalasia balloons [40]. Treatment with Savary is clinically successful or partially successful in 80 % of cases; the majority of patients requiring 1–3 dilation sessions performed 14–21 days after the previous endoscopy [9]. Eder–Puestow metal olives can be used in rectal anastomoses; abundant scar tissue surrounding the stenosis could explain the low perforation rate [9]. Achalasia balloons show a 94–100 % clinical success in patients and have a low complication rate (0–11 %); the mean number of dilations ranges from 1 (29 %) to 4.5 (24 %), and the clinical success decreases from the short (87.2 %) to the long term (66.6 %) [2]. Several removable stents specifically designed for use in the colon are currently available [41]. *SEMS* show a technical success of over 90 % and a clinical success from 63 to 91 %. Covered stents with diameters of less than 25 mm are associated with a high risk of migration, and this complication, associated to obstruction, may limit the role of these devices in benign colonic strictures. Although plastic colonic stents are effective, there is still insufficient evidence for it to be recommended for use in clinical practice [1]. Two studies that included the highest number of patients treated with covered SEMS or *SEPS* to date showed a technical success of 95–96 %, clinical success of 50–63 %, migration in 21.4–32 %, and major complications in 0–25 % [10]. Treatment with *BD stents* is feasible, and high migration rates can be resolved by appropriate improvements in the design of devices [7]. An important problem in the placement of these stents is the required proximity of the anastomosis to the anus because the positioner is relatively inflexible, and it may not be possible to place a stent more than 30 cm from the anus [7]. The role of stenting in the management of refractory ileocolonic anastomotic strictures after resection for Crohn's disease is widely debated with limited data and widely disparate outcomes. A recent review reported that stenting can provide lasting benefit in select patients: technical success 100 %, clinical success 80 %, mean long-term luminal patency 34.8 months, and reobstruction rate 20 % with surgical intervention [42]. Another study evaluated the role of BD stents in patients with stenosing Crohn's disease of the small and/or large intestine: technical success 90 %, early stent migration 27 %, clinical success after a follow-up of 16 months 63.6 %, and major complications 0 % [42]. A higher number of stent options are available for rectosigmoid anastomoses, including the use of esophageal stents: in such patients treatment is possible with TTS and non-TTS stents. Treatment with stents in rectal anastomotic strictures is limited by the required distance of the stricture from the anal verge in order to avoid painful impingement of the device upon the sphincter muscles and by the rigid nature of the delivery devices. Colorectal anastomosis may occasionally close completely, and a variety of endoscopic techniques have been proposed to resolve the problem [43]. In these cases it is possible to use a suprapapillary biliary puncture catheter inserted into the center of the anastomosis; a 0.025 in. guidewire is passed through the catheter into the colon, and balloon dilation is performed up to a diameter of 2 cm. Although this treatment is useful and safe, it should only be performed by skilled endoscopists [43].

13.7 Endoscopic Treatment: A Comparison of Different Procedures

The choice between mechanical and pneumatic dilators refers only to proximal and distal anastomoses because other sites are not reachable with either type, and it is thus indispensable to use balloon dilators (achalasia balloons, considering the possibility of their use in relation to site, can be considered as mechanical dilators) [1, 2]. The main benefits of balloon dilators over mechanical ones are that they enable dilation of strictures in sites that are hard to access with mechanical dilators (TTS balloons have the great practical advantage of being able to be introduced directly into the endoscope), show better tolerability (87 % vs 43 %; Savary dilation inevitably requires multiple device passages which can increase patient discomfort), do not require fluoroscopy in the majority of cases, and allow a larger intraluminal diameter to be achieved; although the association of balloon dilators with a reduced risk of perforation due to their exclusively radial force is still a widely debated issue, it is known that once balloon dilators have reached their established maximum diameter, excessive pressure will cause them to burst, thus avoiding any damage to the bowel wall due to overexpansion [3]. Savary dilators are more rigid (hence their preferential use for extremely severe strictures) and probably offer a more durable result than that achieved with pneumatic balloons. Mechanical dilators are still preferred by some authors because the stricture can be "felt," and in this way, operators, depending on their own experience, are able to monitor dilation process [2, 3]. Neither mechanical nor pneumatic dilators have shown a clear advantage over the other, and it is essential that the operator is familiar with both techniques because they are not always interchangeable [2]. From a cost-effectiveness point of view, Savary dilators are less expensive than balloons because they are reusable, whereas the latter are single-use devices [1–3]. Differences between mechanical and pneumatic dilators are summarized in Table 13.1. Several randomized controlled trials have compared mechanical dilators with TTS balloons for the treatment of benign esophageal strictures; trials often report contradictory results and essentially do not show significant differences between the two procedures in terms of effectiveness or safety (success percentage 93 % with both devices) [15]. One randomized prospective multicentric study comparing Savary dilation with electrocautery incision in 62 patients undergoing anastomotic stricture after esophagectomy did not observe a substantial difference in the clinical success rate (81 % vs 68 %) [26]. Another study comparing TTS balloon dilators with Eder–Puestow dilators in the treatment of postoperative benign rectal strictures found that both techniques were equally effective and safe but that the metal olivary tips were superior to balloon dilators from an economic point of view ($p<0.001$) [40]. Another study prospectively evaluated and compared two different types of dilators (an 18-mm TTS balloon and a 35-mm OTW balloon) in two groups of patients with colorectal anastomotic strictures; the study has shown the advantage of the OTW over the TTS balloon, highlighting a difference of 40 % in the number of sessions required and in the duration of response to dilation, but not detecting a difference in procedure-related complications [2]. A recent nonrandomized study compared the efficacy and safety of completely covered SEPS (Polyflex stent, Boston Scientific, Natick, Massachusetts) with that of BD stents (Ella BD stent, Ella-CS, Hradec Králové, Czech Republic) for the treatment of refractory benign esophageal strictures: while both stents provided long-term relief of symptoms (30 % vs 33 %), BD stents required fewer procedures (SEPS: major complications 10 %, stent migration 25 %; BD stents: major complications 22 %, stent migration 22 %) [20].

Table 13.1 Selection criteria for endoscopic dilators

	Mechanical	Pneumatic
Discomfort	↑	↓
Training	↑	↓
Ease of use	↓	↑
"Tactile feeling"	↑	↓
Fluoroscopy	↑	↓
Costs	↓	↑

13.8 Complications

The complication rate of the treatment of benign anastomotic strictures differs considerably in the literature, ranging from 0.5 to 15 % (minimal events included). Stricture complexity is certainly one of the most important causes of complications but also the skill of the endoscopist plays a determinant role [5, 8]. Endoscopic dilation is a relatively safe technique, and the most serious complications include *mortality* (0.01 %), *hemorrhage* (0.07 %), bacteremia (abscesses 0.2 %), and above all *perforation* (01–1.1 %) [5]. The risk of perforation significantly decreases when "the rule of three" is applied, when dilation is performed gradually (the maximum dilation diameter should not increase by >3 mm per session), and when *guidewire* assistance or fluoroscopic guidance are used (however, repeated endoscopic dilations may increase this risk) [1, 2, 5, 8]. Previous radiotherapy and inflammatory bowel diseases increase the possibility of perforation, as do specific locations, such as cervical esophagus, or anatomic variations, such as voluminous hiatal hernias. Perforation is usually successfully treated conservatively, and surgical examination is often unable to identify the leakage point of perforation in cases of small lesions [1]. As the event may also indicate the potential malignancy of the treated stenosis, histological evaluation of the anastomosis is required when the complication has been resolved [31]. Maloney dilators, passing blindly through strictures, show a higher perforation rate with respect to balloons and Savary-Gilliard dilators, and it is thus advisable to use these devices only for simple stenoses. The overall risk of complications from stent placement ranges from 1 to 15 %, and post-stenting complications are subdivided into early (<30 days) and late (>30 days) events: the former include perforation, major bleeding, pain, and dislocation, while the latter comprise migration, obstruction, mucosal erosion, pressure necrosis, tenesmus, dysphagia, intestinal occlusion, and occasionally perforation [19]. Perforation is undoubtedly the most dangerous complication (2–3 %); stenting has a longer-lasting dilating effect than dilation and usually has a low risk of acute perforation. Stricture dilation before or immediately after stent placement results in a five- to sixfold higher perforation rate (10–18 %) and generally should be avoided, as should stenting in anastomotic strictures with acute inflammation [19]; perforation is also favored by excessive air insufflation (reducible by using CO2 instead of air) and by treatment with bevacizumab. Post-stenting pain, which mainly depends on device diameter and radial expansive force, is common in patients with refractory strictures and is usually of short duration after SEMS and SEPS placement, persisting for longer when BD stents are used [19]. Common complications after BD stent placement for esophageal anastomotic stricture are vomiting and nausea caused by the material (polydioxanone) from which the stent is made [13]. Stent migration is a common problem when covered SEMS and SEPS are used; in the most important studies published, SEMS and SEPS migration varies from 30 to 40 %, whereas migration of BD stents is much lower, ranging from 8 to 30 % [18]. This complication depends on multiple factors such as the location of the stenosis and device features [19]; in the esophagus BD stent migration does not require endoscopic removal of the device because the gastric pH accelerates the material degradation process (in the stomach BD stent half-life is about 13 days) and the risk of obstruction or perforation is negligible [19, 20]. Tissue overgrowth is linked to the material from which the device is made (nitinol stimulates hyperplastic tissue growth), radial force, and stent position inside the lumen (hyperplastic tissue grows more easily when the device is placed in an oblique position) [13, 14, 16, 24, 25]. Stent removal may cause adverse events, the most important being visceral disruption, perforation, intramural rupture, fistula formation, and segmental amputation. A recent retrospective multicenter study examined the safety of esophageal stent removal in 214 patients with benign esophageal disease, taking into consideration fully covered SEMS (52 %) and partially covered SEMS

(28.6 %) and SEPS (19.4 %). Results showed that endoscopic removal was feasible and relatively safe with a major adverse event rate of 2.1 %; fully covered SEMS were associated with a lower rate of adverse events than partially covered SEMS or SEPS [17]. In cases of steroid injection, there is a theoretical risk of Candida albicans intramural infection and perforation [27].

13.9 Cost Analysis and Final Considerations

Cost analysis includes costs pertaining to personnel, material used during each procedure, each endoscopic examination required to establish diagnosis and performed during follow-up, and hospitalization. The only difference in cost between various endoscopic treatments is related to the *equipment* used to perform the procedure, especially when reusable devises are used. Multiple dilation procedures are usually necessary to achieve an adequate clinical outcome, which significantly increases overall therapy costs. The indisputable advantage of mechanical dilators over balloon dilators stems from the low cost of equipment, which consequently lowers the cost of this therapy compared to that of pneumatic dilation (mechanical dilators can be used for a long time, and the cost of a set of 16 Savary dilators is Euro 2,500; single-use balloon catheters cost between Euro 207 and 680 depending on the model; the average cost of Eder–Puestow dilators for each procedure is Euro 22.30) [40]. The Savary-Gilliard method is thus a low-budget technique (bougies can be used almost indefinitely) that is effective, safe, relatively simple to perform, and inexpensive; it can also be carried out in any endoscopic intervention unit. Stents are obviously more expensive than dilators (SEMS cost from Euro 619 to 1,150 depending on device features and the country of purchase) but have the advantage of requiring only one endoscopic session, with consequent cost damping. As stenting often follows an ineffective dilation treatment, with consequent additional costs, it could be an appropriate first-choice treatment in cases of long, tortuous, fibrous strictures. BD stents are more *expensive* than SEMS; however, in cases of stricture recurrence 4–6 months after dilation, the short-term patency of 4 months until stent degradation and the increased likelihood of long-term success make economic sense to consider BD stent insertion. In addition, these stents do not require removal within 4–6 weeks of insertion, thus avoiding the associated cost of removal and potential complications and consequently improving patient quality of life. Stent placement is cost-effective compared with surgery [10, 20, 22, 25]. However, a surgical option should always be considered in the following cases: young patients who do not achieve essential health benefits after 1–2 years of endoscopic sessions, patients who require very frequent dilations or with a previous complicated perforation after endoscopic treatment, individuals cannot tolerate continued dilations for technical or psychological reasons, and patients who have obtained no benefit from adequately executed stenting treatments. It is very important to treat anastomotic strictures in a stepwise manner starting with the least invasive approach. Generally, dilation is the first treatment modality used (usually up to five sessions), but if this approach is not sufficient to relieve symptoms, an alternative treatment approach should be discussed with the patient to evaluate and balance out risks and benefits, especially in cases of refractory lesions (dilation combined with intralesional four-quadrant steroid injection, up to three sessions, and/or incisional therapy, with or without APC, up to three sessions). Stent placement is usually the last endoscopic choice (stenting should only be considered in carefully selected patients who have proven refractory to dilation); when BD stents are used but the stenosis persists or relapses after device degradation, it is possible to place more than one stent or to repeat the dilation procedure. Surgical intervention is the final step, but even after surgery the risk of recurrent stricture formation remains. The algorithm for anastomotic stricture treatment is shown in Table 13.2.

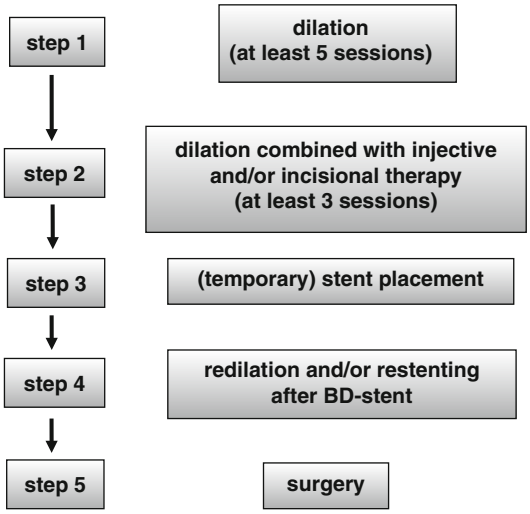

Table 13.2 Benign anastomotic strictures management

Conclusions

Endoscopic treatment of benign anastomotic strictures is a relatively safe and effective procedure: a variety of treatment options can be considered, and therapy modality depends on stenosis peculiarity [1]. Modalities, treatment times, and possible association with medical therapy have not yet been standardized, and each case must be evaluated individually. In the majority patients, mechanical or, more often, pneumatic dilation therapy is the method of choice and either is usually sufficient to treat the stricture. In cases of complex anastomotic strictures, incisional therapy with or without APC is a safe method in experienced hands (local steroid injection is still a widely debated approach) [2, 5, 6, 26, 27]. In refractory anastomotic strictures, stent placement is a promising treatment option and numerous devices, i.e., SEMS, SEPS, and BD stents have been used with various degrees of technical and clinical success. However, the scant data available on the use of stents, strongly recommended in cases of complex stenosis, are conflicting and further studies are needed to compare the various devices and to evaluate medical efficacy, patient satisfaction, and costs; further developments in stent design are also warranted [7, 11–13]. These last treatment modalities should be offered as a second-treatment option after dilation failure, even though stenting can also be considered as a first treatment of choice, especially in complex strictures [15, 18, 19]. However, the optimal treatment strategy for this kind of stricture remains to be defined. Greater efforts are needed to assess the feasibility of combining prolonged dilation using BD stents with a locally applied anti-inflammatory therapy. Drug-eluting devices that deliver pharmacologic therapy to benign strictures over a prolonged period of time are a potentially interesting modification to stent design; however, no clinical experiences of this have been reported to date. Endoscopic treatment of strictures can be burdened, even in expert hands, by important complications. In-depth knowledge of indications, adequate patient selection, accurate imaging, use of appropriate equipment with a wide range of devices, and expert operators are unavoidable presuppositions for an effective and safe procedure [5, 8, 19]. Surgery, often associated with high rates of morbidity and mortality, is usually the final step in the management of anastomotic strictures for patients whose endoscopic treatment has failed [1].

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14 Review: Therapeutic Endoscopy for the Treatment of Anastomotic Dehiscences

Alberto Arezzo, Mauro Verra, Giuseppe Galloro, Mario de Bellis, Antonello Trecca, Raffaele Manta, and Mario Morino

14.1 Background

Anastomotic leakage is a relatively frequent postoperative complication after surgery owing to an increase morbidity and mortality.

There is no uniformity in defining anastomotic dehiscence. In 1991 the UK Surgical Infection Study Group proposed the definition of "leak of luminal contents from a surgical join between two hollow viscera" [1]. The majority of studies define an anastomotic leak as a combination of clinical signs (pain, peritonitis and feculent, or purulent drainage), biochemical findings (fever, tachycardia, leukocytosis), and radiologic findings in addiction to any intraoperative finding.

As regards colorectal surgery, its incidence varies from 3 to 20 % (Table 14.1) [2–16]. The incidence of leak is significantly associated with the distance of the anastomosis from the anal verge. The lowest leak rates are described after small bowel or ileocolic anastomosis (1–3 %), whereas the highest rates occur after colorectal and coloanal anastomosis (10–20 %). Anastomotic leaks are detected in an extremely variable postoperative time interval, with two peaks of incidence on the third and the seventh postoperative day.

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Table 14.1 Literature data for colorectal anastomotic dehiscence

First author	No. of patients	Major leaks (%)	<6 cm (%)
Biondo [7]	211	5.7	
Docherty [12]	652	4.4	
Alves [5]	707	6	
Konishi [10]	391	2.8	
Hyman [2]	1,223	2.7	
Lipska [6]	541	6.5	
Branagan [11]	1,834	3.9	
Sorenson (1999)	333	15.9	
Wong [15]	1,066	3.8	
Platell [9]	1,639	2.4	
Karanjia [14]	219	11	97
Law [3]	196	10.2	100
Gastinger [16]	2,729	14	100
Rullier [4]	131	19	100
Vignali [8]	284	7.8	100

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Intrathoracic anastomotic leakage represents a much more life-threatening event, with high mortality rate. Its incidence is reported to range between 6 and 30 % [17–19].

14.2 Risk Factors

Many risk factors have been demonstrated to be significantly related to anastomotic leak. Patient risk factors include malnutrition, steroids, tobacco and alcohol use, leukocytosis, cardiovascular disease, ASA score, and diverticulitis; intraoperative risk factors include the distance of anastomosis from the anal verge, operative time >2 h, bowel obstruction, blood supply to anastomosis, perioperative blood transfusion, and intraoperative septic conditions; as regards extraperitoneal anastomoses, male gender and obesity are associated to an increased risk of dehiscence [16, 20–22]. Defunctioning loop stoma has been described to reduce the rate of symptomatic anastomotic leakage in low anterior rectal resection [23].

In a large multicenter analysis of oncological and survival outcomes following anastomotic leakage after rectal cancer surgery, oncological outcome was not significantly influenced by anastomotic leakage, even if overall survival was reduced [24].

14.3 Management

Anastomotic leakage management depends on clinical manifestation, on clinical stability of the patient, and on the distance of the anastomosis from the anal verge, particularly if the anastomotic leak is cervical or extraperitoneal, rather than mediastinal or intraperitoneal.

Conventional operative management includes, as regards colorectal anastomosis, explorative laparotomy, peritoneal lavage, and, in at least 80 % of cases, the creation of a derivative stoma. This reduces complications such as peritonitis and sepsis and mortality rate [16], but surgical management leads to a relatively high morbidity rate. Morbidity rate with stoma creation is 30 % and reversal rate in patient with anastomotic leakage is <50 % [25, 26].

As regards intrathoracic dehiscence, surgical management is a highly demolishing surgery with high morbidity and mortality rate.

Technological improvements allowed introduction of new techniques in the management of anastomotic leaks. Endoscopic treatment of anastomotic dehiscence has been proposed as an alternative to operative management in clinically stable patient without generalized peritonitis. In general, patients who present with generalized peritonitis, free intraperitoneal leak or high-grade sepsis with hypotension should be first resuscitated and surgery is mandatory.

Distance of anastomotic dehiscence from anal verge influences subsequent management because of the different probability of free intraperitoneal leak and subsequent generalized peritonitis. Extraperitoneal leaks (e.g., after anterior resection of rectum) often lead to extraperitoneal abscess, such as presacral collections that allow more likely a nonoperative management.

Three main endoscopic options in the management of anastomotic dehiscence are nowadays available:

- Synthesis and suturing devices
- EndoVac therapy
- Covered self-expanding metal stents (SEMS)

14.4 Synthesis and Suturing Devices

Synthesis and suturing devices allow a closure by first intention of the anastomotic defect. Many synthesis and suturing techniques have been described among which clipping is most frequently used. Different clipping devices have been described. Two-pronged endoclips (e.g., Quickclip II, Olympus, Tokyo, Japan, or Resolution Clip, Boston Scientific, MA, USA) with a maximum opening distance of 11 mm are marketed (Fig. 14.1a). TriClip is characterized instead by a third equidistant prong and an opening distance of 12 mm, theoretically owing to the possibility to grasp a larger and a wider amount of tissue (Fig. 14.1b).

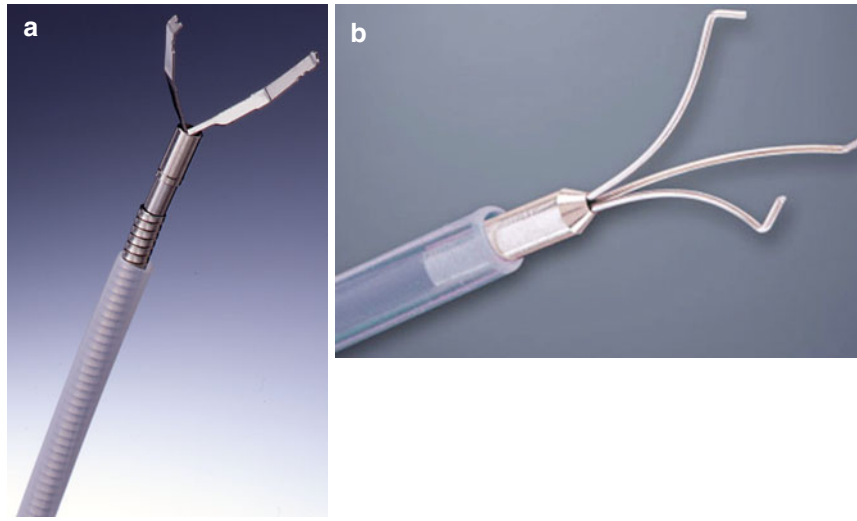

Fig. 14.1 (**a**) Synthesis and suturing devices, the Resolution clip (Boston Scientific, Natick, MA, USA). (**b**) Synthesis and suturing devices, the TriClip (Courtesy of Bloomington, IN, USA)

Table 14.2 Systems ad suturing devices

Author	No. of patients	Cause	Size (mm)	Device	Site	Hospital stay
Fujishiro (2006)	9	ESD	3	Olympus HX-600–090 L	Cecum (2)	12.1
				Olympus HX-5QR	Ascending (2)	
					Transverse (2)	
					Sigmoid (1)	
					Rectum (2)	
Barbagallo (2007)	1	Polypectomy	20	Olympus	Sigmoid	8
Mana (2001)	1	Diagnostic	"Small"	Olympus HX-600–135	Sigmoid	8
Fu (2005)	1	EMR	"Small"	N/A	Ascending	5
Taku (2007)	23	EMR (12)	N/A	Olympus HX–600–090 L	N/A	9.1
		ESD (6)		Olympus HX–5QR		
		Hot biopsy (1)				
		Polypectomy (4)				
Magdeburg (2008)	27	EMR (25)	N/A	Boston Scientific Resolution	N/A	3.5
		APC (1)				
Heldwein (2005)	5	Polypectomy	N/A	N/A	N/A	N/A
Yoshikane (1997)	1	EMR	4	Olympus HX-5QR	N/A	14
Dhalla (2004)	1	Polypectomy	6	Olympus HX-600–135	Cecum	9
Kirshniak (2007)	3	Polypectomy (2)	5	Ovesco OTSC	Splenic flexure	N/A
		Diagnostic (1)				
Trecca (2007)	3	EMR (1)	26	TriClip	Descending (1)	6
		Diagnostic (2)			Sigmoid (2)	

A literature review by Trecca et al. [27] on endoscopic repair of colonic perforation using synthesis devices showed a success rate from 60 to 100 % for nonoperative management of small perforations, in the absence of signs of generalized peritonitis (Table 14.2). This review highlighted the importance of early diagnosis of perforation in order to achieve therapeutic

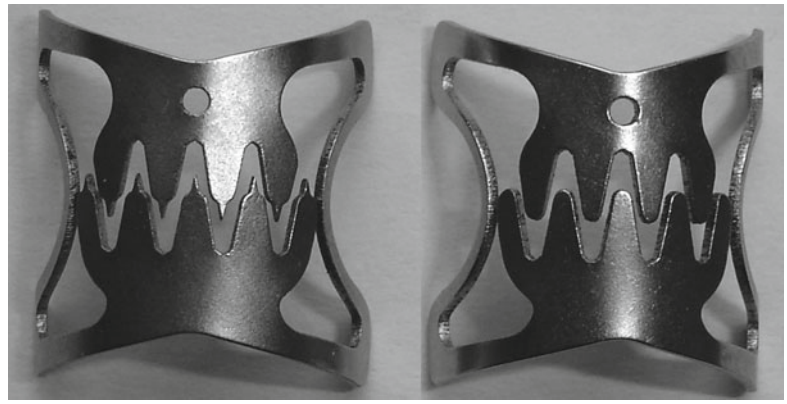

Fig. 14.2 OTSC system (Courtesy of Ovesco GmbH, Tübingen, Germany)

success. Some cases require two or three separate sessions for closure, early diagnosed leaks usually healing within 1 week of clip application, whereas chronic fistulas often require 2- or 3-week-long multiple session treatments.

Many case series report feasibility of endoscopic treatment by using clipping devices in closing anastomotic leakage in esophagogastric surgery [28, 29] and esophago-mediastinal fistula [30, 31]. These two reviews show that endoscopic treatment of small perforations or fistula due to anastomotic leaks with metallic clips can be used safely in selected patients and, alone or in combination with the conservative treatment, may achieve high percentage of leakage closure owing to a reduction of morbidity and mortality if compared with upfront surgical management.

OTSC (over the scope clip) is a clip of new conception. It consists of a nitinol clip, with a shape similar to a bear trap, attached to an applicator, and applied around a cap mounted on the tip of the endoscope. After placing the tip of the scope in front of a visceral defect, orifice margins are retracted with a grasper into the cap and the clip released (Fig. 14.2). Nitinol is a metal alloy with shape memory, so if it is needed to remove the clip, frozen water irrigation allows OTSC to reduce strength so that it can be easily pulled out using an endoscopic forceps [32].

OTSC is nowadays available in different sizes between 11 and 14 mm in diameter. In all cases this device has a wider diameter compared to other kind of endoclips, and the possibility to retract tissue inside the branches allows to close defect up to 20 mm of diameter and larger.

First clinical series on OTSC were published in 2007 by Kirschniak including also bleeding lesions [33]. In a later report from the same group, eight cases of gastrointestinal fistula and 11 cases of perforation were reported. Primary success rate of 100 % was reported with 26 % of recurrence [34].

Our personal series of OTSC includes 21 cases, of which 17 consist of anastomotic leaks following colorectal surgery. Overall primary success rate was 94.1 % (16/17) with a recurrence rate of 18.8 % (2/16). Surgical intervention with stoma creation was necessary in 2/17 cases (11 %). One of the two recurrences was successfully treated by a second OTSC application (Table 14.3).

A recent paper reviewed clinical studies on the use of OTSC on gastrointestinal perforation including also both upper and lower GI anastomotic leaks, over other kind of perforation [35]. A procedural success rate ranging between 80 and 100 % was reported, with an overall clinical success rate ranging from 57 to 100 %. No major complication related to clip application was reported, concluding that the application of OTSC system may reduce the necessity of surgical intervention leaving the option of surgery to failures.

Two further devices have been proposed in order to obtain direct synthesis of gastrointestinal defect: t-tags, Cook endoscopy and Overstitch, Apollo Endosurgery.

T-tag is a suturing device composed by two T-shaped anchors, each one attached to a polypropylene thread and loaded on a needle that is

Table 14.3 OTSC personal series

	Age	Site	Etiology		Time after surgery	Diameter/ margins		OTSC mm	Success	Combined treatment	Follow-up
1.	73	Rectum	Leak colorectal anastomosis	Postradiation	24 months	10	Fibrotic	12	Yes		Primary success
2.	58	Rectum	Leak colorectal anastomosis	Postradiation	21 months	8/5	Fibrotic	12	No		Persistent defect
3.	76	Rectum	Leak colorectal anastomosis	Postradiation	13 days	10	Fibrotic	12	Yes		Primary success
4.	41	Rectum	Leak colorectal anastomosis	Postradiation	16 months	6	Fibrotic	12	Yes		Primary success
5.	59	Rectum	Rectovaginal fistula/anastomotic leak	Postradiation	25 days	5	Fibrotic	12	Yes		Primary success
6.	65	Rectum	Rectovaginal fistula/anastomotic leak		6 days	10	Tender	12	Yes	Stoma	Secondary success
7.	73	Rectum	Leak colorectal anastomosis	Postradiation	15 days	10	Fibrotic	12	Yes		Primary success
8.	56	Rectum	Leak colorectal anastomosis	Postradiation	20 days	10	Fibrotic	12	Yes		Primary success
9.	74	Rectum	Leak colorectal anastomosis	Postradiation	21 months	12	Fibrotic	12	Yes		Primary success
10.	66	Rectum	Leak colorectal anastomosis	Postradiation	13 days	8	Fibrotic	12	Yes		Primary success
11.	69	Rectum	Leak colorectal anastomosis		25 days	9	Fibrotic	12	Yes		Primary success
12.	76	Rectum	Leak colorectal anastomosis		16 days	12	Fibrotic	12	Yes		Primary success
13.	68	Colon	Colocutaneus/anastomotic leak		6 months	5	Fibrotic	12	Yes		Primary success
14.	82	Colon	Colocutaneus/anastomotic leak		6 months	2	Fibrotic	12	Yes		Recurrence of defect
15.	38	Rectum	Rectovesical fistula	Traumatic	120 months	5	Fibrotic	14	Yes		Primary success
16.	63	Rectum	Leak colorectal anastomosis	Postradiation	4 months	15	Fibrotic	12	Yes		Primary success
17.	57	Rectum	Rectocutaneous fistula/anastomotic leak		3 months	10	Fibrotic	12	Yes		Primary success
18.	74	Rectum	Leak colorectal anastomosis		13 days	12	Tender	14	Yes	Stoma	Primary success
19.	74	Rectum	Rectovesical fistula	Perforation during surgery	8 months	10	Fibrotic	12	Yes		Persistent defect
20.	52	Rectum	Rectovesical fistula	Pouchitis	21 months	3	Fibrotic	12	Yes	Fibrin sealant	Persistent defect
21.	75	Rectum	Rectovesical fistula	PPH	72 months	5	Fibrotic	12	Yes		Persistent defect

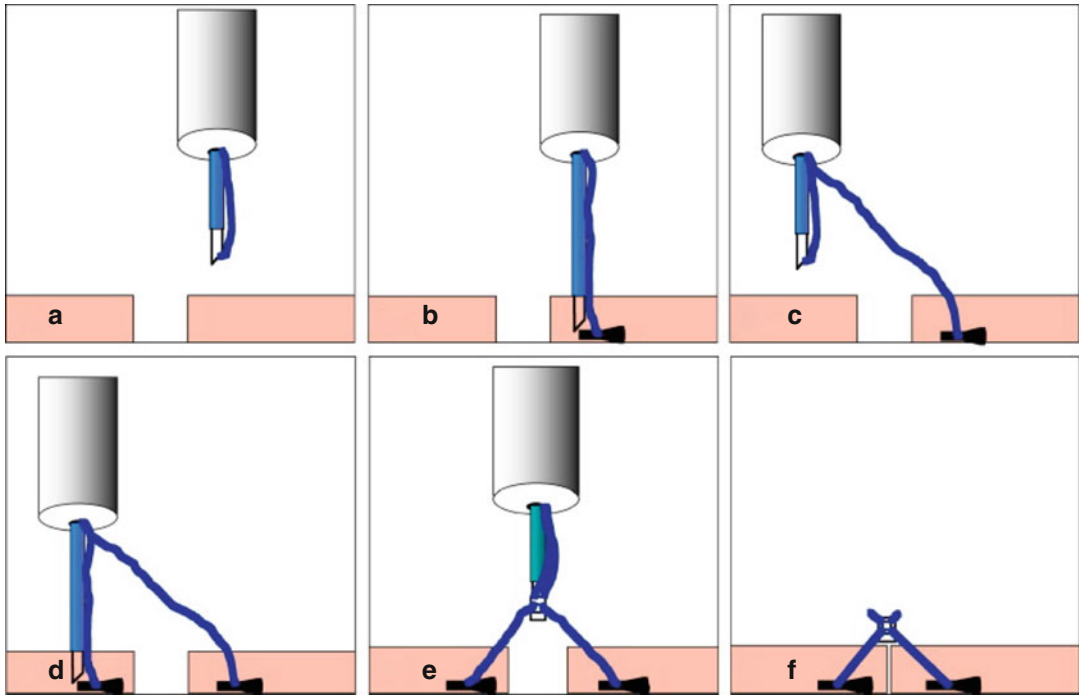

Fig. 14.3 T-tags suturing device (Courtesy of Cook Medical, Natick, MA, USA)

endoscopically advanced into the tissue in order to released one t-tag on each side of the gastrointestinal defect; tissue anchoring is achieved thanks to t-shape. A tie is than advanced in order to lock together the two threads and approximate the two margins of the defect (Fig. 14.3). Several case series on in vivo porcine models [36–38] and a report on three human cases successfully treated (a perforated duodenal ulcer, an anastomotic leakage, and a case of bleeding) [39] are reported, showing promising results and the feasibility of this new technique.

Overstitch suturing system is an endoscopic platform that allows to perform running or interrupted sutures thanks to an oscillating curved needle mechanically passing a polypropylene wire across tissues under direct vision of the endoscope. The device performs an automatic closure of the suture without the need of surgical knot (Fig. 14.4). First case reports on humans have been reported, showing high percentage of success in treating gastrointestinal defects. It has been used up to now to treat gastric anastomotic dehiscence or fistulas and a case of esophagopleural fistula [40, 41].

Many studies on clipping or suturing devices highlight that fibrotic changes on older lesion decrease success rate. Whatever kind of device is employed, success rate strictly depends on early diagnosis and treatment. It is very difficult for synthesis or suturing device to hold on a chronic inflammatory tissue, while higher success rate can be obtained when soft tissues are treated.

Furthermore direct synthesis of a gastrointestinal defect prevents a potential extra-luminal infection site from spontaneous draining with subsequent risk of abscess formation. This is particularly important in intrathoracic leaks where mediastinal infection carries on a high morbidity and mortality risk. Application of suturing and synthesis devices can be applied when the defect is early diagnosed.

14.5 EndoVac Therapy

VAC therapy is based on the principle of applying negative topic pressure to keep clean and drained and favoring granulation tissue formations. This principle can be applied to extra-luminal

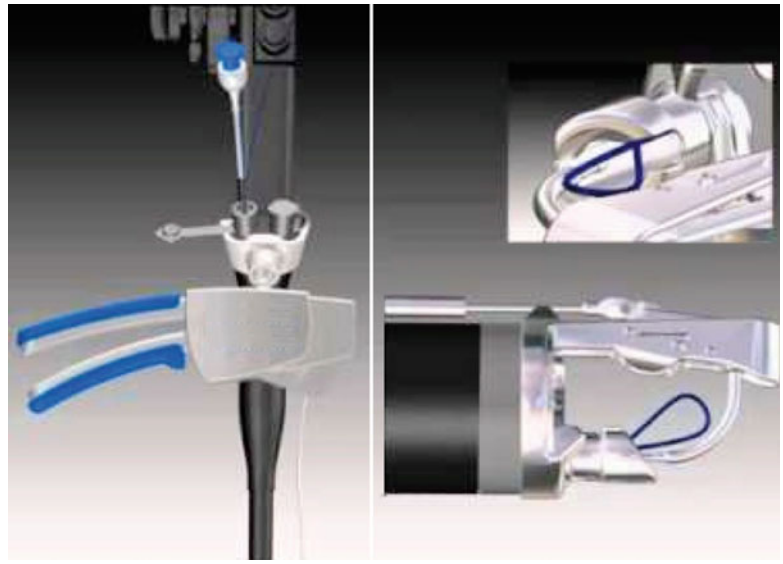

Fig. 14.4 Overstitch suturing device (Courtesy of Apollo Endosurgery Inc, Austin, TX, USA)

cavities or abscess derived from gastrointestinal perforations or anastomotic leakage. EndoVac is composed by an open-cell polyurethane sponge of 7×3 cm that can be cut down till minimum size, depending on the size of the cavity, which is connected to an evacuation tube advanced by a pusher tube with handle into the over-tube once removed the scope. The tube is connected to a vacuum system producing continuum negative pressure up to 200 mmHg (Fig. 14.5). We personally adopt as vacuum system the Renasys Go (Smith&Nephew), a portable device with approximately 20 h of autonomy and 750 cc of capability, able to create up to 200 mmHg in order to be easily adopted by patients during their daily activity.

This device is indicated in the presence of an extra-luminal cavity; the principle is that the endoscope is advanced into the cavity; over the scope an over-tube is advanced; after the scope is removed into the over-tube, the sponge is advanced. Negative pressure makes cavity walls adhere to the sponge, and subsequent granulation and tissue formation allow progressive cavity closure during successive EndoVac positioning cycles.

Creation of an extra-luminal cavity following anastomotic leaks is more likely when anastomosis is made in an extraperitoneal space as pelvic space or mediastinal space. Accordingly vacuum

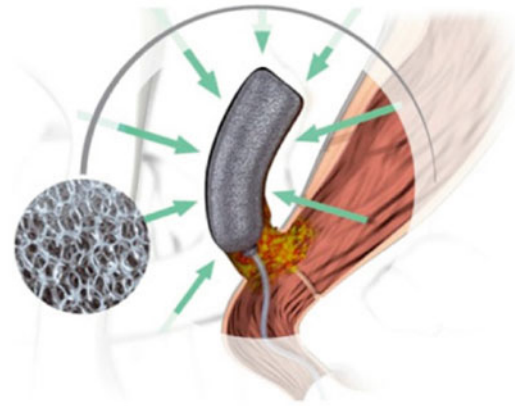

Fig. 14.5 EndoVac system (Courtesy of B Braun Melsungen AG, Melsungen, Germany)

therapy has been described in the treatment of anastomotic leaks following anterior resection of rectum or intrathoracic anastomotic leaks [42–47].

For the management of anastomotic leaks following anterior resection of the rectum, most relevant literature reports case series with an overall success rate of Endo-Sponge treatment ranging from 62 to 100 %, no matter if the patient has a derivative stoma or not (Table 14.4) [42–46]. No major device-related complications were reported. In the larger series [44], 29 cases were reported, a median of 11.4 sessions were needed

Table 14.4 EndoVac series

Authors	*n*	Success rate	%
von Bernstorff et al. [42]	26	23/26	88
Van Koperen et al. [43]	16	10/16	62
Weidenhagen et al. [44]	29	28/29	97
Mees et al. [45]	5	5/5	100
Riss et al. [46]	9	6/9	67
Personal series	15	12/15	80

to close anastomotic defect, and 10 subsequent endoscopic dilatation were required due to stenosis with an overall success rate of 97 %. In our personal series cases of anastomotic leaks following anterior resection, 15 patients have been treated with an overall success rate of 80 %. No major complication due to Endo-Sponge occurred.

Concerning upper intestinal anastomotic leaks, endoscopic vacuum therapy has been imposed as an alternative to primary closure techniques because intrathoracic anastomotic leakage often leads to an infection of the adjacent tissue and primary closure techniques may be applied only if the defect is detected very early or adjacent structures are well drained in order to prevent the formation of extra-luminal abscess. Endo-Sponge applied to mediastinal cavities allows, thanks to its negative pressure, both to prevent contamination and subsequent mediastinal in early detected leaks and to be applied in advanced diseases thanks to the possibility to clean extra-luminal cavities. An important condition for successful endoscopic vacuum therapy is uncompromised local perfusion. A potential risk of bleeding due to erosion of bleeding vessel has been described, but few cases of minor bleeding have been reported. A recent case series by Schorsh report of 17 cases of intrathoracic anastomotic leakage and 7 cases of jatrogenic esophageal perforation with an overall success rate and an average duration of therapy of 94 % and 12 days as regards anastomotic leaks and 100 % and 5 days as regards jatrogenic perforations. One case of esophageal stenosis was encountered during follow-up and treated with endoscopic balloon dilatation [47].

In conclusion endoscopic vacuum therapy allows the treatment of extra-luminal cavities following anastomotic leaks minimizing the risk of abscess formation, thanks to negative pressure, allows a complete healing of a newborn cavity favoring tissue granulation and accelerating tissue formation. This technique carries on the potential risk of bleeding due to erosion of vessels, but very few self-limiting cases have been described, and the risk of luminal stenosis after the healing of the leaks.

14.6 Covered Stents

Temporary endoscopy stent placement has been proposed for esophageal perforations and leaks. Covered stent placement allows to exclude extra-luminal tissues from gastrointestinal fluid passage enabling esophageal wall to heal. As stent placement prevents an extra-luminal cavity to be drained, an external drainage of para-anastomotic fluid collection is often needed; however the absence of extra-luminal undrained fluid collection is mandatory when stent is placed.

Overall success rate is reported to vary from 50 to 100 % with a median of 75 %. Total stenting time to achieve complete healing of the leakage varies from 20 to 135 days with a median of 40 days [48–52].

Overall complications of stent placement are described in 33 % of cases but major complication is quite rare (2 %). Stent migration is the most common complication described in 19 % of cases, ingrowth of benign tissue occurs in 15 % of cases. Food obstruction, pain, and bleeding are described in 4 % of cases. Esophagus rupture during stent removal occurs in 2 %. The median mortality rate is reported to be 10 %, ranging from 0 to 24 %. Endoscopic stent placement may be difficult in some anatomic sites as upper esophageal junction, esophagogastric junction or along gastric tubule with major risk of dislocation or food obstruction. Conversely in presence of stenosis, dislocation is much less frequent [48–52].

Either fully (FSEMS) or partially (PSEMS) covered self-expanding metal stents or self-expanding plastic stent (SEPS) have been employed. No statistically significant differences

on overall success rate have been reported among the kind of stents mentioned above [48–52]. A statistically significant greater risk of tissue ingrowth has been described for partially covered metal stent, while a greater risk of stent migration has been reported for fully covered stent [53, 54].

Partially covered stent should be removed or replaced after 2–4 weeks in order to avoid tissue ingrowth and subsequent complications at the time of stent removal. Fully covered stent may stay in place for a longer period (5–7 weeks).

Few cases of colorectal anastomotic leaks are reported with the use of covered stents. The principle is to place a covered stent across the colonic dehiscence in order to avoid leakage-related complication while it heals. Potential drawback is migration or expulsion of the stent in the absence of stenosis, the risk of colonic perforation and the potential intolerance and tenesmus from the patient if the stent is placed in the low rectum. A randomized controlled trial on porcine models has been published on 16 cases of colorectal anastomotic leaks. No stent-related major complication were reported, all the stents were expelled within ninth postoperative day. In the stent group there was no leakage-related complication, whereas in the control group 63 % developed intra-abdominal infection. On histology, lastly, the study group had statistically significant less visceral wall interruption than the control group [55].

Therefore, endoscopic covered stent as treatment of colorectal anastomotic leaks may be considered in the presence of a stenosis owing to the high risk of migration in its absence.

14.7 Other Techniques

Fibrin glue or cyanoacrylate injection may be an option in the treatment of anastomotic leakage as an alternative option or in addiction to other techniques.

Fibrin glue is a biologic formulation made up of fibrinogen and thrombin, owing to create a fibrin clot, injected into the margin of a gastrointestinal leak that acts as tissue adhesive.

Cyanoacrylate is an acrylic resin that rapidly polymerises in the presence of hydroxide ions forming long and strong chains that bond together two surfaces.

These techniques may be an option in the presence of little leaks or fistulas. Overall success rate in healing anastomotic leakage is reported to range from 20 to 50 %. A large report by Lippert et al. [56] on 52 patients with gastrointestinal anastomotic leakage treated with fibrin glue injection showed an overall success rate of 36 % when glue is used alone and 55 % when combined with other endoscopic techniques. Surgery was necessary in 34 % of cases and mortality rate was 20 %. No major complications associated to endoscopic techniques were reported. The presence of major infection seemed to be a negative prognostic factor of the success of conservative management (50 % of these patients needed surgery versus 13 %) and seemed to define a subgroup of patients with poorer outcome. Each treatment requires multiple session.

Overall success rate of tissue adhesive injection in healing small gastrointestinal perforation seems to be inferior to the one reported for synthesis devices as endoclips, even if the need of surgery is however reduced. These techniques may be an option in the presence of small gastrointestinal defects or fistula in the absence of major infection or symptoms or when application of other clipping devices is not technically feasible or combined with other synthesis or suturing devices.

Conclusion

Recent technology improvement allows today endoscopy to offer many alternative treatment options to surgery in the management of selected cases of anastomotic leakage. Urgent reintervention for anastomotic dehiscence carries on high morbidity rate and a significant percentage of mortality. In selected cases the use of endoscopic devices allows to decrease the need of surgery and, thanks to the low complication rate of endoscopic management if compared to surgery, allows to decrease overall morbidity and mortality rate.

Table 14.5 Stoma creation rate on endoscopic vs surgical groups

Treatment	Sepsis (%)	Secondary stoma (%)	Mortality	Hospital stay
Surgery	43	86	0	26
Endoscopy	38.5	54	0	25

An absolute contraindication to endoscopic management is considered hemodynamic instability, the presence of free intraperitoneal leak or high-grade sepsis with hypotension. In these cases, the patient has to be resuscitated and surgery is mandatory.

Early diagnosis is an important prognostic factor on the success of endoscopic treatment because overall success rate is significantly higher when vital tissues are treated.

As regards colorectal anastomosis dehiscence, conventional surgical management consists in the creation of a diverting stoma. This is necessary in about 80–90 % of cases and carries on up to 30 % stoma-related complication and a reversal rate of less than 50 %. A recent prospective report on 20 consecutive patients with anastomotic leaks after anterior resection of rectum compares upfront endoscopic and surgical management. As showed in Table 14.5, stoma creation was needed in 86 % versus 54 % in the endoscopic group. The two groups were comparable as regards clinical features, and no major complication due to endoscopic treatment was reported [57]. This signifies improvements of quality of life due to the lower stoma rate creation, and as a consequence lower stoma-related complications, in endoscopically treated patients.

In general a small leakage up to 20 mm of diameter may be managed with endoscopic clips, OTSC clips having showed the higher success rate. Fibrin glue injection may be used combined to other endoscopic techniques or alone if leakage or fistula is not clinically significant or clipping is not technically feasible.

Bigger anastomotic dehiscence >30 % of the circumference can be treated with EndoVac therapy if an extra-luminal cavity is present. This happens most of the time in extra-cavital districts as extraperitoneal pelvis or mediastinum. EndoVac allows drainage of extra-luminal abscess as well as healing of the defect thanks to tissue granulation preventing contamination from gastrointestinal contents.

Partially or fully covered stents may be used and temporally taken in place owing to exclude extra-luminal tissues from contamination while healing anastomotic leaks. Absence of extra-luminal infection or its good external drainage is necessary. It can be an option in intrathoracic leaks even if its success probability is lower at the level of esophagogastric junction, upper esophageal sphincter, or sometimes in esophagogastric anastomosis. The presence of concomitant stenosis improves success rate decreasing covered stent displacement.

It is desirable that future technological improvements, mainly in the field of synthesis and suturing devices, will increase possibility to treat endoscopically gastrointestinal tract surgical complications.

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Hemostatic Procedures in the Bleeding Anastomosis

15

Bjorn Rembacken

15.1 Background

Ulceration and bleeding from a surgical anastomosis is a relatively unusual complication which has been reported to occur following 2–4 % [1–4] of upper GI surgical procedures.

The true incidence is difficult to ascertain as most reports are retrospective and prone to bias. The largest retrospective series consisting of data from 5,839 gastrectomies reported an overall complication rate of 10.5 % but included no reports of bleeding from a surgical anastomosis [5].

A retrospective review of 40 cases of incisional hernia repair following open gastric bypass surgery reported one case of anastomic ulceration and bleeding requiring emergency surgery [6]. A larger and more recent retrospective review of outcomes of 1,213 patients who had undergone laparoscopic gastric bypass for morbid obesity identified ten patients with perforated ulcers at the gastrojejunal anastomosis [7]. However, this study only included perforated ulcers and the incidence of all anastomotic ulceration, following bariatric surgery, was found to be higher (2.4 %) in another large review of outcomes in 540 patients [8].

Perhaps the most likely anastomosis to ulcerate and bleed is following pancreatoduodenectomy. In a retrospective study [9], 18 % (9/53) of patients who had undergone a Whipple's procedure with Roux-en-Y gastrojejunostomy developed an anastomotic ulcer and 6 of cases presented with bleeding. In contrast, in a group of 33 patients who had undergone Billroth-II type of reconstruction, there was only one reported anastomotic ulcer. Anastomotic ulceration has also been described after small bowel transplantation [10].

Less commonly, anastomotic ulceration and bleeding has also been described following lower gastrointestinal procedures. A retrospective search for anastomotic ulceration following ileocolonic anastomosis was carried at the Mayo Clinic Arizona. Over a 5-year period, only 6 such cases were reported, giving a calculated incidence of 0.06 %. These patients all presented with anemia which resolved with iron supplementation and stopping NSAID therapy or treating the underlying inflammatory bowel disease [11]. This study may have missed cases of ulceration as another, smaller but more detailed study of 1,316 laparoscopic colectomies, reported 29 cases of postoperative bleeding [12].

15.2 Etiology of Bleeding

The etiology of bleeding is unknown. Following Roux-en-Y gastrojejunostomy, lack of inactivation of pepsin by bile acids, ischemia [13], or reverse peristalsis have all been proposed as an

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underlying mechanism. For this reason, prophylactic therapy with proton pump inhibitors and even bilateral truncal vagotomy has been advocated [14–16]. In a systematic review comparing open versus laparoscopic Roux-en-Y gastric bypass, the risk of bleeding was found to be significantly higher following the laparoscopic procedure, suggesting that ischemic injury may be an important etiological factor [3].

15.3 Management of Extra-Luminal Bleeding

Following surgery, patients may bleed into the abdominal cavity or into the lumen from the anastomosis [17]. Some have proposed that the primary role of placing drains at the site of anastomosis is to allow the early diagnosis of postoperative hemorrhage and to distinguish this from an anastomotic or staple line leak [18]. However, drains are not always a reliable indicator, particularly if the bleeding is intraluminal. For this reason, monitoring of clinical signs is very important in the postoperative patient. A large quantity of bloody fluid from the abdominal drains, hemoperitoneum, tachycardia, a drop in the hemoglobin level, bright red blood per rectum, hematemesis, and melena have all been found to indicate postoperative hemorrhage [19].

Patients with evidence of extra-luminal hemorrhage usually require abdominal re-exploration using either a laparoscopic or open approach. The operative goals are to evacuate the majority of the clots, attempt to identify and control the site of hemorrhage, or, if there is no obvious bleeding point, to oversew all staple lines.

In an interesting study [20], endoscopy was used intraoperatively to assess the anastomosis at the time of primary surgery. A total of 118 patients underwent resectional surgery and 5 were found to have bleeding at the site of the anastomosis at the time of surgery. Unfortunately, in the follow-up phase, a further 8 cases of anastomotic bleeding were reported. These cases had not bled at the time of the surgery; it is therefore possible that intraoperative endoscopy identifies early, self-limiting bleeding points but is unable to prevent cases of delayed bleeding perhaps developing as a consequence of ischemic injury. A smaller study, using a similar intraoperative endoscopic assessment of the surgical anastomosis, reported some benefit during bariatric procedures [21]. However, it is still uncertain if this approach should become part of the standard intrasurgical assessment of the anastomosis.

15.4 Role of Endoscopy to Manage Anastomotic Bleeding

There is evidence that bleeding from anastomotic ulcers are difficult to treat endoscopically. A retrospective analysis of 427 patients with bleeding from an anastomotic ulcer reported an odds ratio of 3.39 (95 % CI 1.37–7.29) for therapeutic failure [22].

In a smaller, retrospective review of 393 patients who had undergone laparoscopic-assisted gastrectomy, all cases of bleeding could be managed endoscopically [23]. I am only aware of a single report of fatal bleeding from an anastomotic ulcer [24].

Emergency gastroscopy is able to identify the site of bleeding in approximately 95 % of cases of peptic ulcer bleeding [25, 26]. However, there is no corresponding data available on the success rate for bleeding anastomoses. Nevertheless, it seems reasonable to initially attempt endoscopy with the aim to (1) identify the source of hemorrhage, (2) stop the bleeding, (3) assess the risk of rebreeding, and (4) outline a strategy of how the case should be managed if bleeding cannot be stopped or recurs.

Naturally, not every patient who develops bleeding following surgery suffers bleeding from the surgical anastomosis. Other causes to be considered include ischemia, “stress” ulcers, reflux esophagitis, coagulopathy, and aortoenteric fistula. Patients with an intraluminal upper GI source of bleeding will usually present with hematemesis and/or melena. Intraluminal bleeding in the lower GI tract would normally present with rectal bleeding.

15.4.1 A Team Effort

Patients with a bleeding anastomosis are managed by a team approach involving the endoscopist, surgeon, interventional radiologist, and hematologist in case of massive bleeding. Patients with major comorbidities or who are showing signs of decompensation should be stabilized and managed together with an intensivist in the intensive care unit [27]. Endoscopy after endotracheal intubation should be considered to protect the airway in patients with severe bleeding, patients in shock, and patients with respiratory decompensation.

15.5 Endoscopic Therapies

The management of a patient with early postoperative gastrointestinal bleeding does not differ significantly from the management of common GI hemorrhage. After the bleeding site has been identified, it should be risk stratified depending on the stigmata of recent hemorrhage (SRH). Major SRH includes active arterial bleeding or a non-bleeding visible vessel [28]. Intermediate SRH includes an adherent clot on an ulcer or an ulcer that is oozing slightly without concomitant major SRH. Minor SRH includes ulcers with a pigmented flat spot or a clean ulcer base. Ulcers with major SRH have the greatest risk of continued bleeding or rebleeding without endoscopic therapy, whereas minor SRH have the lowest risk of rebleeding even without endoscopic therapy [29–32]. Ulcers with intermediate SRH have an intermediate risk of bleeding without endoscopic therapy [33]. Although this stratification was developed for bleeding peptic ulcers, it would be reasonable to assume that the same is true for bleeding ulcers at the anastomotic site.

Bleeding sites should first be treated with an initial injection of dilute adrenaline to provide tamponade. In bleeding peptic ulcers, adrenaline provides initial hemostasis in around 80 % of bleeding peptic ulcers [34, 35]. Unfortunately, bleeding may recur after 20 min as the adrenaline is absorbed [26].

The use of a sclerosing agent such as alcohol or ethanolamine does cause tissue injury at the site of the anastomosis and should be avoided. Furthermore, there is no evidence that they provide any advantage. In a study of 170 cases of bleeding peptic ulceration, injecting a sclerosant did not provide any better hemostasis than adrenaline [36]. The use of histoacryl tissue glue has been shown to be of benefit in bleeding gastric varices but is associated with risks of embolization [37] and is unproven in the treatment of bleeding from surgical anastomoses.

Fibrin, when injected into the bleeding vessel, may aid the formation of a clot. Unfortunately, clinical studies have not demonstrated any clear advantage over adrenaline in bleeding peptic ulcers. In a European multicenter trial [38] of more than 800 patients, bleeding ulcers were initially treated with adrenaline. The ulcers were then either injected with sclerosant (group A), fibrin glue (group B), or an intensive program of multiple fibrin glue injections over several days (group C). Initial hemostatic success was similar in the groups (92.5 % vs 95.1 % vs 96.4 %). However, patients in group C were less likely to rebleed than in group A (10.0 % vs 18.1 %). These results were corroborated in a subsequent, smaller study encompassing 135 patients. In this study, bleeding peptic ulcers treated with a single injection of adrenalin were just as likely to rebleed as ulcers treated with single injection fibrin glue (24 % vs 21 %) [39]. There has been one case report of the successful use of tissue glue to treat a bleeding varix at the site of a surgical anastomosis [40].

Hemoclips are short endoscopic clips only available in countries which do not solely rely on disposable equipment (such as the UK). Initial results were very promising with an Italian study reporting a rebleeding rate of 21 % following heater probe therapy versus only 1.8 % after the placement of hemoclips [41]. Unfortunately, a subsequent study [42] did not replicate the initial, promising results. Injection therapy achieved initial hemostasis in 85 %, compared with 63 % for hemoclips, or 75 % when a combination of clips and injection therapy was used. At the site of a

small bowel anastomosis, clips have the theoretical advantage that relatively little tissue injury is incurred by their use. Furthermore, the main shortcoming of hemoclips is that the main simply scrape the surface of a firm and sclerotic peptic ulcer. At a fresh, bleeding ulcer at a small bowel anastomosis, less fibrosis may be expected.

Proton pump inhibitor (PPI) therapy is recommended for patients with bleeding peptic ulceration as the neutralization of gastric acid stabilizes clots [43–45], reduces the need for endoscopic therapy, and reduces the risk of rebleeding but has no proven effect on mortality [46]. However, when the bleeding is from an anastomotic ulcer, the effect of PPI therapy is unproven and cannot be recommended.

The largest series reporting on the outcomes of treating a bleeding anastomosis was published by Lee et al. [47] which included a series of 50 patients with anastomotic ulcer bleeding following Billroth-II procedures. The bleeding ulcers were usually found at the level of the anastomosis (64 %) or at the anastomotic bifurcation (20 %). The ulcers were classified as Forrest Ia (32 %), Ib (38 %), IIa (20 %), or IIb (10 %). A total of 20 patients were treated with hemoclips and 30 with a combination of adrenaline and heater probe coagulation. In all cases, initial hemostasis was achieved. However, the risk of rebleeding was significantly greater (33 % vs 5 %) following adrenaline + heater probe coagulation than after endoclip application. The likely reason for this is the combination of tissue ischemia, a thin small bowel wall and tissue damage from the heater probe. Endoscopic therapy for non-anastomotic bleeding is associated with a 0.5–1.0 % risk of gastrointestinal perforation [48, 49] and the risks when treating a bleeding ulcer at a surgical anastomosis are probably greater.

As previously outlined, bleeding from colorectal stapling anastomoses is uncommon. In study of 438 patients [50], only 6 patients were found to have ulceration at the site of the surgical anastomosis. Furthermore, the bleeding is less severe and usually settles with supportive care. In a study by Cirocco and Golub [51], only 1.8 % of patients developed an anastomotic hemorrhage and almost every case (82 %) settled with supportive care.

Conclusion

There is little evidence from published studies to guide the endoscopist when asked to help in the case of a postsurgical intraluminal bleed. Nevertheless, much of the training and techniques used in the management of peptic bleeding will also help at the anastomosis. The main caveat should be an awareness that the surgical anastomosis will be thin and less able to withstand thermal therapies. For this reason, injection therapy, followed by the application of clips, is preferable.

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16 Endoscopic Treatment of Anastomotic Complications After Bariatric Surgery

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16.1 Introduction

With advances in technology and improved surgical techniques, the mortality following bariatric surgery is nowadays less than 1 % in centers of excellence. Approximately 9–25 % of patients have late complications following bariatric surgery [1]. Considering that bariatric surgery is increasing in number annually, endoscopists need to be familiar with the bariatric surgical operations and the new endoscopic anatomy in order to diagnose and treat early and late complications [2, 3].

Nausea, vomiting, and abdominal pain are among the most commonly encountered symptoms after bariatric surgery and may result from one or several structural and functional etiologies. Symptoms are frequently associated with dietary noncompliance as to the volume and type of foods eaten, rapid ingestion, or inadequate chewing. Patients with persistent symptoms should be carefully evaluated, because these symptoms may indicate the development of marginal ulcers, gastrogastric fistulas, or partial or complete anastomotic obstruction.

Endoscopy is the preferred strategy, unless there is a suspicion of leaks or fistulas, when contrast radiography is more appropriate. Patient history may be helpful in differentiating the etiology of pain and in guiding the type of investigation. Nausea, vomiting, abdominal distention, and bloating alone or in conjunction with abdominal pain can suggest an obstructive cause, such as strictures. Marginal ulcers are typically seen 1–6 months after surgery and may present with abdominal pain, bleeding, or nausea, although they may also be asymptomatic [4]. Clinical manifestations of leaks include tachycardia, fever, nausea, vomiting, and abdominal or chest pain.

General principles, when an endoscopy is considered in a patient who had bariatric surgery, involve the endoscopist to be aware of the operative procedure performed and the findings on pre-endoscopy imaging studies; he must understand the expected anatomy, including the extent of resection and the length of surgically created limbs. In patients who are in the early postoperative period, air insufflation may have potentially detrimental effects in the presence of leaks and/or tenuous anastomoses. If there is suspicion of a leak, then again the endoscopist should consider contrast radiography as an initial diagnostic test. Contrast studies are complementary to an endoscopy and are also helpful in delineating anatomy.

Accordingly to each bariatric surgical operation, the next section provides an overview of the most common normal and pathological endoscopic findings. Finally, major anastomotic complications are described, as well as their endoscopic therapy.

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16.2 Surgical Key Points and Normal Endoscopic Postsurgical Anatomy

Two types of surgical procedures are currently performed:

- Restrictive procedures aiming to reduce gastric capacity (vertical banded gastroplasty (VBG) and laparoscopic adjustable gastric banding (LAGB))
- Procedures combining a reduction in gastric capacity with maldigestion/malabsorption (Roux-en-Y gastrojejunal bypass, RYGB), sleeve gastrectomy (SG), or duodenal switch and biliopancreatic diversion (BPD-DS)

Among these, VBG, RYGB, SG, and BPD-DS involve gut anastomosis creation (Fig. 16.1).

It is important for endoscopists to understand the different types of operation, the resulting anatomical alterations, and the different complications that can arise following these procedures.

16.2.1 VBG: Vertical Banded Gastroplasty

In this restrictive procedure, both band and staples are used to create a small stomach pouch. The surgery isolates a small section of the stomach for processing food, limiting the size of meals to approximately 1 oz, and slows digestion by forcing the food to pass through a restrictive ring and thence onto the remainder of the gastrointestinal tract. The isolated pouch is usually made using the lesser curvature of the stomach, virtually bypassing the gastric fundus; a trangastric window is made 6–8 cm below the His angle using a circular stapler, and a linear stapler is placed to create a pouch of 30 ml. The narrow outlet of 10–11 mm is surrounded by a non-distensible collar of polypropylene mesh of PTFE (polytetrafluoroethylene) or a silicon ring, to avoid enlargement. The gastric pouch is small generally 15–30 ml in volume. The expected endoscopic findings after VBG consist of a clean gastric channel 6–8 cm long, with a rosette at the distal end and snug passage of an 11-mm scope without difficulty. Special care should be made to examine the pouch and suture line for fistulas and ulcerations. Retroflexion of the tip of the endoscope in the distal stomach allows inspection of the caudal aspect of the staple-line partition and the remainder of the gastric fundus.

16.2.2 RYGB: Roux-en-Y Gastric Bypass

Roux-en-Y gastric bypass involves stapling the upper stomach into a small proximal 15–30-ml pouch along the lesser curvature, attached to the jejunum through a narrow (11 mm) anastomosis, bypassing a large part of the stomach and duodenum. There are two anastomoses: gastrojejunal and jejunojejunal.

The gastric pouch is small generally 15–30 ml in volume. The expected endoscopic findings after RYGB include a normal esophagus and gastroesophageal junction. The size of the gastric pouch varies. The pouch may have several different configurations and may be long and narrow or shot and wide. Special care should be made to examine the pouch and suture line for fistulas and ulcerations. The gastrojejunal stoma should be easily visible within several centimeters of the gastroesophageal junction and should be carefully examined. The width of the anastomosis is generally 10–12 mm in diameter. Beyond the anastomosis, a short, blind limb is often visible alongside the efferent jejunal limb. The jejunojejunal anastomosis can sometimes be reached with an upper endoscope, depending on the length of the Roux limb. It should be noted that the length of the Roux limb after an RYGB can vary significantly from standard Roux limbs created for nonbariatric procedures and can range from 50 to 150 cm. The distal or excluded stomach cannot be visualized in the absence of a fistula with a regular gastroscope.

16.2.3 SG and BPD-DS: Sleeve Gastrectomy and Biliopancreatic Diversion with Duodenal Switch

Biliopancreatic diversion with duodenal switch (BPD-DS) includes both restrictive and malab-

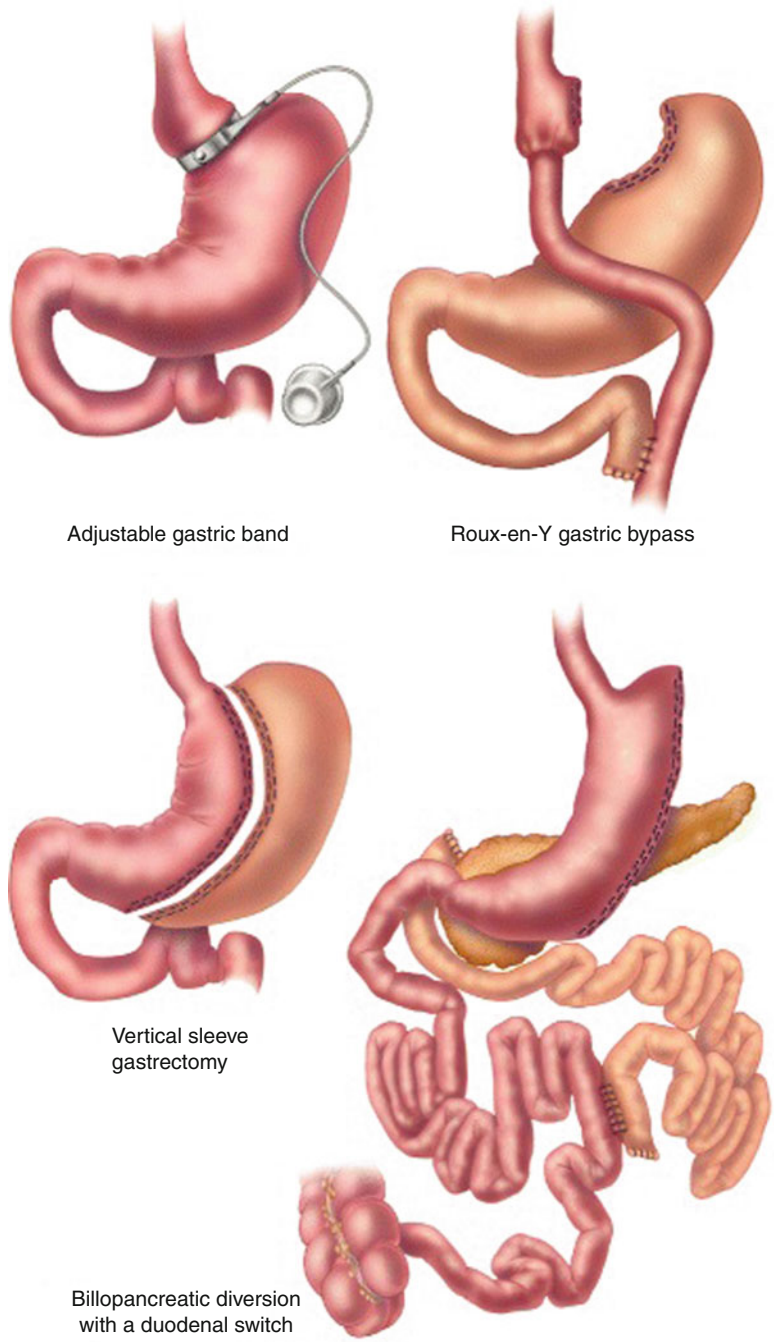

Fig. 16.1 Schematic representation of main bariatric procedure. *VBG* vertical band gastroplasty, *SG* sleeve gastrectomy, *RYGB* Roux-en-Y gastric bypass, *BPD-DS* biliopancreatic diversion with duodenal switch (reproduced with permission from [73])

sorptive components. Restriction is incurred by a sleeve gastrectomy (SG) in which the greater curvature or left side of the stomach is surgically removed. The surgeon accomplishes this resection by a linear stapler, starting at a point about 5–8 cm to the left of the pylorus along the greater curvature. The stapler line continues vertically upward, roughly paralleling the lesser curvature, until the upper edge of the stomach is reached near the angle of His.

The malabsorptive component of the BPD-DS is a result of two anatomic changes: first, the overall length of the alimentary limb is decreased (duodenal–ileal anastomosis or gastric–ileal

anastomosis if the BPD follows a partial distal gastrectomy). Second, the intermixing of bile and pancreatic juices is limited to the distal portion of the alimentary limb, generally 50–100 cm in length (ileoileal anastomosis).

There are no real anastomoses in the SG but only a suture line alongside the grater gastric curve, while in BPD-DS two anastomoses are created.

On endoscopic evaluation of SG, the stomach will appear to be quite long and narrow. The fundus is absent. The stomach is limited in expansion by a staple line that parallels the lesser curvature. The staple line should be examined for defects and ulcerations.

In BPD-DS, immediately below the pylorus, the proximal anastomosis will be traversed. For unclear reasons, the formation of strictures at the duodenoileostomy is rare.

16.3 Anastomotic Complications: Incidence, Diagnosis, and Endoscopic Treatment

16.3.1 Stomal/Marginal Ulcer

Marginal ulcers are typically seen 1–6 months after surgery and may present with abdominal pain, bleeding, or nausea, although they may also be asymptomatic. Ulcerations on the gastric side of the anastomosis (stomal ulcers) (Fig. 16.2) or on the jejunal surface of the anastomosis (marginal ulcers) are thought to arise from a number of factors, including local ischemia, staple-line disruption, effects of acid on exposed intestinal mucosa, and the presence of staples or suture material [5]. Factors that increase the risk of marginal ulcers include smoking and nonsteroidal anti-inflammatory drug use, whereas proton pump inhibitor use appears to decrease the risk. The true incidence of a marginal ulcer after an RYGB is uncertain, with reports that range from 1 to 36 % [6, 7].

Marginal ulcer can coexist with gastrogastric fistula (VGB and RYGB) or suture leak (SG and BPD-DS). In a large series of 1292 consecutive divided Roux-en-Y gastric bypass with 17.6 months of follow-up [8], 15 patients (1.2 %) presented for endoscopic evaluation and were found to have gastrogastric fistulas. Of these, 12 (80 %) complained of nausea, vomiting, and abdominal pain. Four patients (27 %) presented because of failure in losing weight. On endoscopic examination, eight patients (53 %) were found to have a coexisting marginal ulcer.

The cause of true stomal ulcers is thought to be ischemic in nature, whereas the cause of marginal ulcers is poorly understood [9]. Multiple mechanisms have been proposed to explain marginal ulcers. Local ischemia, larger pouch size leaving retained parietal cells that produce gastric

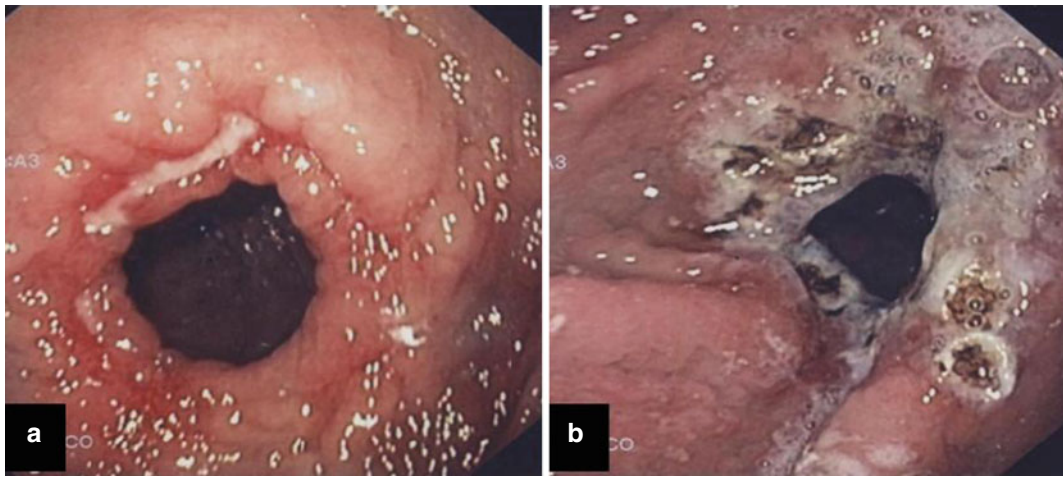

Fig. 16.2 Dilated anastomosis following gastric bypass (**a**), 2 years after surgery. Note the marginal ulceration at the gastric side. In (**b**) the same patient after APC treatment

acid, acidic gastric secretions poorly tolerated in the jejunum, NSAID use, alcohol use, smoking, a coexisting gastrogastric fistula, and the presence of a foreign body such as nonabsorbable suture material have been implicated [10–13]. To evaluate the predictors of endoscopic findings, a retrospective review of 1001 RYGB [4] showed that smoking, NSAID use, and abdominal pain predicted the presence of marginal ulcers at endoscopy; smoking and NSAID use also predicted staple-line dehiscence. Age, gender, surgical technique, and surgeon experience did not predict abnormal findings at endoscopy.

Refractory ulcers should raise concern for the presence of a gastrogastric fistula.

Moreover, also time of presentation from surgery can predicted findings for the presence of stomal ulcers and stomal stenosis. In another RYGB large series [14], presenting more than 6 months after surgery was associated with a lower likelihood of stomal ulceration or stenosis. In contrast, presenting after 6 months was associated with a greater likelihood of staple-line dehiscence [14].

In treating marginal ulcer, it is advisable to remove nonabsorbable sutures when visible intraluminally to assist with healing, prevent gastrogastric fistulas, and relieve chronic abdominal pain in patients who underwent bariatric surgery. Long-term treatment with oral proton pump inhibitors therapy, along with antibiotics for coexisting H. pylori infection, has led to healing of fistula. The role of Helicobacter pylori is still not clear. In one study, marginal ulcer and associated gastrogastric fistula responded to a combination of PPI therapy and fibrin glue injections [15]. Healing times for ulcer resolution vary from 8 weeks to 6 months but were longer in the presence of an untreated or undiagnosed fistula [16].

Bleeding duodenal ulcers have been rarely reported following Roux-en-Y gastric bypass [17]. Early postoperative bleeding in RYGB most likely originates at the gastrojejunostomy.

Endoscopic management of early postoperative intraluminal bleeding is challenging and controversial due to the risk of dehiscence and perforation at the surgical anastomosis. Endoscopy is usually not necessary because bleeding is mild and self-limited in most cases but should be considered in patients in whom bleeding is severe (hemodynamic instability and/or ≥2 g drop in hemoglobin) or when rebleeding occurs. If endoscopy is performed, air insufflation should be minimized to prevent disruption of the anastomosis. Close communication with the surgeon is essential. Data of endoscopic findings and management of early postoperative bleeding show that most patients (20/27; 74 %) underwent endoscopy in an operating room and were endotracheally intubated (19/27; 70 %). Bleeding stigmata seen at the gastrojejunostomy included active oozing (48 %), visible vessel (26 %), and adherent clot (26 %). Endoscopic therapy was performed in 85 % of patients and included epinephrine injection, heater probe coagulation, combination epinephrine injection and thermal coagulation, and hemoclip placement in 3 (13 %), 4 (17 %), 14 (61 %), and 2 (9 %) patients, respectively. Hemostasis was achieved in all patients, but 5 (17 %) patients required surgery to control hemorrhage and complication occurred (pulmonary aspiration and perforation) [18].

On occasion, postoperative nausea and vomiting may lead to a bleeding Mallory–Weiss tear, which can be managed endoscopically.

Summarizing, stomal and marginal ulcer can successfully be treated conservatively with PPI; bleeding ulcers can be endoscopically treated in more than 2/3 of the case. Success of the endoscopic treatment depends mainly on the severity of the bleeding.

16.3.2 Stomal Stenosis

Stomas are generally 10–12 mm in diameter and stenosis is defined as a diameter <10 mm.

Stenosis of the stoma has to be divided into the immediate postoperative, early postoperative (<3 months), and late postoperative (>3 months) period, as edema or edema with early scar formation respond well to dilation and the outcome in late scarring is rather poor. Stomal obstruction in the initial postoperative period has been simply solved by waiting to see whether the stomal edema and swelling subside after replacement of a nasogastric tube [19]. Stenosis occurring later is believed to result from fibrosis or an inflammatory reaction (occurring around the band in VGB).

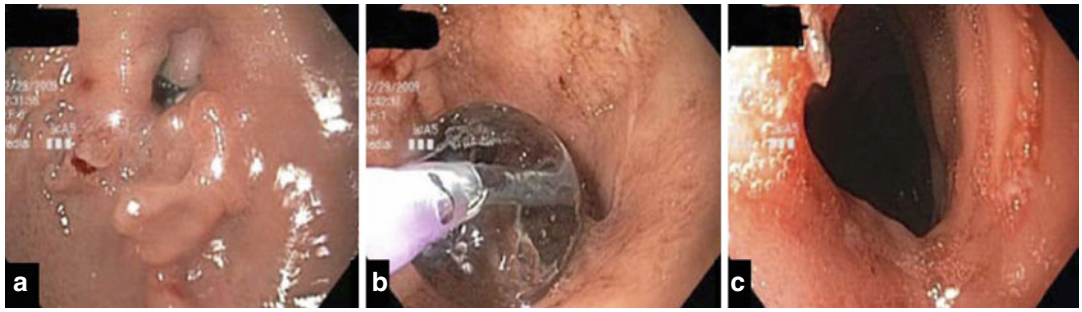

Fig. 16.3 Stomal stenosis following gastric bypass (**a**). In (**b**) CRE balloon dilatation and in (**c**) the anastomosis after treatment

Stomal stenosis occurs in as many as 4.73–27 % of patients undergoing RYGB [20, 21]. These patients typically present with dysphagia, nausea with vomiting, or early satiety as previously noted. The primary endoscopic intervention is balloon dilation up to 15–18 mm, which has been associated with a greater than 93 % success rate in symptom resolution and subsequent weight loss [22, 23] (Fig. 16.3). Dilation with Savary-Gilliard bougie (Cook Endoscopy; Winston-Salem, NC, USA) may be considered and is an effective intervention. In one review, both methods required 2–3 sessions of therapy, with a complication rate of 3 % [24]. Endoscopic fluoroscopy-guided balloon dilation has been demonstrated safe, effective, and durable [25–28].

Gradual dilation over a few sessions is likely the best; dilatation should not be performed to >15 mm, as this may be associated with future weight gain. For symptomatic patients presenting with refractory vomiting, thiamine repletion should be considered early and before exogenous glucose administration to prevent the precipitation of Wernicke encephalopathy [29].

16.3.3 Gastrogastric Fistula

In VBG and RYGB, the gastric suture line can present one or more dehiscences allowing an opening communication between the pouch and the excluded stomach, known as a gastrogastric fistula.

Because of the communication, it is a particular type of suture dehiscence, always presenting on endoscopy as fistula completely or partially re-epithelized and so far different from other anastomotic leaks.

Most large series report that gastrogastric fistulas occur in 1.2–1.8 % of patients undergoing gastric bypass [30]. However, incidence rates from zero to as high as 46 % have been reported, with substantial improvements in recent years because of modifications in the surgical technique [31].

Usually patients complain for weight regain or for not being able to lose weight.

Because of the high rate of morbidity and mortality associated with surgical revision of gastrogastric fistulas, initial treatment has evolved from surgical interventions to endoscopic management, with variable success. Reported endoscopic techniques (Fig. 16.4) include the use of fibrin glue sealants [32, 33], insertion of a Surgisis fistula plug (Cook Surgical, Inc, Bloomington, IN, USA) with or without a self-expanding stent [34], endoluminal stent placement [35], the use of mucosal suturing devices for tissue apposition [36], and local debridement following argon plasma coagulation [37]. The optimal method of treatment is unknown, as comparison studies and randomized controlled trials are lacking.

16.3.4 Anastomotic Rupture/ Dehiscence/Leaks

Published incidence rates for leaks following bariatric surgery range from 0.4 to 26 %, and leaks are associated with a mortality rate of 1.5 % [38].

Gastric leaks are potentially serious complications of bariatric surgery and occur in 1–6 % of

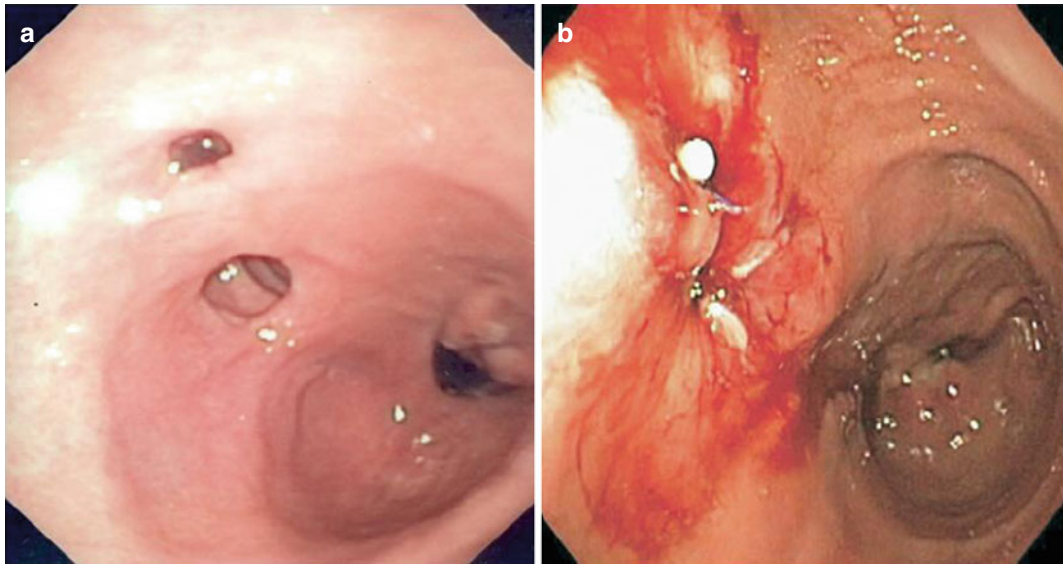

Fig. 16.4 Gastrogastric fistula following VBG (**a**). In (**b**) and endoscopic view after argon plasma coagulation (APC) and fibrin glue

patients in gastric bypass and 0.7–4.6 % in sleeve gastrectomy [39, 40]. Next to pulmonary embolus, intra-abdominal sepsis secondary to leaks is the most serious life-threatening complication associated with bariatric surgery. The potential causes of leaks are multiple: tension on the anastomosis, staple or stapler malfunction, suture or staple-line seepage, poor surgical technique, obstruction, hypovascularization, and hematomas [41].

Leaks require early recognition of symptoms, detection, and prompt treatment to prevent loss of life. Clinical manifestations include tachycardia, fever, nausea, vomiting, and abdominal or chest pain.

In RYGB most leaks occur at the gastrojejunal anastomosis, with nearly all the rest occurring in the remnant (excluded) stomach; leaks from the jejunojejunal anastomosis are less common but do occur and usually require reoperation. In sleeve gastrectomy, the critical areas for leak are the top of the suture line and the transition point between sequential cartridge.

The primary diagnosis is done using radiologic techniques: upper gastrointestinal imaging (UGI) and CT scans. Because of patient obesity, both of these tests have limited diagnostic sensitivity [42, 43]. Despite this limitation, radiologic evaluation is important in the early detection of leaks in the postoperative setting [44]. The primary diagnostic tool used to assess for postoperative leaks is a UGI study with an oral water soluble contrast. This study is typically performed on postoperative day 1 or 2 and has shown variable sensitivity in detecting leaks (many leaks occur after a UGI study).

Management of bariatric leaks has traditionally consisted of drainage, antibiotics, and specialized nutrition. In patients with hemodynamic instability, a surgical approach is preferred. In recent years there has been an increase in the nonoperative management of leaks after bariatric surgery as most leaks are well contained and do not require operative control.

There is little role for an endoscopy in the presence of known leaks or fistulas in the early postoperative period. An endoscopy can be considered if the patient is clinically stable, there is uncertainty of the diagnosis, or if there is a planned endoscopic intervention [35, 45].

Chronic fistulas may be found in the presence of marginal ulcers, and patients may present with nausea, vomiting, epigastric pain, and weight gain.

Recent reports demonstrate that endoluminal interventions are effective in healing anastomotic breeches. Multiple investigators are reporting the successful placement of covered endoluminal

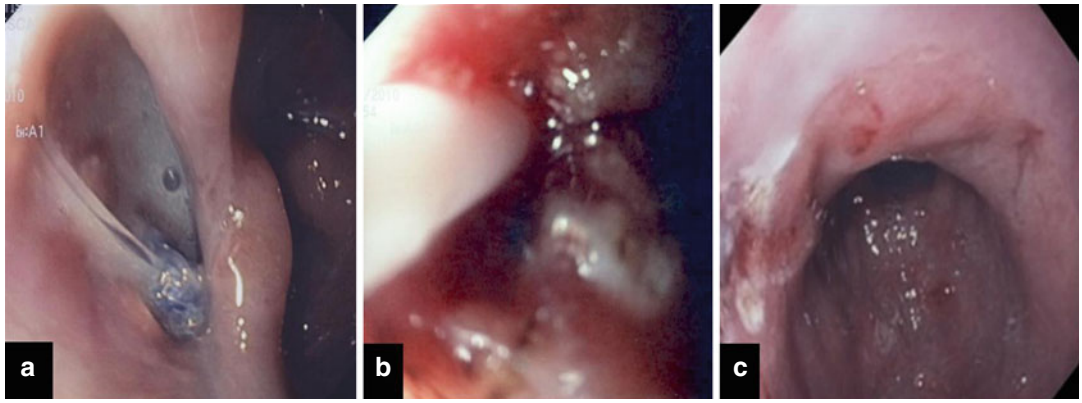

Fig. 16.5 Suture leak following sleeve gastrectomy. In (**a**) endoscopic view of the fistula. At the bottom it is possible to recognize a surgical stitch. In (**b**) endotherapy with APC and fibrin glue application. In (**c**) endoscopic appearance after 1 month after endoscopic treatment

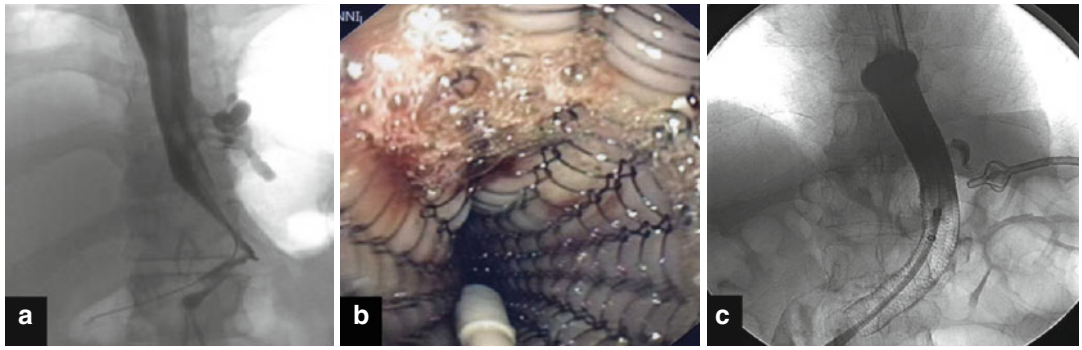

Fig. 16.6 Endoscopic therapy for postoperative fistulas with self-expanding stent. In (**a**) fluoroscopic appearance of the fistula before treatment. In (**b**) endoscopic view during self-expanding stent release and in (**c**) post placement fluoroscopic control

stents and the initiation of oral nutrition leading to recovery from this postoperative complication [46–48].

Endoscopic therapy for postoperative fistulas has been performed also by using fibrin glue injection (Fig. 16.5) [49, 50] or self-expanding stents [51–53] (Fig. 16.6). A possible adjunct in managing postsurgical leaks involves minimally invasive techniques using stents placed with endoscopic and fluoroscopic guidance. Covered stents can be placed in the bowel lumen at the site of the leak in a minimally invasive fashion. Stents offer several treatment advantages that can simplify surgical management of postoperative leaks. A stent prevents or greatly diminishes further peritoneal contamination by excluding the leak site from enteral secretions. This in turn is thought to promote and accelerate leak healing. Stent placement results in a rapid improvement in abdominal pain as a result of decreased peritoneal contamination. Shielding of the leak site also permits nutrition to be given orally in many cases. Parenteral nutrition is seldom necessary.

These stents are designed to be compressed and are packaged in a removable sheath as part of the delivery system. When the sheath is withdrawn, the stent expands to a predetermined size and with a radial force that is designed to avoid bowel perforation. An outer coat of silicone is impermeable and prevents intestinal mucosa and fibrotic tissues from being incorporated into the gaps in the stent. This property allows the stents to be removed, usually within 8 weeks.

Stent placement for leaks is currently associated with a high complication rate. It is common for patients to experience substernal chest pain with radiation to the back, and patients often have nausea that can be difficult to treat. Treatment with pain medication and multiple antiemetics for the most part controls patients' symptoms. Occasionally, however, the stent must be removed due to intolerable symptoms.

The most common complication is stent migration up to 40 % [54]. Most of these could be recovered or repositioned by upper endoscopy. More recently, a partially covered nitinol stent, the WallFlex partially covered esophageal stent (Boston Scientific), has been used. The proximal flare on the stent is uncovered for 3 cm, allowing mucosal and fibrotic incorporation into this portion of stent. This mucosal tissue ingrowth results in anchoring the stent. The metal partially covered stents resulted in less migration compared with covered stents. On the other hand, due to the uncovered part, these stents can be difficult to remove, however, and during its removal a 3-cm circumference of the bowel wall could be removed.

Case reports and small case series indicate that fistula closure may also be achieved by using various combinations of mucosal ablation, glue, the application of endoscopic clips, the placement of self-expanding stents, and endoscopic suturing devices [45, 55, 56]. However, these interventions cannot be routinely recommended at this time, because of a lack of controlled data.

Nonsurgical interventions were found to result in the healing of anastomotic leaks in 81 % of affected patients [52].

16.3.5 Dilated Anastomosis

A dilated anastomosis and/or a dilated gastric pouch after bariatric surgery results in weight gain as a consequence of loss of satiation and increased caloric intake. Eighteen to thirty percent of bariatric patients experience a near-total weight regain following bariatric surgery, constituting surgical failure [57, 58]. Although weight regain or failure is typically related to dietary indiscretions, failure to exercise [59], or failure in regulatory gut hormones [60], other causes have been identified. Some investigators point out that stomal size correlates with the risk of weight regain for bariatric patients [61]. Therefore, when patients present with weight regain or failure to lose weight, endoscopic evaluation and radiologic studies should be considered [62]. When an enlarged gastrojejunal stoma is found, potential endoscopic interventions that promote restriction and facilitate additional weight loss include (1) sclerotherapy of the site using 6–30 mL of sodium morrhuate injected circumferentially, which is associated with a 72–75 % success rate [63–67]; (2) "ROSE" procedure (revision obesity surgery endoscopic procedure) [68–70]: the use of an endoscopic tissue plication system to reduce the size of the anastomosis and the gastric pouch; (3) endoscopic tissue plication device known as StomaPhyX (EndoGastric Solutions; Redwood City, CA, USA) to reduce the pouch size [71]; and (4) application of the endoclip to reduce the size of the gastrojejunal anastomosis [72]. Weight regain may also indicate the presence of a gastrogastric fistula, which may be addressed endoscopically in a similar manner.

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