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New Technical Proposals

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GASTROINTESTINAL SURGERY - NEW TECHNICAL PROPOSALS

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Contributors

Cihangir Akyol, Suleyman Utku Celik, Can Konca, Rodolfo José Oviedo, Raashid Hamid, Nisar Bhat, Mansoor Ahmad, Balvinder Singh, Șerban Vifor Gabriel Bertești eanu, Alexandru Nicolaescu, Raluca Grigore, Popescu Bogdan, Rahman Barry, David Denning, Thao Wolbert

Notice

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Meet the editor

Vincenzo Neri, Prof. Dr. Med, was born in Bari, Italy, on March 15, 1946. He graduated in 1970 in Medicine and Surgery at the University of Bari, where he carried out a great part of his academic activity (Assistant Professor from 1974 to 1982 and Associate Professor from 1982 to 2001). He obtained the Diploma of "Maitrise Universitaire en Pedagogie des Sciences de la Santé" at the Université Paris-Nord Bobigny. In 2010–2011, while in the ERASMUS-Program, he developed a seminar on "Cystic tumors of the pancreas" at the University of Gent, Belgium. Some of his past positions include President of the Course of Degree of Medicine and Surgery, University of Foggia, from 1996 to 2002 and Director of the Department of Surgical Sciences, University of Foggia, from 2002 to 2008. Currently, he is Full Professor of General Surgery at the Department of Medical and Surgical Sciences, University of Foggia (since 2002), Director of the Division of General Surgery (since 1997), and Director of the Residency School of General Surgery, Policlinic University of Foggia (since 2008). His main research interest is hepatobiliary pancreatic surgery. He is a member of the following scientific associations: SIC, IHPBA, AISP, EASL, NESA, and SLS.

Contents

Preface XI

Chapter 1 **Metabolic and Bariatric Surgery: Evolution, Techniques, and Management 1**
Rodolfo José Oviedo Barrera

Chapter 2 **Prosthetic Reconstruction of the Upper Digestive Tract 27**
Șerban V.G. Bertești, Alexandru Nicolaescu, Bogdan Popescu and Raluca Grigore

Chapter 3 **Choledochal Cyst (CDC) 41**
Raashid Hamid, Nisar A. Bhat, Mansoor Ahmad and Balvinder Singh

Chapter 4 **Diverticular Disease 55**
Can Konca, Suleyman Utku Celik and Cihangir Akyol

Chapter 5 **Gastrointestinal Stromal Tumors (GIST) 75**
Rahman G. Barry, Thao T. Wolbert and David A. Denning

Preface

Gastrointestinal surgery has experienced a considerable acceleration of change. In recent years, the choices to be made in the surgical management of many of the most common digestive diseases have been modified from the perspective of better connections with new concepts in pathophysiology, new diagnostic tools, and new evidence of therapeutic efficacy and results.

In many areas of gastrointestinal surgery, new therapeutic and technical perspectives have seen the wide employment of mini-invasive and laparoscopic procedures.

The chapter " Metabolic and Bariatric Surgery: Evolution, Techniques and Management" shows a historical reconstruction of the evolutions in the surgical treatment of morbid obesity. The main surgical procedures, such as adjustable gastric band, sleeve gastrectomy, Roux en Y gastric bypass, biliopancreatic diversion with duodenal switch, and other less frequently employed procedures are described, related to the pathophysiology of morbid obesity.

The chapter "Prosthetic Reconstruction of the Upper Digestive Tract" demonstrates a huge technical surgical challenge. The curative surgical procedure for the treatment of advanced cancer of the hypopharinx and cervical esophagus is followed by a new technique of prosthetic reconstruction of the upper digestive tract.

The chapter "Choledochal Cyst (CDC)" presents a complete exposition of these congenital bile duct anomalies. The diagnosis is based on image exams such as ultrasound and magnetic resonance cholangiopancreatography within the variable clinical presentations. Finally, therapeutic management is discussed.

The chapter "Diverticular Disease" develops the very complex topic of the most common digestive disease. New acquisitions of the pathophysiology, which explain the evolution of the pathology features, are highlighted. The therapeutic program is very articulate in relation to the clinical evolution of the disease, the clinical characteristics of the patients, and the new perspectives of minimally invasive approaches.

The chapter "Gastrointestinal Stromal Tumors" develops the topic of the most common mesenchymal malignancies of the gastrointestinal tract. The chapter summarizes the complex pathobiology, clinical presentations, and diagnostic procedures of these neoplasms. Global management includes different therapeutic choices and approaches related to the evolution of the gastrointestinal stromal tumor as primary or advanced disease.

Prof. Vincenzo Neri
General Surgery
University of Foggia
Italy

Chapter 1

Metabolic and Bariatric Surgery: Evolution, Techniques, and Management

Rodolfo José Oviedo Barrera

Additional information is available at the end of the chapter

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Abstract

Metabolic and bariatric surgery involves more than altering the stomach and small bowel anatomy to provoke structural changes in the gastrointestinal tract from a mechanical point of view to treat morbid obesity. Its profound impact on the body's metabolism goes beyond anatomy and enters the realm of physiology. This is one of the most challenging and influential surgical subspecialties today due to its proven beneficial impact on the worldwide obesity epidemic and its millions of patients. A brief but comprehensive overview of the history of this fascinating yet challenging discipline and its advancement into the minimally invasive arena will be presented. Moreover, the body of this chapter will provide evidence-based data dealing with its indications, approaches, minimally invasive techniques including robotic surgery, the most common operations and the most recently introduced procedures, and management of complications. The impact of the laparoscopic revolution at the end of the twentieth century and the relevance of the robotic revolution from this century will be emphasized. An important point that will be made is the very specialized discipline of revisional bariatric surgery and its crucial role on the treatment of complications and failures that require extensive training and experience.

Keywords: metabolic, bariatric, surgery, minimally invasive, laparoscopic, robotic, evolution, techniques, management, approaches, indications, complications

1. Introduction

Bariatric surgery is the discipline of general surgery that encompasses the alteration of gastrointestinal anatomy, either by reducing the volume of the stomach, or the absorptive capacity of the intestine, or a combination of both, to provoke controlled physiologic changes that allow for a sustained and significant weight loss in morbidly obese patients. Metabolic

surgery, on the other hand, includes the physiologic aspect of this subspecialty due to its multiple benefits and effects on the body's metabolism and hormonal components that contribute to controlling and eradicating chronic medical conditions such as diabetes mellitus type 2, hypertension, hyperlipidemia, obstructive sleep apnea, and gastroesophageal reflux disease, among others.

In other words, bariatric surgery has long been associated by patients and the public in general as the subspecialty of general surgery that consists of altering the anatomy of the stomach and the small bowel, in some instances, to limit gastric capacity, promote restriction of volume, and malabsorption when applicable. Metabolic surgery goes beyond this definition, since it is recognized as the more scientific term due to its implication of change in the body's metabolism and its potential to control and eradicate some chronic diseases for which medical therapy is no rival [1]. This chapter will detail this fascinating discipline from the viewpoint of both definitions which complement one another and which should be devoted well deserved attention, especially in the setting of a worldwide morbid obesity epidemic which is affecting developed and underdeveloped countries. A detailed overview of its history, indications, approaches, minimally invasive techniques, and management of complications will be presented.

After a brief but comprehensive overview of the history of this discipline and its advancement into the minimally invasive arena, the body of the chapter will include several sections that will present the literature and high-quality evidence-based data dealing with its indications, approaches, minimally invasive techniques including robotic surgery, and management of complications. Emphasis will be made on the impact of the laparoscopic revolution at the end of the twentieth century and the relevance of the robotic revolution from this century. An important point that will be made consists of the very specialized discipline of revisional bariatric surgery and its crucial role nowadays, especially since several restrictive operations such as laparoscopic adjustable gastric band are now leading to complications that require highly trained surgeons with plenty of experience and a skill set that can only be attained with commitment to excellence.

Metabolic and bariatric surgery is not the surgery of the future, for it has been present for decades and has overtaken the place among the most challenging surgical subspecialties [2]. It has already begun, and we live in its era. This discipline deserves to be studied in detail, with a critical eye for the literature and minimally invasive techniques that will continue to elevate its high standards to new levels. The world has seen a change in the aspect, the behavior, and the diseases present in our society. The international morbid obesity epidemic that has dominated developed countries for years has already established its roots in underdeveloped countries. Metabolic and bariatric surgery must be an integral part of the twenty-first century advanced minimally invasive procedures offered to help our patients to achieve a better quality of life and survive medical conditions that were not as dominant in the past [3].

2. Historical context

Before the rise of the laparoscopic revolution at the end of the twentieth century, bariatric and metabolic surgery came to existence through the milestones and achievements of a few

individuals who continued to advance the technique and apply physiologic concepts to treat a condition that seemed impossible to manage with non-surgical options. Morbid obesity had not been specifically defined yet, but surgeons recognized its significance and began to perform operations to alter the stomach's capacity by restricting its volume either with foreign bodies or by excluding portions of it. Later, the understanding of the significance of decreased absorptive capacity of the small bowel on weight loss was applied to this field. Such an understanding arose from oncologic operations performed a century earlier, particularly for gastric cancer, when a Roux en Y reconstruction of the gastrointestinal tract revealed that the longer the Roux limb of intestine, the more pronounced the weight loss was for the patient.

The first bariatric procedure ever recorded, at least in terms of its purpose and its consistency with the definition of bariatric surgery, was a significant small bowel resection planned for purposes of weight loss by Henrikson, which was followed by the development of the jejunoileal bypass by Kremen. Both occurred in the 1950s. Subsequently, in the 1970s, Mason introduced the vertical banded gastroplasty as the first dedicated procedure where the stomach took a fundamental role as the primary object of anatomy alteration of the gastrointestinal tract to treat morbid obesity. A few years earlier, specifically in 1967, the same surgeon took Roux's idea of the Y configuration for gastrointestinal reconstruction and introduced the concept of the Roux-en-Y gastric bypass as a bariatric operation, which was performed starting in the 1980s. However, because of the inherent disadvantages of open surgery when applied to the challenging field of bariatric surgery, and given the expected complications that may occur when bariatric operations are performed via the open approach, the Roux-en-Y gastric bypass became the object of criticism among the surgical community and patients in general. On a separate area of this young subspecialty at that time, Scopinaro introduced the biliopancreatic diversion, while Hess, Legacé, and Marceau developed an early form of the nowadays well-known sleeve gastrectomy during the duodenal switch creation [4, 5].

The 1991 National Institutes of Health (NIH) consensus became the most fundamental event that gave validity and relevance to Bariatric Surgery when it established that the vertical banded gastroplasty and the gastric bypass were the two safest surgical options for morbid obesity at that time. The laparoscopic revolution took precedence in the 1990s and facilitated the performance of these operations with improved outcomes compared to those seen in previous decades. Bariatric surgery began to become accepted again and respected as a surgical subspecialty with powerful effects and demanding an advanced skillset to perform it. In fact, the first laparoscopic gastric bypass with a six-trocar technique was performed by Wittgrove, which consisted of a circular anastomosis retrocolic retrogastric bypass. Although the adoption of laparoscopic techniques facilitated the performance of the vertical banded gastroplasty, it eventually became less frequently performed not only due to the more complex but also efficient and successful gastric bypass. The Roux en Y gastric bypass itself has seen a variety of change in its technique, including a retrocolic retrogastric, a retrocolic antegastric, or an antecolic antegastric fashion, with circular or linear stapling techniques or with the hand-sewn laparoscopic or robotic approaches.

There is strong evidence in the literature that the Roux-en-Y gastric bypass continues to be the gold standard in bariatric surgery, despite the introduction of the adjustable gastric band and later the laparoscopic sleeve gastrectomy. Finally, to add to the historical perspective, the

robotic revolution of the late 1990s and early twenty-first century has made a powerful presence across the world and has produced multiple publications that show that robotic surgery can be successfully applied not only to complex bariatric procedures and revisional surgery but also to more routine bariatric procedures with efficiency and safety.

3. Physiology and mechanisms

The physiology of bariatric surgery, and its corresponding counterpart of metabolic surgery, is incredibly complex. In fact, it is now known after multiple animal and human studies over the last two decades that the typical understanding of restriction versus malabsorption is not the only responsible mechanism for weight loss. Rather, the gut-brain axis and its multiple components play a role when a bariatric procedure is performed, particularly when gastric and intestinal hormones and peptides that regulate metabolism are either activated or inhibited by the significant changes introduced by such operations [6, 7]. Trying to detail the immense body of knowledge that is available regarding this complex subject goes beyond the scope of this chapter. Nevertheless, it is important to understand that hunger and energy metabolism are affected not only by one hormone such as Ghrelin but also by restricting the stomach's volume or bypassing a specific length of small intestine. Instead of viewing the role of bariatric surgery as either restrictive or malabsorptive, attention must be paid to the hormonal changes that are caused by it, for they are more important to the gut-brain axis and the energy metabolism mechanisms that explain why some patients are able to lose more weight than others and why other patients regain some or most of their weight over a few years even when dietary indiscretions do not play a role.

By the same rationale, it is now logical to see how the Roux en Y gastric bypass is the gold standard of bariatric surgery, not because the excess weight loss achieved by it is superior to that of the sleeve gastrectomy on any given patient, but because of its effect on diabetes mellitus type 2 and hypertension, hypercholesterolemia, and gastroesophageal reflux. While Ghrelin is the fundamental hormone that is referred to when a sleeve gastrectomy is discussed with patients or colleagues, the Roux en Y gastric bypass can affect more hormones that interact with the gut-brain axis and provoke changes on energy metabolism, in addition to the gut microbiome and the bile acid concentration [8].

Regarding the interesting concept of the gut-brain axis and the role that the vagus nerve plays when bariatric operations are performed, it is known through neuroimaging studies that structural changes become normalized and brain connectivity improves so that morbidly obese patients can have an improved post-operative eating behavior. Hormones such as peptide YY3-36, GLP-1, ghrelin, neurotensin, and others participate in the regulation of eating behavior after surgery [9]. As it can be discerned, there is more than restriction versus malabsorption when it comes to understanding such an elegant field where science continues to advance and make discoveries that enhance the patients' quality of life. As a result of these effects on the metabolism of the body, studies such as the STAMPEDE trial continue to demonstrate that metabolic surgery is superior to medical therapy for the treatment of diabetes,

but also hypertension, hypercholesterolemia, and other chronic comorbidities compared to medical therapy [10]. The effects of the Roux en Y gastric bypass and the sleeve gastrectomy on diabetes control and eradication have been tested by time and have endured it with good outcomes over the years [11].

4. Adjustable gastric band

The laparoscopic adjustable gastric band is typically regarded as the only remaining truly restrictive procedure. It was approved in the United States in 2001, but it was already being performed in other countries prior to that. It consists of the implantation of a gastric band that is connected to a subcutaneous port and is manipulated by the surgeon usually in the outpatient setting by filling it or emptying it according to the patient's symptoms and weight loss response. The technique has been well described by other authors and it has evolved over the years. The most commonly performed technique involves its implantation in the proximal stomach by choosing a perigastric approach via the lesser curve into the lesser sac to pass it around the stomach and secure it anteriorly, and providing a plication of the gastric fundus over it.

A relevant fact is that the most common procedure related to the adjustable gastric band is not its implantation, but its explantation. The removal of an adjustable gastric band and its conversion to a sleeve gastrectomy or a Roux en Y gastric bypass, either as a two-stage or a single-stage operation, has become a frequent revisional bariatric operation at academic centers, particularly as of 2013 [12]. Compared to the more powerful effects of the sleeve gastrectomy or the Roux en Y gastric bypass, it is logical to see the reason for not choosing this procedure nowadays, since it lacks the metabolic component that the other two operations mentioned above offer, and it has a potential to produce a 30% excess weight loss at 1 year, which is lower than the excess weight loss produced by the sleeve gastrectomy or the Roux en Y gastric bypass.

Although some patients keep their adjustable gastric bands and see their surgeon on a regular basis for band adjustments in the office, it is known that the band's effects are typically stronger for the first 4 years [13]. After that, patients usually seek alternatives such as a band removal with conversion to another bariatric procedure, especially considering its potential complications such as band slippage with partial obstruction of the proximal stomach, incarceration, ischemia, and ulceration with or without band erosion into the gastric lumen.

5. Sleeve gastrectomy

The laparoscopic (and more recently robotic) sleeve gastrectomy has become the most frequently performed bariatric procedure in the United States and other countries due to its relative simplicity compared to the gastric bypass, in addition to the elegant nature of the physiologic changes that it has on the body's metabolism by restricting the stomach's volume and by reducing the Ghrelin concentrations by virtue of resecting the fundus, which is

responsible for gastric production of this important hormone [14]. It was initially introduced as a first stage, planned procedure for the biliopancreatic diversion with duodenal switch or for super obese patients who eventually would benefit from a Roux en Y gastric bypass and were too high risk to undergo such a procedure at the beginning [15].

It is superior to the adjustable gastric band in terms of its excess weight loss, which is 60% at 1 year, and its morbidity and mortality profile is superior to that of the gastric bypass, but at the expense of its weaknesses mostly in three specific cases where this operation is not the most effective one compared to the gold standard. These conditions are super morbid obesity (body mass index >50), diabetes mellitus type 2 which is insulin-dependent, and severe gastroesophageal reflux disease. In these specific cases, the gastric bypass offers more advantages to patients and a better metabolic profile. Having said this, the sleeve gastrectomy is highly effective and can be performed safely by experienced surgeons with reproducible results if some basic principles are respected and followed during surgery. To name a few, it is essential to standardize the caliber of the gastric sleeve by using a Bougie and prevent a stenosis of the gastric lumen, especially at the incisura angularis of the lesser curve, in addition to resecting the fundus completely to prevent a saccular dilation over time that will contribute to worsening reflux and increase the risk of weight regain.

Overall, however, if these principles are followed, the laparoscopic sleeve gastrectomy is an excellent single-stage bariatric operation without the need to convert to a gastric bypass or a duodenal switch later, as long as its outcomes for the patient are fulfilled [16]. As a result, the American College of Surgeons 2011 report's conclusion is that the sleeve gastrectomy morbidity and effectiveness is in between the adjustable gastric band and the Roux en Y gastric bypass [17]. Once again, it is easy to realize why this operation has become so popular over the years since it was introduced as a single-stage procedure by itself, based on its relative simplicity and its results which include a percent excess weight loss of >50%, and in most cases, up to 60% [18, 19].

The indication to perform a laparoscopic or robotic sleeve gastrectomy is either a body mass index greater than 40 kg/m^2 or a body mass index greater than 35 plus an obesity-related comorbidity such as diabetes mellitus type 2, hypertension, dyslipidemia, obstructive sleep apnea, gastroesophageal reflux disease, or other less frequently included medical conditions such as osteoarthritis, polycystic ovarian syndrome, and pseudotumor cerebri. However, it is important to remember that significant gastroesophageal reflux disease that occurs daily and not controlled with medical therapy is also a relative contraindication due to the risk of exacerbating this condition as a result of the high-pressure system that is created with the sleeve anatomy. On the other hand, a body mass index greater than 50, or super obesity, is also a relative contraindication due to the failure of this operation to maintain the weight loss over time in this context. Finally, for insulin-dependent diabetes mellitus type 2, a Roux en Y gastric bypass is a more efficient operation with superior results.

The following steps are this author's preferred approach to performing a robotic sleeve gastrectomy while following some essential principles that ensure a safe operation with a minimal risk of complications:

a. With the patient in reverse Trendelenburg and after establishing pneumoperitoneum via the Veress needle or the optical trocar technique, or a combination of both, the standard robotic ports and the liver retractor are placed in a foregut surgery configuration.

b. The greater curve of the stomach is approached first with a bipolar, ultrasonic, or vessel sealer instrument, by dividing the gastrocolic ligament while staying close to the stomach at the mid-point on the greater curve between the pylorus and the angle of His. The division of the gastrocolic ligament first approaches the distal greater curve and stops at 5 cm proximal to the pylorus to preserve the blood supply and integrity of the antrum and pre-pyloric region (**Figure 1**).

c. The division of the gastrocolic ligament continues proximally toward the short gastric arteries while protecting the spleen and, if necessary, coming into contact with the fundus if it is too close to the spleen to avoid the splenic capsule (**Figures 2** and **3**).

d. The left crus of the diaphragm is dissected along with the right crus to verify whether there is a hiatal hernia that needs to be repaired. If there is one, it should be repaired in a primary fashion and, less frequently, with mesh to prevent exacerbation of gastroesophageal reflux or development of de novo reflux (**Figure 4**).

e. With a 36–40 Fr Bougie in place and with its tip at the pre-pyloric area, a gastrointestinal stapling device, whether laparoscopic or robotic, with or without polymer reinforcement for the staple line, is used to transect the stomach and create a vertical sleeve gastrectomy, usually with the first three firings of the stapler being appropriate for the thickest tissue at the distal stomach. It is essential not to stay too close to the Bougie to cause stenosis of the gastric lumen, especially at the incisura angularis (**Figure 5**).

f. Verification that the staple line is hemostatic and not too close to the Bougie is important, especially in the distal stomach, where the pylorus is identified and intact, with the last 5 cm of gastrocolic ligament preserved (**Figure 6**).

g. Gastric transection continues to the angle of His, where the entire fundus is divided to complete the staple line while staying close to the Bougie but without causing stenosis at the gastroesophageal junction (**Figure 7**).

Figure 1. Division of the gastrocolic ligament begins along the greater curve of the stomach to enter the lesser sac and mobilize the greater curve, first distally, to 5 cm proximal to the pylorus.

Figure 2. Division of the gastrocolic ligament continues proximally to approach the short gastric vessels.

Figure 3. The short gastric vessels are divided while protecting the spleen and, if necessary, while coming into contact with the gastric fundus to avoid rupturing the splenic capsule.

Figure 4. The left crus of the diaphragm is dissected in addition to the right crus to detect a hiatal hernia, which should be repaired if present either primarily or with mesh.

h. A leak test is performed, ideally with intraoperative endoscopy while clamping the prepyloric region with atraumatic graspers to prevent passage of air into the small bowel and while submerging the gastric sleeve under saline solution to look for air bubbles. Upper gastrointestinal endoscopy also reveals whether the gastric sleeve staple line is hemostatic in the lumen and if there is any potential stenosis especially at the incisura.

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Figure 5. The surgical stapler is used to transect the stomach and create a vertical staple line while staying close to a 36–40 Fr Bougie, but without causing stenosis of the lumen, especially at the incisura angularis.

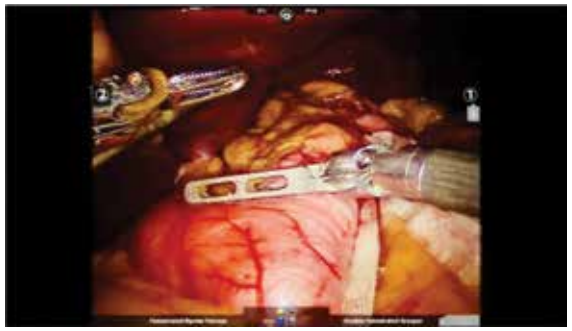

Figure 6. Constant verification that the staple line is hemostatic is essential, in addition to avoidance of gastric lumen stenosis caused by excessive proximity to the Bougie during stapler deployment.

Figure 7. The vertical staple line is completed by transecting the stomach proximally, including the fundus, and staying close to the Bougie at the angle of His.

In addition, the use of the Firefly technology is an adjunct to the leak test, if available, by having the Anesthesia team inject indocyanine green (ICG) to visualize any potential ischemic areas, especially the proximal end of the gastric sleeve, where a leak is more likely to occur.

i. The product of the sleeve gastrectomy is extracted via the longest laparoscopic incision corresponding to the stapler port.

j. A fascial closure device is used to close the fascial defect at the stapler port site to prevent a port site incisional hernia.

k. The liver retractor and the ports are removed, and the incisions are closed with absorbable sutures.

6. Roux en Y gastric bypass

The gold standard of bariatric surgery continues to be the Roux en Y gastric bypass, which has been established and documented with multiple studies over the last three decades with an overwhelming body of literature and evidence. While the sleeve gastrectomy is a much simpler procedure to perform, the gastric bypass involves a much more complex set of skills that, in the end, produce results that surpass the areas where the sleeve gastrectomy cannot perform well. Specifically, the Roux en Y gastric bypass is a better tool to control diabetes, especially insulin-dependent, in addition to significant gastroesophageal reflux disease, and super (BMI > 50) or super-super obese (BMI > 60) patients. The gastric bypass has proven superior in terms of controlling hypertension, hypercholesterolemia, and obstructive sleep apnea, although many times authors quote almost similar rates when referring to the sleeve gastrectomy.

A Roux en Y gastric bypass could be performed on any morbidly obese individual, with a few exceptions such as those with Crohn's disease, due to the small bowel involvement that is expected at some point during the evolution of that disease. Patients who are of childbearing age or thinking about becoming pregnant also have to exert caution when choosing their bariatric procedure, since electrolyte abnormalities and nutritional deficiencies are expected and must be prevented and treated during the post-operative recovery. Moreover, patients on hemodialysis may consider the less complex sleeve gastrectomy, particularly due to the fact that it lacks a malabsorptive component.

Critics of this operation often mention its higher morbidity when compared to the sleeve gastrectomy or the adjustable gastric band, which is mostly caused by the well-known possibility of internal herniation through one of the mesenteric defects that are created during this operation. The possibility of internal herniation can be minimized with attention to detail and good technique, including closure of mesenteric defects at the jejunojejunostomy or the transverse mesocolon for retrocolic gastric bypass or a narrow mesenteric defect at the mesentery of the Roux limb when it meets the gastric pouch to minimize the risk of a Petersen hernia. Some experts even use biosynthetic mesh at these mesenteric defects in a prophylactic fashion, although it is not common. In any case, even if an internal hernia is present months or years later, a high index of suspicion is required to avoid small bowel ischemia or necrosis and to act promptly to prevent worse complications. Internal hernias, in other words, can be prevented and can be promptly treated by expert bariatric surgeons or by general surgeons, all of whom should be familiar with this complication.

The other complication that is often quoted is an anastomotic leak, which nowadays has the same risk as a staple line leak from a sleeve gastrectomy, approximately 2%, and in expert hands at experienced centers, lower than that. Therefore, this is no longer a valid criticism. The risk of anastomotic marginal ulcers is also a significant consideration and must be decreased by particular attention to meticulous dissection and respect of the blood supply to the gastric pouch to avoid future ischemia, in addition to abstention from taking non-steroidal anti-inflammatory drugs (NSAIDs) or smoking. The most significant disadvantage for patients, on the other hand, is the fact that they must commit to a life of vitamin supplements and medications such as iron and calcium compared to only a year requirement for a sleeve gastrectomy [20–23].

A Roux en Y gastric bypass is expected to produce an excess weight loss of up to 70–75% at 1 year. In terms of the technique, although it was initially described with the retrocolic, retrogastric technique, it has eventually evolved into the retrocolic, antegastric variant and more recently the antecolic, antegastric procedure, which is more widely used by the new generations of bariatric surgeons due to its simplicity and the fact that, if a reoperation is required, it is much easier to perform it without having to dissect the Roux limb from the posterior plane of the transverse colon. The disadvantage of the antecolic, antegastric technique lies in the fact that tension is often encountered when mobilizing the Roux limb to the epigastric area, therefore requiring division of the mesentery of the jejunum for at least 3–5 cm sometimes to allow for the tension to be minimized while respecting the blood supply to the biliopancreatic limb and the Roux limb at the same time.

The indications for a laparoscopic or robotic Roux en Y gastric bypass are the same as those for a sleeve gastrectomy, i.e., when the body mass index is greater than 40 kg/m^2 or greater than 35 with an obesity-related comorbidity. Nevertheless, a gastric bypass is especially indicated where the sleeve gastrectomy shows weakness, specifically when the patient exhibits significant symptoms of gastroesophageal reflux disease that is refractory to medical therapy, or insulin-dependent diabetes mellitus type 2, or when the body mass index is greater than 50. In all cases, but especially under these specific circumstances where the sleeve gastrectomy fails to provide durable weight loss or control of comorbidities, a gastric bypass produces excellent outcomes and demonstrates why it is still considered the gold standard of bariatric and metabolic surgery. Specifically, in terms of gastroesophageal reflux disease, the Roux en Y anatomy has been known to be the ultimate surgical treatment for this condition due to the fact that the gastric secretions would have to travel at least 1 m downstream via the biliopancreatic limb, plus another meter upstream via the Roux (alimentary) limb to the gastric pouch in order to eventually cause the symptoms and signs of reflux, which is extremely difficult to achieve with this reconstruction of the gastrointestinal tract. Diabetes mellitus type 2 that is insulin-dependent is better controlled with the gastric bypass, which has been shown by numerous studies including the original STAMPEDE trial and its follow-up papers, among others. Finally, super obese and super-super obese patients experience a durable weight loss that is maintained over the years with this operation.

The following steps are considered the most important components of the antecolic, antegastric Roux en Y gastric bypass, in this case via the robotic approach, although it can be easily extrapolated to the laparoscopic method:

a. After pneumoperitoneum is obtained via the Veress needle technique or the optical trocar technique, or both, and after placing the ports in the typical foregut surgery configuration, with the liver retractor in position and with the patient in slight reverse Trendelenburg, the jejunojejunostomy anastomosis is created first. The proximal jejunum is identified at the ligament of Treitz, and 50 cm are counted distal to it to transect the jejunum with a gastrointestinal stapler to create a biliopancreatic limb and a Roux limb. It is essential to keep the correct orientation of the bowel after the division to avoid complications related to the creation of an anastomosis in the wrong portion of the bowel. Usually, the biliopancreatic limb (proximal) is kept at the right of the screen, while the Roux limb (distal) is kept at the left (**Figure 8**).

b. The mesentery of the jejunum at the transection site should be divided 3–5 cm in a straight fashion perpendicular to the bowel to prevent ischemia of either end of the biliopancreatic or the Roux limb (**Figure 9**).

c. Once the jejunum is transected, while keeping the orientation, 150 cm are counted distal to the staple line on the Roux limb to identify the site of the jejunojejunostomy anastomosis, where antimesenteric enterotomies are created on the biliopancreatic limb and the Roux limb (**Figure 10**).

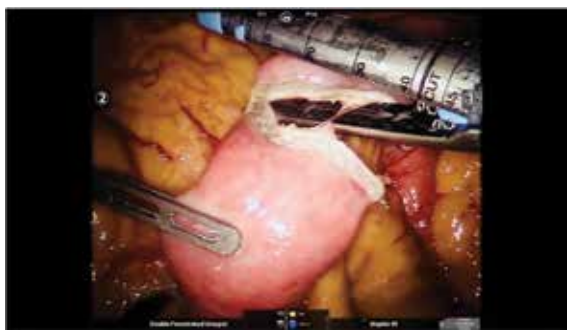

Figure 8. At 50 cm distal to the ligament of Treitz, the jejunum is transected to create a biliopancreatic limb and a Roux limb.

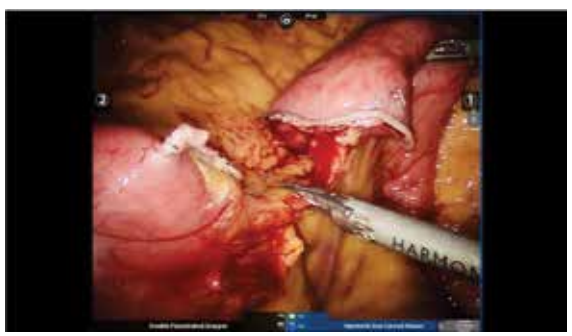

Figure 9. The mesentery of the jejunum is divided vertically for 3–5 cm to decrease the amount of tension on future mobilization of the Roux limb to meet the gastric pouch.

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Figure 10. Antimesenteric enterotomies are created at 150 cm distal to the jejunal transection site after selecting the site of the future jejunojejunostomy anastomosis.

d. A stapled side-to-side, functional end-to-end jejunojejunostomy is created with a linear stapler, ideally long, to prevent stenosis when closing the common enterotomy used to introduce the stapler (**Figure 11**). This author's preferred technique involves a bi-directional linear anastomosis, with the stapler fired to the right and to the left, so that the central common antimesenteric enterotomy is stapled with another linear stapler (**Figure 12**). Alternatively, the common enterotomy may be closed with the two-layer technique, first with absorbable suture with full-thickness bites and then with permanent suture with seromuscular bites.

e. The jejunojejunostomy mesenteric defect is identified and closed with running non-absorbable suture to minimize the risk of future internal herniation (**Figure 13**).

f. The greater omentum must be divided into half along the midline, starting at the level of the transverse colon and heading toward the greater curve of the stomach to allow the Roux limb to ascend to meet the future gastric pouch without excessive tension caused by the amount of greater omentum present in morbidly obese patients (**Figure 14**).

g. A retrogastric plane is identified along the lesser curve of the stomach by dissecting the gastrohepatic ligament and protecting the left gastric artery. Once the posterior wall of the stomach is seen, a linear stapler is used to transect it first horizontally at 5 cm distal to the gastroesophageal junction and then vertically toward the angle of His, all of this with confirmation that the orogastric tube inserted by Anesthesia at the beginning of the case has already been removed so that it is not stapled with the stomach (**Figure 15**). All of this is done to create a 30 cc capacity, vertical gastric pouch completely separated from the gastric remnant. Many times, using a 36–40 Fr Bougie as a sizer in the gastric pouch is necessary prior to firing the stapler vertically to ensure that the gastric pouch lumen is not too constricted or too wide. If a significant hiatal hernia is present, it should be repaired, although it is known that the Roux en Y anatomy will decrease and potentially eradicate the incidence of reflux.

h. An anterior or posterior gastrotomy is created on the gastric pouch with respect to the horizontal staple line, while an antimesenteric enterotomy is created on the Roux limb. A linear stapler is used to create a stapled side-to-side, functional end-to-end gastrojejunostomy anastomosis approximately 3 cm in length but not longer than that (**Figure 16**).

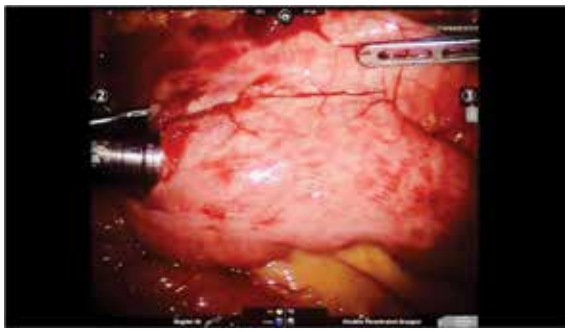

Figure 11. A bi-directional, stapled side-to-side, functional end-to-end jejunojejunostomy anastomosis is constructed at the 150 cm mark to give rise to the common channel (the stapler firing from right to left is shown here, with an additional left to right firing deployed next).

Figure 12. The central common enterotomy is transected and closed with an additional one or two linear firings of the stapler, with extreme care not to narrow the lumen of the bowel at the biliopancreatic or Roux limbs, or at the common channel.

Figure 13. The jejunojejunostomy mesenteric defect is closed with non-absorbable suture to prevent future internal herniation.

i. The common gastrotomy and enterotomy are closed with the two-layer technique in an intracorporeal suturing fashion, first with absorbable suture with full-thickness bites, followed by non-absorbable suture with seromuscular bites to imbricate the first suture line (**Figure 17**).

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Figure 14. The greater omentum is transected along the midline from the level of the transverse colon to the greater curve of the stomach to allow the Roux limb to reach the future gastric pouch with minimal tension in an antecolic, antegastric fashion.

Figure 15. Once the retrogastric plane is identified from the lesser curve approach while protecting the left gastric artery, a 30 cc capacity, vertical gastric pouch is created at 5 cm distal to the gastroesophageal junction, first with a horizontal firing of the stapler, with subsequent vertical firings toward the angle of His, to completely separate the gastric pouch from the gastric remnant.

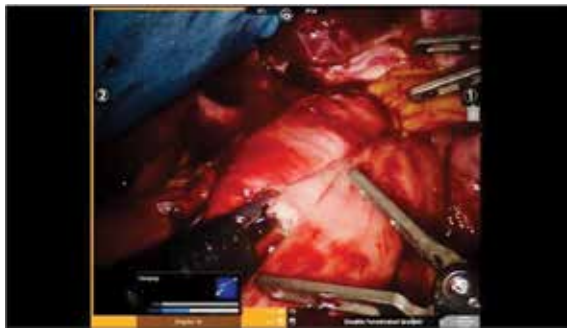

Figure 16. After creating an anterior or posterior gastrotomy on the gastric pouch and an antimesenteric enterotomy on the Roux limb, a linear stapler is used to create a 3 cm gastrojejunostomy anastomosis, with loss of a few millimeter during closure of the common gastrotomy and enterotomy.

j. A leak test is necessary, ideally with intraoperative upper endoscopy performed by the surgeon. In addition, the use of ICG and Firefly technology can help to detect areas of ischemia at the anastomosis prior to firing of the stapler or even afterward.

Figure 17. The common gastrotomy and enterotomy at the gastrojejunostomy are closed with the two-layer intracorporeal suturing technique, with absorbable running full-thickness bites, followed by non-absorbable running seromuscular bites, followed by a leak test with or without intraoperative endoscopy.

k. Once both anastomoses are inspected and hemostasis is ensured, the liver retractor and ports are removed after closing the stapler site fascial defect with a fascial closure device. The incisions are closed with absorbable suture.

7. Biliopancreatic diversion with duodenal switch

The most powerful metabolic procedure is well known by a few expert bariatric surgeons and mostly misunderstood by most surgeons and the public due to some biased reports of complications that deviate themselves from the excellent outcomes derived from this operation that requires a level of expertise that surpasses that of the Roux en Y gastric bypass. This surgery is not meant to be performed by all surgeons. It is meant to be done by a few individuals who have not only mastered the technical rigor required to carry it out but also the complex potential complications and the medical and nutritional management that are associated with the duodenal switch [24]. In general, it is known that the excess weight loss at 1 year is >75%, sometimes approaching 80–85%. However, this is not the only advantage of this fascinating operation. This is the origin of the sleeve gastrectomy, when such procedure used to be performed as the first stage of the duodenal switch.

When performed correctly, with attention to detail while minimizing the risk of complications, the duodenal switch yields significant results and quality of life scores that are usually maintained over the years, even at 10 years of follow-up in some cases [25, 26]. Some critics argue that this operation produces a high percentage or reoperation cases due to complications, many times up to 40% or higher, along with nutrient and protein deficiencies in approximately 10% of patients [27]. While this may be true, it is important to realize what a tremendous impact the duodenal switch has on the super obese and the super-super obese patients' metabolism and comorbidities, with high and sustainable success rates that cannot be achieved even with the gastric bypass sometimes. This is the very reason that the duodenal switch cannot and should not be offered to all bariatric patients. This is an operation that demands a superior level of commitment and discipline on behalf of the patient and the

surgical and bariatric team, not only during the perioperative period but also, especially, during the long-term follow-up that is expected, ideally for life.

The fundamental indications for a laparoscopic or robotic biliopancreatic diversion with duodenal switch are the same as those for the sleeve gastrectomy or Roux en Y gastric bypass, i.e., a body mass index greater than 40 kg/m^2 or greater than 35 with an obesity-related comorbidity. However, in addition to these essential indications to qualify for bariatric surgery, it is understood that the patient must belong to the category of significant, uncontrolled insulin-dependent diabetes mellitus type 2, with a body mass index of at least 50 (super obesity) or 60 (super-super obesity), all of this in the context of excellent display of psychological maturity, reliability, medication compliance, and discipline, especially considering the potential vitamin and nutrient deficiency complications that could arise from this powerful operation. Having said that, the biliopancreatic diversion with duodenal switch, as it has been previously presented, has the most significant effect on excess weight loss, even superior to the Roux en Y gastric bypass. Although the duodenal switch exhibits lower rates of reflux compared to the sleeve gastrectomy due to the nature of a larger sleeve anatomy in this case, the Roux en Y gastric bypass surpasses it in this respect because it does not involve a sleeve reconstruction, and therefore there is not a high-pressure system in a gastric bypass that would exacerbate reflux. The biliopancreatic diversion with duodenal switch, therefore, cannot occupy the place of gold standard for bariatric and metabolic surgery simply because it should only be reserved to those patients who meet these rigorous criteria, for their own safety. On the other hand, no other metabolic procedure has the potential to impact the patient's quality of life, metabolism, and health than the duodenal switch.

In general, it is widely accepted that this operation involves the following steps:

a. After pneumoperitoneum creation and placement of foregut surgery arranged ports and a liver retractor, the procedure begins with creation of a vertical gastric sleeve that has a larger diameter than produced during a typical sleeve gastrectomy, this time using a 54 Fr Bougie or larger.

b. The terminal ileum is identified, and 100–150 cm are counted retrograde while running the bowel, with marking stitches placed to identify the future site of the ileoileostomy anastomosis and the creation of the common channel.

c. From the marking stitches on the distal ileum that represent the future site of the ileoileostomy, another 150 cm are counted retrograde to identify the point of transection to divide the ileum and create a long biliopancreatic limb proximally, and a 150-cm alimentary limb distally. The ileum is divided here.

d. The end of the alimentary limb is secured to the mesentery of the bowel in the right upper quadrant with temporary stay sutures in preparation for the post-pyloric dissection and transection.

e. The duodenal bulb is subjected to retroduodenal blunt dissection very carefully while protecting the gastroduodenal artery and the head of the pancreas from injury, all of this with proper traction on the duodenum. Alternatively, the dissection may be performed from

the greater curve of the stomach in the pre-pyloric region and carried out to the duodenal bulb to dissect in the posterior plane.

f. Once the duodenal bulb is mobilized, while ensuring that the common bile duct insertion into the second portion of the duodenum has not been violated, the duodenum is transected 2 cm distal to the pylorus with a linear stapler.

g. The divided end of the alimentary limb, which was secured to the right upper quadrant bowel mesentery, is now anastomosed to the duodenal bulb in an end to side fashion (duodenum to ileum) in two layers, with the intracorporeal suturing technique, with absorbable suture first, and with non-absorbable suture next. A leak test is performed, ideally with intraoperative endoscopy. ICG testing with Firefly technology is also useful to detect ischemia prior to the anastomosis creation.

h. Finally, once the duodenoileostomy is created, the ileoileostomy is constructed in a stapled side-to-side, functional end-to-end fashion with a linear stapler at the site where the marking sutures were placed at 100–150 cm proximal to the ileocecal valve, between the divided end of the ileum on the biliopancreatic limb and the distal ileum, to create the common channel.

i. A surgical drain is left in the epigastric region overlying the duodenoileostomy, but it is not required.

j. The liver retractor and ports are removed after the stapler fascial defect is sutured and closed with an endoscopic fascial closure device. The incisions are closed with absorbable suture.

8. Other procedures and devices

The mini gastric bypass has gained popularity over the years, but has not proven to be as widely accepted as the Roux en Y gastric bypass despite some evidence that it produces similar weight loss effects and control of comorbidities compared to the Roux en Y gastric bypass [28]. Nevertheless, although it appears to be simpler to perform due to the eradication of the need to create two anastomoses, the concept of a loop gastrojejunostomy without the benefit of a Roux en Y anatomy produces a higher incidence of anastomotic marginal ulcers in addition to bile reflux.

A more recently published and developed procedure, the single anastomosis duodeno-ileal switch (SADIS), has begun to gain more acceptance in the United States and other developed countries in terms of a valid metabolic operation that still requires Institutional Review Board approval in the American healthcare system, but has promising results regarding weight loss and control of comorbidities. In the same fashion as the mini gastric bypass, the concept of a single anastomosis appears to be appealing to many surgeons and patients, although it still carries a high incidence of macronutrient deficiencies on follow-up studies as the classic biliopancreatic diversion with duodenal switch does [29].

The realm of endoscopic alternatives to surgical procedures for morbid obesity treatment includes the development of devices that mimic the malabsorptive mechanisms that surgery provides. Such an example is the EndoBarrier Gastrointestinal Liner, or duodeno-jejunal bypass sleeve (DJBS). A meta-analysis conducted on a few randomized controlled trials and several observational studies revealed up to 12.6% excess weight loss when compared to dietary modification, but there was a high level of bias detected on the studies [30].

The recently introduced AspireAssist device, which consists of an endoscopically placed gastrostomy tube that allows drainage of up to 30% of consumed calories after every meal, has been reported to have superior results to those of lifestyle modification, with up to 25% excess weight loss in some patients. Some of its complications are inherent to the fact that this requires the presence of a foreign body in the stomach which is constantly used to drain its contents [31]. Other devices such as the intragastric balloons have already shown some of the complications that arise from this limitation of having a foreign body in the gastric lumen, which is something that is surpassed by surgery.

Whether these procedures affect restriction, or malabsorption, or decrease the number of calories that are consumed, they serve mostly as an adjunct to bariatric surgery, as a bridge to an operation for those patients who are not medically optimized at the beginning, or as a means to lose weight for those who do not qualify for surgery yet. In any case, these devices do not offer the ability to change and impact the body's metabolism, which is something that surgery provides.

9. Revisional bariatric surgery

Although an entire chapter should be dedicated to this challenging and fascinating field of metabolic and bariatric surgery, it is important to recognize that revisional surgery is becoming a common type of operation in this subspecialty due to the complications that are seen from prior bariatric procedures that either were not performed well, or were performed appropriately but on the wrong surgical candidates, or were properly done but eventually failed to maintain the expected weight loss and comorbidity control. To perform this type of surgery represents an enormous responsibility, since revisional bariatric operations are known to be extremely challenging and technically demanding [32–34]. In general, the following categories detail the types of revisions that are commonly performed:

a. Removal of adjustable gastric band, with or without conversion to sleeve gastrectomy or Roux en Y gastric bypass as a single-stage or a two-stage procedure

b. Revision of sleeve gastrectomy (re-sleeve)

c. Roux en Y gastric bypass anastomotic revision (gastrojejunostomy, jejunojejunostomy, or both)

d. Roux en Y gastric bypass reversal

e. Sleeve gastrectomy conversion to Roux en Y gastric bypass

f. Vertical banded gastroplasty conversion to Roux en Y gastric bypass

g. Closure of internal hernia, with or without anastomotic revision.

These are some examples of the operations that have shaped the field of revisional bariatric surgery over the years. It is essential to understand that the main purpose of revisional bariatric surgery is to first define the anatomy that was created with the original bariatric procedure, which must be done with meticulous technique, with enterolysis and adhesiolysis performed with patience to eventually identify the anatomic components involved in the operation in question. Once the anatomy is defined, the next step is to revise the operation by performing the task that is demanded with the same care exercised during a new bariatric procedure that is not a revision. In other words, first the anatomy must be defined, anastomotic limbs must be identified, staple lines and fistulae must be seen, and anastomoses must be studied with intraoperative endoscopy as much as possible along with strictures or stenoses, so that at the end of the first stage of the operation, a plan of action can be implemented with relative simplicity because the most difficult task has already been executed.

It must be clear, at the same time, that all bariatric procedures may produce complications [35–37]. These are technically demanding surgeries that are not exempt from causing adverse outcomes. For instance, laparoscopic sleeve gastrectomy leaks may be treated with endoscopic therapy including placement of stents, but eventually they may require resection and conversion to Roux en Y gastric bypass. In the same manner, gastric bypass leaks may require a revision of the anastomosis in question, or a more complex type of procedure such as resection and construction of a new anastomosis, if endoscopic therapy fails. Stenotic or strictured gastric sleeves may be subjected to myotomy or gastroplasty procedures or simply treated with conversion to Roux en Y gastric bypass or duodenal switch. At the end, basic surgical concepts always apply to the most difficult revisional surgeries, with meticulous dissection, respect of the blood supply, gentle handing of tissues, avoidance of excessive tension, appropriate sizing of anastomoses, and performance of leak tests with intraoperative endoscopy, ideally, as much as possible.

10. Robotic bariatric surgery

Although the purpose of this chapter is not to discuss robotic surgery, it is essential to admit that the robotic revolution has already reached bariatric surgery and has become a part of this subspecialty to the point that several high-quality studies have already supported the observation that the surgical robot is extremely useful in this field, especially during challenging procedures such as Roux en Y gastric bypass, duodenal switch, or revisional surgery that require creation of anastomoses and closure of enterotomy or gastrotomy defects with delicate precision. Several studies have presented excellent outcomes with a hybrid or a fully robotic approach to complex procedures such as gastric bypass or duodenal switch [38–41]. However, the surgical robot is also useful for more simple procedures such as

sleeve gastrectomy due to the multiple advantages offered by the robotic platform, such as improved dexterity with wristed articulation, superior visualization with the robotic endoscope, the ability to control three arms simultaneously in addition to the camera, and most of all, the power to maneuver the instruments and the camera without the need to depend so much on the assistant, who can now focus on other important tasks such as retraction and exposure, for example.

The surgical robotic platform offers advantages to the surgeon that conventional laparoscopy cannot provide. While an excellent set of surgical skills is an essential requirement to perform challenging procedures with laparoscopic techniques, the robotic approach enables the surgeon to carry out tasks that are extremely difficult to do with laparoscopy, particularly when it comes to the first stage of any bariatric revision, i.e., the establishment and definition of the original operation's anatomy. The dissection is facilitated by the robotic technology, which is much easier to do once the surgeon has overcome the learning curve that is inherent to the adoption of any new technique.

For more details on the use of the robotic technology for the field of bariatric surgery, including its safe adoption in community hospitals that are not considered major academic centers and its application to the treatment of non-bariatric conditions on obese and morbidly obese patients such as hernia repairs, please see other studies published by this author [42–44].

11. Endoscopic management of complications

A point that has been consistently made on this chapter is the fundamental role that upper gastrointestinal endoscopy has both during and after surgery. However, the role of endoscopy on the pre-operative evaluation of the bariatric patient must not be ignored, for it is very important and most of the times necessary to perform a thorough evaluation of the gastric lumen prior to performing a bariatric operation due to its ability to detect the presence of severe ulceration, *Helicobacter pylori* infection, and significant hiatal hernias that must be repaired during surgery, especially for sleeve gastrectomy, or even the presence of gastric tumors.

Nonetheless, regardless of whether surgeons consider pre-operative endoscopy as an essential component of the bariatric surgery evaluation, it cannot be denied that intraoperative endoscopy serves an important function for many reasons. First of all, it provides valuable information regarding the lumen of the stomach, whether a gastric sleeve or a gastric pouch, including hemostasis of the staple line or the anastomosis, the diameter of the anastomosis, the absence or presence of stenosis, and of course, verification of a staple line or anastomotic leak. While it is true that a staple line or anastomotic leak test can be performed without endoscopy, usually with an orogastric tube or methylene blue injection into the gastric lumen while compressing distally, the information that intraoperative endoscopy provides cannot be surpassed. In some instances, the findings at the time of endoscopy lead to a change in the operative procedure and require a revision in the same setting.

With respect to complications, such as staple line or anastomotic leaks, sleeve stenosis, gastrojejunostomy stenosis, gastrogastric fistulae, gastropleural fistulae, and others, the preferred approach of any experienced bariatric surgeon is usually endoscopic, not surgical. Endoscopic intervention has the ability to provide good results with less morbidity and mortality compared to revisional surgery, unless there is no more room for endoscopy after failure of this type of therapy [45–47]. The use of esophageal stents initially developed for the treatment of esophageal cancer has revolutionized the treatment of bariatric complications and is a skill that must be learned by all bariatric surgeons. It requires an excellent set of endoscopic skills which can be acquired over time and perfected to the point that the need for revisional surgery will become a rare event. This skillset also includes the ability to suture endoscopically to close fistulae or revise and reduce anastomoses or to inject fibrin glue or deploy clips, all of which are maneuvers that can be learned by a surgeon and do not have to be exclusively associated with our gastroenterology colleagues. In the end, although revisional bariatric surgery is always a challenging and exciting field, in the interest of the patient, it is best to try endoscopic therapy prior to committing to an operation that carries a higher morbidity and mortality.

12. Conclusion and personal message

Bariatric and metabolic surgery is not for everybody. It is dedicated to the treatment of patients with morbid obesity and its associated comorbidities in a way that has proven to be more effective than the most rigorous medical therapy. The benefits are so palpable and reproducible that the body of knowledge acquired over decades of basic and clinical scientific research is outstanding.

The gold standard par excellence continues to be the Roux en Y gastric bypass, whether laparoscopic or robotic, due to its metabolic profile as a reliable operation with durable effects on the patients and superior control and eradication of metabolic and chronic comorbidities such as diabetes mellitus type 2, hypertension, hyperlipidemia, obstructive sleep apnea, and gastroesophageal reflux disease. The sleeve gastrectomy is an excellent choice, too, but has limitations in particular with super obese patients, those with insulin-dependent diabetes, and individuals with severe reflux. It is less complex than the gastric bypass but offers good outcomes to patients, especially to those who are not so severely obese and are young, including female patients of childbearing age and those with Crohn's disease or on hemodialysis. The biliopancreatic diversion with duodenal switch is the most powerful bariatric procedure and should be reserved to super- or super-super obese patients with uncontrolled comorbidities who exhibit discipline and commitment to a lifetime of follow up and management of nutritional and vitamin deficiencies. The surgical robot provides the surgeon with the ability to perform bariatric operations with more versatility and more tools once the learning curve is mastered, with outcomes comparable and sometimes superior to those of laparoscopy in expert hands. Revisional bariatric surgery, whether performed with the robot or with conventional laparoscopy, is an incredibly challenging field that demands full concentration, attention to detail, meticulous dissection, and proper technique to initially define the anatomy and identify the components of the original operation and to then perform the revision with safety, ideally with assistance from intraoperative endoscopy, which is also used to treat com-

plications with multiple tools that must be known to bariatric surgeons who always look for ways to improve their skills to benefit the patients.

On the other hand, bariatric and metabolic surgery is not for all surgeons. It is the dominion of those who are courageous enough to change millions of lives while taking care of patients at high risk of morbidity and mortality with minimally invasive techniques and with a life-long relationship, in many instances, that can only be comparable to surgical oncology. The impact that metabolic and bariatric surgery has on the patient cannot be measured with simple numbers reflecting a body mass index or percent excess weight loss. It cannot be measured by hemoglobin A1C or lipid profiles or even the lack of anti-hypertensive medications. This impact goes beyond the numbers and surpasses any concept of external or inner beauty. The benefits produced by this type of operation are so significant to our patients that their quality of life truly increases, their willingness to live and achieve self-improvement becomes stronger, and they may serve as an example to others in a way that usually cancer patients do. As a result, those who are brave enough to become excellent metabolic and bariatric surgeons are humbled by this realization that we have become part of something grand, something greater than ourselves, in ways that we cannot imagine. After all, did we not go into surgery for this very reason?

Author details

Rodolfo José Oviedo Barrera

Address all correspondence to: rodolfo.j.oviedo@gmail.com

Metabolic and Bariatric Surgery, Robotic Advanced Gastrointestinal Surgery, Winchester Medical Center, Valley Health Metabolic & Bariatric Program, Winchester, Virginia, United States of America

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Chapter 2

Prosthetic Reconstruction of the Upper Digestive Tract

Șerban V.G. Berteșteanu, Alexandru Nicolaescu,
Bogdan Popescu and Raluca Grigore

Additional information is available at the end of the chapter

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Abstract

In cases of locally advanced cancers involving the junction between the hypopharynx and cervical oesophagus, the curative surgical treatment is total circular laryngo-pharyngectomy with resection of the upper cervical oesophagus, coupled with modified radical neck dissection. Techniques used to re-establish the continuity of the digestive tract have been pectoral transposition flap, gastric pull-up, jejunum or colon transposition and free pedicled fascial-cutaneous flap reconstruction. Prosthetic reconstruction was thought of and used only as a temporary solution. In our clinic, we adapted the Montgomery oesophageal prosthesis as more than just a temporary solution and used it in 63 patients operated from 2004 to 2014 with advanced (stages III and IV) cancer involving most of the hypopharynx or extending towards the upper cervical oesophagus. Following total circular laryngo-pharyngectomy with bilateral modified radical neck dissection, prosthetic reconstruction was performed using the Montgomery oesophageal tube. Patients were followed up on, and their status was monitored. Favourable results encouraged the authors to further develop a new active prosthesis, with advanced design and materials that better mimic the anatomy and physiology of the replaced segment. Prosthetic reconstruction of the upper digestive tract following radical oncologic surgery is a viable option, with advantages compared to other laborious plastic techniques. The new active model is under development, hopefully offering soon a safe and more cost-effective alternative to the other techniques.

Keywords: laryngo-pharyngectomy, prosthetic reconstruction, Montgomery tube, active prosthesis, Cristian Radu Popescu

1. Introduction

Cancer of the head and neck is generally a low prevalence type of malignancy, amounting to roughly 3% of all cancers in the United States [1]. This is a broad term used to address all

types of cancer in this anatomic region, but to put things in perspective, there are more than 10 different organs in the head and neck region (that is excluding the brain and the eye—each studied by a separate surgical specialty), some with more than three subsites and each with more than five types of cancer that may arise in it and, depending on the organ, subsite, extension and type of malignancy, a different treatment approach.

The central and arguably the most important aspect of the neck region is the intersection between the airway and the digestive tract. Seeing as breathing and feeding are both vital functions performed through the upper aerodigestive tract, by a complex interaction between the nose, pharynx, tongue and larynx, tumours which develop in this region will affect these essential functions.

The treatment of malignant tumours involving the pharynx and larynx depends on the subsite involved, extension of the tumour (classified using the AJCC TNM staging system), histologic type, general condition and preference of the patient.

Options include surgical resection of the tumour (referred to as treating the T—from the TNM classification) [2] coupled with excision of the lymph nodes that provide the lymphatic drainage from the respective area (called addressing the N, following the same logic), radiation therapy or chemotherapy. The more advanced the tumour, the more aggressive and complex the treatment must be, and usually a combination of surgery, radiation and chemotherapy is used.

A particular situation arises when treating locally advanced tumours that involve the whole circumference of the hypopharynx or extend to the upper cervical oesophagus. To respect the oncologic principles, the resection needs to encompass all of the hypopharynx as well as the larynx and depending on the case a portion of the upper cervical oesophagus. The result is a large defect between the base of the tongue and the rest of the cervical oesophagus. This defect needs to be repaired if oral feeding is to be re-established.

2. Relevant anatomy and physiology of deglutition

Depending on the grounds for classification (embryologic, gross anatomy, regarding bleeding—clinical basis), the upper digestive tract is defined as the anatomic area stretching from the mouth to the duodenum, colon or ileum. For the better part of our knowledge, prosthetic reconstruction has not been utilised elsewhere in the gastrointestinal tract except for the larynx, pharynx and upper oesophagus, so for simplification and to better serve our purpose, we shall further refer to the upper digestive tract as the area stretching from the mouth to the cervical oesophagus.

The major structure of the aerodigestive tract is the larynx. It is a complex cartilaginous, mobile structure, which is essential to four functions: breathing, speaking, swallowing and physical effort [3]. Around it lies the pharynx—the third and inferior part of the pharynx to be exact, called the hypopharynx (or laryngopharynx). They are connected by the three separate constrictor muscles of the pharynx: the superior, middle and inferior constrictor muscles.

These two structures are inseparable because of their role in performing the two most essential functions of the human body—breathing and eating. During breathing the larynx keeps the airway open, by pulling the vocal cords apart from each other and pushing the epiglottis in an upright position, to exert minimal resistance to the passage of air from the nose and mouth through the trachea. During deglutition (swallowing) however, the airway needs to be protected from aspiration of food and liquids into the trachea and lungs. Then the larynx is moved forwards and upwards; the epiglottis descends into a horizontal position, acting as a cover for the vocal cords. These at the same time come together to form an airtight seal of the trachea. The hypopharynx relaxes, and the upper oesophageal sphincter opens, so as to create a clear path for the food and liquids to pass through this region downwards to the stomach [4].

3. Cancer of the pharyngo-oesophageal junction

3.1. Diagnosis and treatment

Malignant tumours may affect the pharyngo-oesophageal junction area by arising at this site (rare cases of chondrosarcoma of the cricoid ring) or by extension from other neighbouring areas (most frequent: tumours of the hypopharynx—the pyriform sinuses and the posterior wall of the hypopharynx—the larynx, especially subglottic tumours; as well as tumours of the cervical oesophagus) or even as metastases from other organs. A not-so-rare occurrence is the so-called skip lesions of the oesophagus—two or more synchronous tumours at various subsites of the oesophagus—with direct contact between them [5].

Signs and symptoms of tumour extension to the pharyngo-oesophageal junction are nonspecific and for this reason are often overlooked. These include odynophagia (pain on swallowing); progressive dysphagia (difficulty swallowing), first for solid food and, later on, as the tumour grows, for liquids; and weight loss [6]. Other signs may be due to lymph node involvement—the presence of neck masses, ulceration of the tumour with infection of the necrotised tissue—fever, elevated white blood cell count and inflammatory response (elevated sedimentation rate, C reactive protein, fibrinogen).

Diagnosis is based on clinical examination, endoscopic examination, imagery (contrast enhanced CT scan or MRI—which have to include the neck and thorax—to proper evaluate the whole oesophagus as well as the lungs and liver, organs where metastases frequently occur), and the definitive diagnosis is based on the histologic findings; therefore, biopsy is compulsory [7].

After definitive diagnosis, based on the AJCC TNM classification, the disease is classified in two major categories: local disease and systemic (metastatic) disease. In the first situation, if surgically resectable (excluding T4b tumours), if the patient has a good enough general status to permit surgery and if it is desired, treatment should be surgical resection with reconstruction so as to obtain an functional outcome [7].

3.2. Methods of reconstruction

The principles that should govern how we choose a reconstructive technique are one-step procedure, low mortality, low morbidity, reduced hospital stay, shortest possible time to oral feeding, shortest time to vocal rehabilitation, minimal or no interference with subsequent radiation therapy and lowest cost [6].

Techniques used for reconstruction of the upper digestive tract following total laryngo-pharyngectomy are fascial-cutaneous pedicled-free grafts, local transposition flaps, gastric pull-up technique, jejunum-free transfer or colon transposition [8].

Complex interventions require trained specialists in plastic surgery and even general surgery. Performing such laborious surgery requires a multidisciplinary approach, with one team performing the excision of the larynx and pharynx as well as the neck dissection while the other harvests the ileum or colon or prepares the graft for implantation. Such surgeries are very demanding in terms of resources and time, routinely lasting more than 7 or 8 h.

The advantages of these techniques are that they use homografts, tissues from the patient's body—which are the ideal material for reconstruction. Once properly healed, the result is definitive, and a satisfactory functional outcome is achieved.

However, they are still prone to necrosis by way of vascular thrombosis, either postoperatively or at a later time, during chemo- or radiation therapy. This leads to septic complications and salivary fistulae, which if left untreated extend gradually. Complications impair oral feeding, thus the necessity for a second plastic revision surgery or a gastrostomy/jejunostomy, which in turn may lead to higher hospitalisation time and a higher mortality rate.

4. Patients and methods

Until the year 2001, most patients with tumours we would nowadays consider resectable which involved the pharyngo-oesophageal junction were either referred to radiation therapy (after tracheotomy and gastrostomy) or to specialised tertiary-care centres with both plastic and general surgery clinics where one-stage plastic reconstructions were performed. The few cases operated in our clinic had a poor quality of life after surgery—because the reconstruction was performed at a later moment (two stage surgery), meaning oral feeding was impossible for months. From 2001, Professor Popescu started using the Montgomery oesophageal prosthesis to rebuild the continuity of the digestive tract, first as a bridging solution—a temporary state—until definitive reconstruction using homografts was performed. From 2004 until 2014, 63 patients with locally advanced tumours involving the pharyngo-oesophageal junction were operated in the ENT Head and Neck Surgery Clinic of Colțea Clinical Hospital Bucharest. In all 63 cases, after total circular laryngo-pharyngectomy with bilateral cervical lymph node dissection (**Figure 1**), reconstruction was performed using the C.R. Popescu technique (using a Montgomery oesophageal tube). No other reconstruction technique was used on these

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Figure 1. Intraoperative aspect after total circular laryngo-pharyngectomy—with both carotid arteries visible, as well as the trachea and cervical oesophagus.

patients, and all of them were followed up, and data was recorded regarding survival, complications and complementary oncology therapies.

5. Prosthetic reconstruction: the C.R. Popescu technique

The technique developed by Professor Cristian Radu Popescu, first used in 2004, in the ENT Clinic of "Colțea" Clinical Hospital Bucharest, is an adaptation, which uses an already existing product —the Montgomery® oesophageal tube (manufactured by Boston Medical Products® Shrewsbury, Massachusetts, USA) (**Figure 2**). This was intended as a temporary prosthesis between the first, ablative, step of surgery and the second, reconstructive, step of the total pharyngo-laryngectomy with plastic reconstruction, using one of the multiple methods described.

However, Professor Popescu observed that the health status of the patients implanted with this prosthesis was rapidly improved and that oral feeding was quickly re-established (14 days post-operatively). That this method permitted the subsequent radiation therapy and chemotherapy

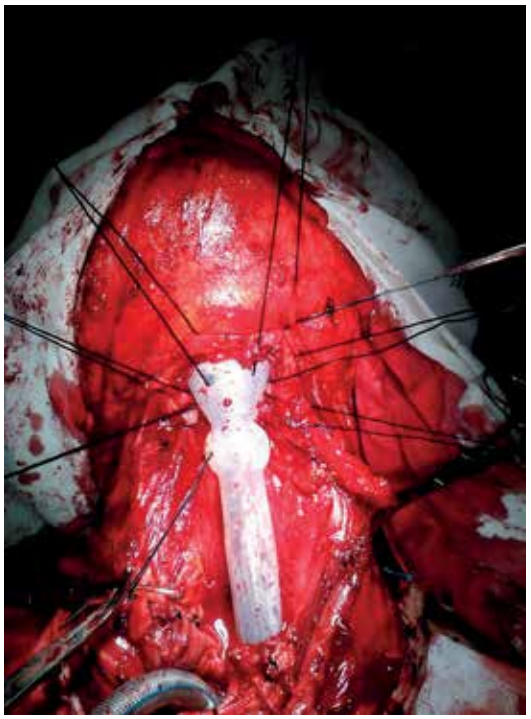

Figure 2. Montgomery oesophageal tube in place, with sutures placed along the cranial end, tying it to the tongue base and the oropharynx.

was an added advantage, and it was observed that complication rates were similar to those obtained by primary plastic reconstruction using autografts.

The procedure is straightforward, in that after total circular laryngo-pharyngectomy, the Montgomery tube is placed into position, with the wider cranial end towards the tongue base

Figure 3. Initial salivary fistula which evolved to a necrosis of the skin and underlying tissues, exposing the otherwise functioning prosthesis. A sternocleidomastoid cutaneous pedicled flap was used to repair the defect, with favourable result.

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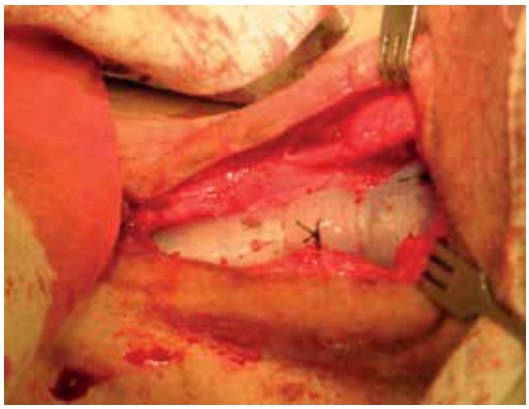

Figure 4. Design of the active pharyngo-oesophageal prosthesis—patent number A00292—developed by the team of Assoc. Professor Dr. Berteșteanu and under the guidance of Professor Cristian Radu Popescu, with support from colleagues from the Physics Faculty of the Politehnica University of Bucharest.

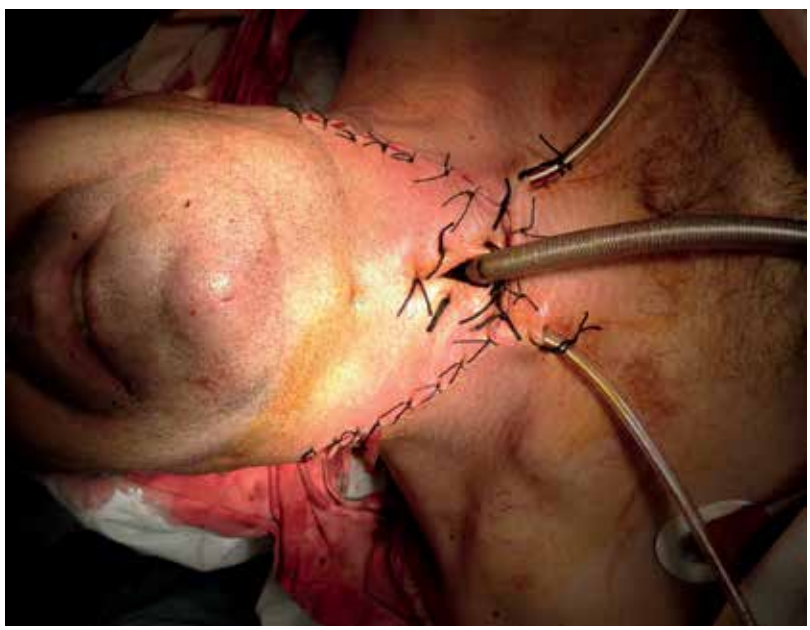

Figure 5. Prosthesis spontaneous expulsion due to improper fixation and dehiscence of the tongue base suture lines.

and the narrow distal end placed into the cervical oesophagus [6]. After approximation, the cranial end is sutured to the tongue base with non-resorbable silk 2.0 sutures (usually no more than six sutures along the whole radius of the tube) (**Figure 2**).

From our experience and the complications we encountered, two more suture lines should be placed, stabilising the prosthesis to the prevertebral fascia, so as to prevent slipping towards the tongue base (**Figures 3** and **4**).

After prosthesis placement and fixation, the prelaryngeal strap muscles are approximated to the tongue base forming a layer over the silicone tube, using slow resorbable sutures. A nasogastric feeding tube is placed through the prosthesis, to act as a protection measure. The rest of the procedure is similar to a normal laryngectomy, with the creation of the permanent tracheostoma, and wound closure (**Figure 5**).

Postoperative measures are enteral feeding through the nasogastric tube for 14 days minimum, broad spectrum antibiotics for 7 days, antisecretory medication for reducing salivary secretions (atropine) and proton-pump inhibitors for the as long as the feeding tube is in place. Ancillary measures we use in these patients are nutritional support using special enteral formulas, so as to correct malnutrition. After testing for salivary fistulae, the feeding tube is removed, and oral feeding is commenced. Barring complications, the patient is discharged around 7 days post-op [8].

6. Results

After performing an in-house analysis of this method on the 63 cases operated from 2004 to 2014 [6], data showed a higher prevalence of the disease in men 54 patients (86%) versus women 9 patients (14%). Patient age varied from 34 years to 73 years, with a mean age of 56 years. Ninety-two percent of the cases were confirmed after histopathological examination as squamous cell carcinomas. Ninety-three percent of patients were smokers, having smoked more than 20 years on average one pack of cigarettes per day. All of the cases were staged using the AJCC TNM [2] classification as III, IV A and IV B stages of disease. Biologic measurements were available in 90% of the patients (height and weight—permitting us to calculate the body mass index), and all of them had malnutrition, with less than 20 kg/m^2 BMI.

Survival data were obtained only in 28 patients, because of the lack of follow-up. In these patients, survival after 2 years was 56.14% and at 5 years post-op. Only 14.28% were still alive.

Complications encountered were gastro-oesophageal acid reflux (diagnosed only on clinical examination) in 33% of cases, wound infections in 20.63% of cases, salivary fistulae in 17.46% of cases and dysphagia (due to obliteration of the caudal end of the prosthesis) in 12.69% of cases.

Concerning operative time, the mean was 4 h and 20 min, (from skin opening to skin closure, including neck dissection), and hospital stay was a mean of 16 days, with a mean preoperative hospitalisation of 4 days and 13 days postoperative until discharge.

7. Advantages and limitations

The C.R. Popescu technique is a surgical method that permits tackling a difficult surgical intervention without the need for another specialist surgeon (plastic or general surgeon). It is time efficient, shortening the duration of surgery, and has a relative short ICU stay and hospitalisation period. The patient is quickly reintroduced to oral feeding, and complication rates are similar, if not lower to other techniques of plastic reconstruction [9, 10].

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Its limitation is due to the prosthesis itself and the interaction with the tissues surrounding it. The shape and the simple construction mean that the lumen is always open and the only force acting on the ingested food or liquids is gravity. This, associated with a widening of the upper oesophagus (due to accommodation of the caudal tip) and the loss of the peristaltic movements and sphincter action of the hypopharynx, leads to regurgitation and acid reflux. The

Figure 6. Stabilisation of the prosthesis with sutures to the prevertebral fascia and muscles.

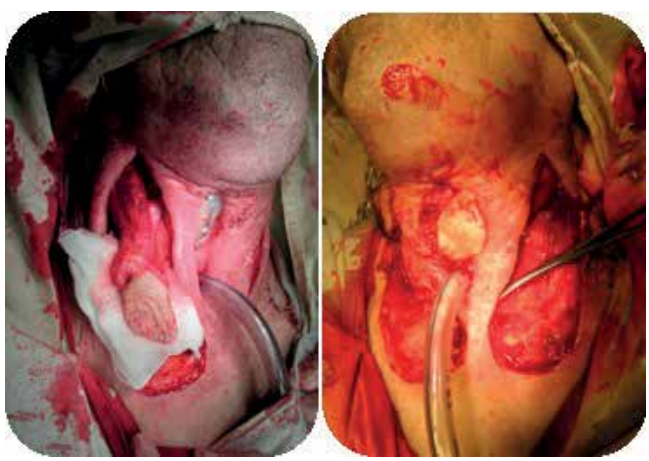

Figure 7. Endoscopic evaluation of the Montgomery prosthesis 14 days after implantation, with biofilm formation and bacterial and Candida colonies all around the circumference of the tube.

material of the prosthesis provides no defence against bacterial colonisation, and we have found that even 2 weeks after implantation, the whole length of the prosthesis is already colonised by bacterial biofilm formation (**Figure 6**).

Due to foreign body reaction, as well as the septic environment and constant acid reflux, we have found that in almost 13% of cases, dysphagia appears. Salivary fistulae appeared in 17.4% of patients. Endoscopy showed in all these cases the obliteration of the caudal end of the prosthesis with granulation tissue. Dysphagia renders the prosthesis useless; therefore, either a second plastic reconstruction using autologous tissue or a gastrostomy is necessary (**Figure 7**).

8. Active prosthesis

The shortcomings of the simple Montgomery tube, as well as the newer devices with active coatings that prevent biofilm formation and subsequent degradation (the indwelling vocal prostheses) [11], have prompted the authors to design a new model of implantable prosthesis. The goal was to create a perfect device—biocompatible, effective, with resistance to biofilm formation and, therefore, long life. This was achieved with the design of the active pharyngo-oesophageal prosthesis (patent number A00292/29.04.2015) (**Figure 8**).

The shape of the prosthesis is optimised for surgical placement and suturing to the tongue base, and it also has two widenings with holes prefabricated so as to permit stabilisation to the prevertebral fascia and to facilitate sealing of the cervical oesophagus (**Figure 5**). The materials used are biocompatible and do not interfere with CT scans and neither with radiation therapy.

Figure 8. Immediate postoperative aspect of a patient following total circular laryngo-pharyngectomy with Montgomery oesophageal tube prosthetic reconstruction.

The design tries to replicate the anatomy of the pharynx, by having three distinct layers. The external layer represents the hard casing of the prosthesis. It is made from a high-density medical-grade silicone derivate, so as to act as an inert surface, to minimise the risk of foreign body inflammatory reaction and subsequent granulation tissue formation. The middle layer is composed of a series of incomplete rings and represents the active part of the prosthesis. These rings have the capacity to contract in a complex fashion so as to mimic the physiologic peristaltic movements of the hypopharynx and oesophagus. The compound action propels the food bolus towards the stomach, even against the force of gravity. The third and inner-most layer is a thin, flexible layer, coated with a low adherence substance, that mimics the mucosa found in the digestive tract. It hopes to defend against biofilm formation and bacterial colonisation. The swallowing movements of the active prosthesis are controlled by a microprocessor with sensors implanted in the tongue base, so as to activate the food bolus propulsion when stimulated by the base of tongue contraction.

The active prosthesis is still under development awaiting production, and clinical studies have yet to begin.

9. Discussion

Prosthetic reconstruction after total circular laryngo-pharyngectomy represents an accessible, easy-to-perform alternative to the plastic reconstructions using autologous tissues. The main disadvantage of this method, in the authors' view, is the fact that once implanted the body reacts to the prosthesis as to all foreign bodies. From this immunological response stems, the major complications were associated to this type of method.

As unnerving as they are for the surgeon, complications that may necessitate the removal of the prosthesis should be viewed as the perfect opportunity to perform a second-stage plastic reconstruction. Our experience with this method has shown a comparable complication rate to the plastic reconstruction methods (as found in existing literature data). Radiation resistance is better than all the methods that use autologous tissue for reconstruction—which in our view should advocate the use of this technique on a large scale for patients who undergo complementary radiation therapy after the surgical treatment of the tumour.

The main advantages of the C.R. Popescu prosthetic reconstruction method recommend it for primary closure of the resulting defect. The dichotomy between temporary and permanent is always a "hot potato" topic regarding this subject (as well as prosthetics in general). However, the authors' feel that because of the high mortality of this cancer type, as well as the lower morbidity associated with prosthetic reconstruction, this method should be classified as a "permanent-until-proven-otherwise" solution.

Advances in prosthetics, as shown by the authors' quest to develop a novel, safer and more effective "biomimetic" pharyngo-oesophageal prosthesis, should render the discussion even more in favour of choosing prosthetic reconstruction over laborious homologous tissue reconstruction techniques.

10. Conclusions

From our experience the C.R. Popescu method of prosthetic reconstruction of the digestive tract following total laryngo-pharyngectomy is advantageous for the ENT head and neck surgeon because it offers the best compromise between efficiency and cost-effectiveness while not compromising patient safety.

This technique permits the ENT physician to perform a one-stage surgical procedure in a reasonable amount of time, without having to rely on other specialty colleagues and schedule harmonisation. The time-effectiveness also leads to less time under general anaesthesia which is important bearing in mind that patients with advanced tumours of the hypopharynx and cervical oesophagus are malnourished and have an impaired general health status.

Patient oral intake of nutrients may commence 10–14 days after surgery, and discharge from hospital takes place around day 14 post-op, which in turn lowers the financial burden on the institution and decreases the risk of healthcare-related bacterial infections.

Long-term survival appears to be slightly positively influenced using this prosthetic reconstruction, but it still is very low, with barely 14% of patients alive at 5 years after surgery. Theoretically, the low-survival rates associated with this type of malignancy should represent more reason to choose an inexpensive and easy-to-perform technique for reconstruction.

Its main disadvantage, the foreign body reaction, is no more significant than in other prosthetic implants and should not represent a major contraindication to using this technique.

Complications associated with the use of the Montgomery oesophageal tube for reconstruction have led the authors towards developing a new active prosthesis. Hopefully, this active prosthesis will offer a facile, cost-effective and efficient solution to patients and physicians involved in the treatment of head and neck cancer.

Author details

Șerban V.G. Berteșteanu[1,2], Alexandru Nicolaescu[1,3]*, Bogdan Popescu[1,2] and Raluca Grigore[1,2]

*Address all correspondence to: alexandru87nicolaescu@gmail.com

1 ENT Head and Neck Surgery Department, General Medicine Faculty, University of Medicine and Pharmacy "Dr. Carol Davila" Bucharest, Bucharest, Romania

2 ENT Head and Neck Surgery Clinic, "Colțea" Clinical Hospital Bucharest, Bucharest, Romania

3 ENT Head and Neck Surgery Compartment, "Professor Dr. Dimitrie Gerota" Emergency Hospital Bucharest, Bucharest, Romania

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Chapter 3

Choledochal Cyst (CDC)

Raashid Hamid, Nisar A. Bhat, Mansoor Ahmad and Balvinder Singh

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Abstract

Choledochal cysts are congenital bile duct anomalies. These cystic dilatations of the biliary tree can involve the extrahepatic biliary radicles, the intrahepatic biliary radicles, or both. The etiology remains unknown, but choledochal cysts are likely to be congenital in nature. Cyst excision is the definitive treatment of choice for choledochal cyst because of the high morbidity and high risk of carcinoma after internal drainage, a commonly used treatment in the past. CDC is a congenital anomaly involving cystic dilatation of various ducts of biliary tree. The precise etiology of extrahepatic cysts continues to remain unclear. The most commonly accepted theory is an anomalous pancreatobiliary duct junction (APBDJ) and abnormal function of the sphincter of Oddi. Proper imaging plays an essential role in preoperative planning. Proper diagnosis evaluation and management is essential for optimal management. Type I cysts are the most frequently encountered. Choledochal cysts can have variable presentations. Hepatobiliary ultrasound and MRCP are the present day standards for imaging; early diagnosis should be the norm to avoid possible late complications of cholangitis, cirrhosis, hepaticolithiasis and spontaneous perforation. Excision of the cyst with hepaticojejunostomy is the best approach.

Keywords: choledochal cyst, abnormal pancreatico biliary duct junction, common bile duct

1. Introduction

Choledochal cyst (CDC) is the congenital dilatation of the bile ducts. The condition is a relatively rare abnormality with an estimated incidence of 1 in 13,000–15,000 in Western populations. However, this condition is far more common in the East, with an incidence of 1 per 1000 in Japan [1, 2]. The etiology remains unknown, but choledochal cysts are likely to be congenital in nature.

Other proposed theories include distal obstruction, Abnormal Pancreatico-biliary Duct Junction (APBDJ), sphnictor oddi dysfunction. The pathologic features of the CDC frequently include an anomalous junction of the pancreatic and common bile ducts pancreaticobiliary malunion (PBMU), intrahepatic bile duct dilatation, and various degrees of hepatic fibrosis. Anatomically choledochal cysts are usually classified into three groups. However, based on the cholangiographic findings of intrahepatic ducts or pancreaticobiliary malunion (PBMU), the so-called long common channel, other forms and subgroups have been described. Left untreated, choledochal cysts can undergo malignant transformation and promote progressive hepatic fibrosis. About 20% case present during adulthood [3]. The gallbladder or bile duct malignancy has been reported as 6–20% and 15–20% in the United States and Japan, respectively [4, 5]. Therefore, treatment includes complete excision of the cysts with Roux-en-Y hepatojejunostomy and close surveillance.

2. Aetiopathogenesis

The etiology of choledochal cystic disease remains ill-defined; however, these malformations are considered congenital because they occur in fetuses and in newborns. The most commonly accepted theory for choledochal cysts is based on the observation that they are frequently associated with an anomalous pancreatobiliary duct junction (APBDJ). The "long common channel theory" explained that APBDJ allows reflux of pancreatic enzymes into the common bile duct. The reflux of pancreatic juice results in dissolution of the ductal wall and obstruction at distal end of cyst due to edema/fibrosis [6].

Another theory proposed that this disease results from derangement in normal embryologic remodeling of ducts and causes varying degrees of destructive inflammation and segmental dilatation [7, 8]. Kusunoki et al. demonstrated suboptimal number of ganglion cells in the narrow portion if the common bile duct in patients with a choledochal cyst, as compared with controls [9, 10]. Based on an experimental study in which cystic dilatation of the common bile duct was produced by ligation of the distal end of the common bile duct in the neonatal lamb, an obstructive factor in the early developmental stage was described as a causative factor.

APBJ is defined as a junction between the pancreatic and bile ducts and is located outside of the duodenal wall [11]. Babbitt analyzed that most choledochal cysts were complicated by APBJ [12]. APBJ is classified into two types (P-C and C-P type) by analyzing the fusion pattern between the pancreatic and bile ducts. In the P-C type, the main pancreatic duct joins the common bile duct, while the common bile duct appears to join the main pancreatic duct in the C-P type [13].

In 1991, Komi et al. classified APBJ into three groups type I, II, and III according to the running of the accessory pancreatic duct and dilatation of the common channel Types I and II correspond to the C-P type, P-C type and type III was named as complex type of APBJ [14]. The incidence of type I, II, and III APBJ was 35.3, 21.6, 43.1%, respectively (**Figures 1** and **2**).

In 2003, Tashiro et al. analyzed 1627 patients of CDC and found patients with APBJ overlapped with that in normal cases. Furthermore, reflux of the pancreatic juice was reported in patients without APBDJ. Considering the conditions similar to APBJ, APBJ should be defined as when the long common channel with out any relation to sphincter of Oddi contraction [15].

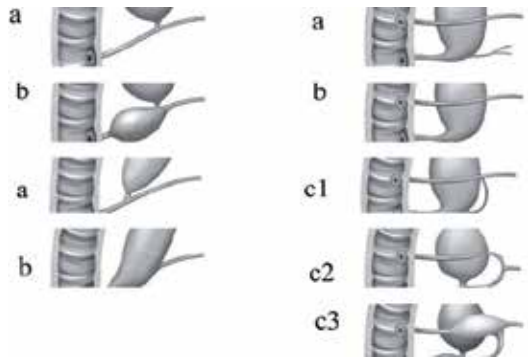

Figure 1. Classification of anomalous union between pancreatic and bile ducts.

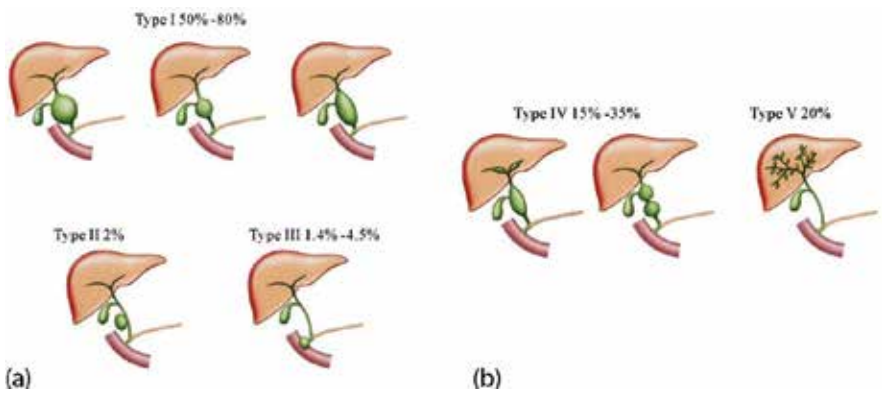

Figure 2. a & b; Different types of CDC.

3. Classification of choledochal cyst

Based on the site of cystic changes five types of CDC have been described by Todani and colleagues Type **I–V** (**Figure 2**). **Type I** constitutes about 50–80% of all CDC, **Type II** (2%), **Type III** (1.4–4%), Type IV (15–35% of all CC) and **Type V** or Caroli's disease(20%) [16].

Type I cysts typically appear as anechoic cystic lesions, which communicate with the biliary tract. Type 1 is further divided into; (1A, 1B, or 1C). In type IA, the gallbladder arises from the choledochal cyst and a dilated extrahepatic biliary tree is seen while the intrahepatic ducts are normal in size and appearance. Type IB an isolated dilatation of the most distal aspect of the CBD. In Type 1C a smooth fusiform dilatation of the common hepatic duct (CHD) and CBD is associated with pancreaticobiliary malunion.

Type II cysts are diverticula of CBD which appear as anechoic cyst juxtaposed to CBD with CHD. Type II cysts appear as anechoic cysts juxtaposed to the CBD with a normal appearing gallbladder and CHD. Cholangiography demonstrates opacification of a true diverticulum arising from the CBD7 and can resemble gallbladder duplication.

Type III cysts, **or choledochoceles,** comprise 1–4% of CC and are characterized by their intraduodenal location at the pancreaticobiliary junction. Type III cysts are also more likely to be diagnosed using ERCP and are associated with a much lower incidence of malignant transformation (2.5%). Additionally, APBD is less commonly seen in choledochoceles in comparison with other types of CDC.

Type IV CDC can include both intrahepatic and extra-hepatic duct involvement. Type IVA CDC dilatation extends from the CBD and CHD into the intrahepatic biliary tree. Type IVB CC consists of multiple dilations of the extrahepatic biliary tree. **Finally, type V CC, or Caroli's disease** is the intrahepatic saccular or fusiform dilatation with no underlying obstruction or extrahepatic biliary tree involvement. Type V CDCs are at times associated with polycystic kidney disease, an autosomal recessive inherited condition associated with mutation in PKD1 gene [17]. Investigators note the different clinical courses, management, and complication rates of the 5 types of CC, thus have challenged the modified Todani classification.

Forme Fruste Choledochal Cyst (FFCC); FFCC is characterized by non-specific changes of bile duct mucosa such as mucosal ulceration/sloughing, fibrosis, and inflammatory cell infiltration. Patients with FFCC may be at a high risk for carcinogenesis in the extrahepatic bile duct. These changes are similar to that seen in cystic or fusiform type choledochal cysts [18].

Pathologic changes in the liver including portal fibrosis, central venous dilataion, parenchymal inflammation, and bile duct proliferation. Furthermore, fibrosis of cyst wall lined by columnar epithelium, lymphocytic infiltration and mucosal dysplasia is also seen. Histologic appearances in Type I (and sometimes type IV) CDC is lack biliary mucosa; type II CDC closely resemble gallbladder duplication. Type III cysts are lined by duodenal mucosa, while type V cysts can have extensive hepatic fibrosis [19]. In the walls of CC there is increasing rate of epithelial metaplasia and biliary intraepithelial neoplasia with advancing age. Although the incidence of malignancy at diagnosis of CDC increases with age at diagnosis, the risk of developing a future malignancy in an existing benign CDC during one's remaining lifetime likely decreases with advancing age. Carcinogenesis is thought to occur via multistep genetic events where early K-ras and p53 mutations are seen in more than 60% of CC-related carcinomas, followed by a late occurring DPC-4 gene inactivation [20].

Gallbladder carcinoma is identified in 10–25% of CDC-related malignancies 5.10 Malignancy is most commonly associated with types I and IV cysts, while types II, III, and V CC have minimal neoplastic risk. Most reported cases of malignant transformation are cholangiocarcinoma. The presence of an APBDU is thought to play a role in carcinogenesis and hepatocellular damage due to reflux of pancreatic contents into the bile duct [21].

4. Clinical features

4.1. Prenatal diagnosis

Choledochal cysts are being diagnosed with increasing frequency on prenatal sonography. Ultrasound typically reveals a cyst at the porta hepatis. The differential diagnosis of a cyst in the porta hepatis includes duodenal atresia, mesenteric or omental cysts, hepatic cysts, intestinal

duplication, gallbladder duplication, and ovarian cysts [27]. Because choledochal cysts are rare anomalies, prenatal diagnosis can be challenging. Sensitivity and specificity of prenatal ultrasound for choledochal cysts increases if sonologist performing the prenatal ultrasound is experienced MRI does not add significantly to the information found on ultrasound, but both imaging techniques may be complementary to each other.

Choledochal cysts historically presented in two broad categories:

(1) The infantile form, indicated by obstructive jaundice.

(2) The adult form, generally presenting with obstructive jaundice, pancreatitis, or ascending cholangitis.

4.1.1. Infantile form

The infantile form present as obstructive jaundice. Jaundice in choledochal cyst is often intermittent because the obstruction is rarely complete unlike in biliary atresia. Character of jaundice is an important ominous symptom in differentiating obstructive jaundice due to biliary duct cystic dilatation from obstructive jaundice due to biliary atresia. Many of these neonates may have choledochal cysts in conjunction with complete or nearly complete biliary obstruction. Some authors report these patients as having biliary atresia in association with choledochal cyst, whereas others may term these patients as having surgically correctable biliary atresia. Distinguishing between cystic biliary atresia (CBA) and CDC is important because delayed therapy in CBA results in irreversible long-term sequelae. Unlike BA, CDC and CBA can typically be identified with prenatal ultrasound; however, these lesions are often all thought to be CC until surgical intervention [25]. On ultrasound, CBA on USG appears smaller with less dilatation of intrahepatic ducts [28].

Those with an infantile form need surgical excision and reconstruction within the first several weeks of life to avoid potential complications of cholangitis and hepatopathy. It is recommended to perform operation for asymptomatic choledochal cysts diagnosed prenatally within the first year of life. Congenital anomalies Associated with CC include double common bile duct, sclerosing cholangitis, congenital hepatic fibrosis, pancreatic cyst, and annular pancreas. Thirty one percent of pediatric patients with CDC have congenital cardiac anomaly and are most commonly manifested in infancy [29, 30].

However, CBA patients are symptomatic at earlier ages (less than 3 months old), and one-third of CBA patients develop liver failure or require liver transplantation. Triangular cord sign (a thickness of the echogenic anterior wall of the right portal vein just proximal to the right portal vein bifurcation) and the presence of biliary sludge are characteristic features suggestive of CBA rather than CDC.

4.1.2. Adult form

Common presentations in children in adults include abdominal pain, jaundice, and right upper quadrant mass and are most commonly seen in pediatric patients. The classic triad of abdominal pain, right upper quadrant mass, and obstructive jaundice, although still rare is seen in the pediatric population.

Adults are more likely to present with biliary or pancreatic symptoms and abdominal pain. Abdominal mass and Jaundice are feature sin childhood [26]. Adults with CC may present with symptomatic gallstones or acute cholecystitis, both of which are attributed to biliary stasis. Pain similar to recurrent pancreatitis has been described by some patients [22]. However, these patients may truly be having pancreatitis as a result of mucous plugging in the APBDJ.

Complications in Choledochal cysts in adults include development of cholelithiasis, liver cirrhosis, portal hypertension, hepatic abscess, and biliary carcinoma [23]. Thus, the incidence of postoperative complications is quite high even after primary cyst excision.

5. Imaging

5.1. Ultrasonography

Ultrasonography is a preliminary imaging modality for detecting choledochal cysts, which shows a cystic mass in the right upper quadrant apart from the gallbladder. The sensitivity of Ultrasonography for diagnosing choledochal cysts is 71–97%. In recent years, the number of patients who are diagnosed by antenatal ultrasonography is increasing. This method also clearly demonstrates IHBD dilatation and the state of the liver parenchyma. Caroli's disease, polycystic liver disease and primary sclerosing cholangitis have similar in radiographic appearance. Cysts in polycystic liver disease do not communicate with the biliary tree, while primary sclerosing cholangitis is associated with a distal biliary obstruction and inflammatory bowel disease. A CBD measuring greater than 10 mm in an adults is an indication for further imaging in order to differentiate type I cysts from type IVA disease. Other features suggestive of CDC are a right upper quadrant cyst separate from the gallbladder and presence of a direct communication between the biliary tree and the cystic duct [24].

5.2. HIDA scan

If a choledochal cyst is suspected on ultrasound. The Technectium-99 HIDA scan has varying sensitivities, with 100% for type I cysts and 67% for type IV. It is particularly useful for showing continuity with bile ducts and diagnosis of cyst rupture in patients with choledochal cysts. Hepatobiliary scintigraphy complements other diagnostic tools in the diagnosis of choledochal cysts in pediatric patients [31]. A HIDA scan is be helpful for distinguishing between choledochal cyst and biliary atresia. Choledochal cyst will have contrast entering the duodenum, whereas in patients with biliary atresia will lack of contrast emptying into the duodenum.

5.3. CT scanning

CT scanning is a useful imaging tool for detecting choledochal cysts, but it is difficult to delineate pancreatic and bile duct union. Multidetector computed tomography (MDCT) provides detailed information on the pancreatic and bile ducts. In patients with suspected APBJ. Intrahepatic ducts, distal common bile ducts, and the pancreatic duct, are reliably identified on CT scan, thus useful in identifying type IV and type V cysts. CT cholangiography is

now a historical imaging modality in CDC. The sensitivity of CT cholangiography is 90% for diagnosing choledochal cysts, and only 64% for characterizing the pancreatic duct [31]. The obvious drawbacks of CT or CT cholangiography are nephrotoxicity or hepatotoxicity and radiation exposure. Because of better investigations the use of CT is now very limited.

5.4. Magnetic resonance cholangiopancreatography (MRCP)

MRCP being a noninvasive investigation provides excellent delineation of pancreatico biliary ducts. It can replace ERCP as a diagnostic method for evaluation of biliary- pancreatic tract. MRCP reliably identifies APBDJ. Sensitivity and specificity of MRCP in diagnosing CDC is (70–100%) and (90–100%), respectively [32]. Although MRCP is limited in its ability to detect minor ductal abnormalities or small choledochoceles. 88 Magnetic resonance Cholangiopancreatography cannot be used for therapeutic purposes; therefore its utility remains limited as a diagnostic tool. Another advantage of MRCP over ERCP is that the pancreatic duct can be visualized upstream to an obstruction [33].

5.5. ERCP, PTC, intraoperative cholangiography

Invasive imaging studies also play a role in diagnosis and evaluation of the biliary anatomy. These modalities include cholangiography through endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and intraoperative cholangiogram. Endoscopic retrograde cholangiopancreatography (ERCP) is the gold standard for diagnosis of APBJ. ERCP is a type of invasive direct cholangiography, which may be associated with significant morbidity and mortality. ERCP can be challenging with respect to cannulization of the ampulla, due to recurrent inflammation and scarring. Cholangiography will delineate the anatomy and PBM and filling defects caused by stones, stenosis, or carcinomas. ERCP can be challenging with respect to cannulization of the ampulla. Cholangitis and pancreatitis after invasive cholangiography is higher than in the general population. A high volume of dye load is often required for adequate visualization, especially in the setting of large cysts [34].

6. Management

The surgical treatment of choledochal cystic disease has evolved and been refined over the past century. Aspiration and marsupialisation were the earliest forms of surgical therapy, the development of external biliary fistulae. Complete cyst excision and internal drainage by hepaticoduodenostomy (McWhorter in 1924) however, unacceptable mortality rates were encountered. Gross advocated internal drainage by choledochocystduodenostomy in 1933 because of unacceptably high risk of cyst excision at that time. Subsequent patient evaluation, however, revealed morbidity rates approaching 50%, primarily a result of cholangitis from duodenal reflux. The transection level of the common hepatic duct and currently, complete excision of a cyst with cholecystectomy and Roux-en-Y hepaticojejunostomy reconstruction (RYHJ) is the standard therapy in Types I and IV-A cysts [39]. Although the overall morbidity was diminished, the risk of malignant degeneration within the cystic remnant was recognized. Persistent, although markedly diminished episodes of cholangitis in RYHJ reconstructions

led to the development of a valved jejunal interposition. No studies have independently confirmed the efficacy of valved intestinal conduits in the prevention of reflux-induced cholangitis. Pericystic inflammation may prevent safe complete-cyst excision. An internal approach, as described by Lilly, requires mucosectomy of the inner epithelial lining prior to reconstruction, but avoids the danger of a difficult posterior dissection.

7. Cyst excision

A laparotomy through a high transverse or oblique right upper quadrant incision gives excellent exposure. The appearance of the liver, spleen, and pancreas is noted. If the anatomy has not been clearly defined preoperatively, an intraoperative cholangiogram should be performed. Aspirated the bile from the cyst and send it for culture and measurement of amylase/lipase. With large cysts, dye should be injection directly into the lower end of the common bile duct and into the common hepatic duct using a butterfly needle. Direct injection into a large cyst may obscure filling of the distal duct, it is important to try to identify the junction of the pancreatic and bile ducts [35]. If the cyst is extremely inflamed and adhesions are very dense, mucosectomy of the cyst should be performed rather than full-thickness dissection to minimize the risk of injuring the surrounding structures such as portal vein and hepatic artery (**Figure 3**). Where the bile duct begins to narrow down inferiorly, it is dissected circumferentially and encircled. The distal common bile duct is dissected to just within the head of the pancreas and transected. Common channel should be cleared with combination of saline irrigation, balloon catheters and, when possible. Intraoperative endoscopy helps removing plugs. Distal bile duct stump is transfixed with an absorbable suture [36] (**Figure 4**).

After dissection of GB and cyst, the portal vein is exposed. At times the right hepatic artery crosses in front of the cyst and is adherent to its wall and in this situation right hepatic artery must be carefully freed and preserved. The common hepatic duct is divided at the level of the bifurcation, where it should appear healthy and well vascularised (**Figure 5**).

To allow a wider bilio-enteric anastomosis, left duct is incised 5–10 mm. Anastomosis to a narrow common hepatic duct should be avoided because of the long-term risk of stricture. The duodenojejunal flexure is identified and the Roux loop jejunum anastomosed at duct bifurcation using fine, interrupted, absorbable monofilament sutures (6/0 or 7/0 PDS) (**Figure 6**).

Dilatation of the peripheral portion of the IHBD is associated with late complications which include recurrent cholangitis, stone formation, and anastomotic stricture. Intrahepatic cystenterostomy, or balloon dilatation of the stenosis at the time of cyst excision are options for dilatation of IHD.

Type II cysts: Excision of the diverticulum and repair of the common bile duct is performed in type **II** a satisfactory procedure for this rare variety of choledochal cyst.

Type III cysts: Large choledochoceles can be removed transduodenally. Sphincteroplasty or endoscopic sphincterotomy are the two options for smaller choledochoceles with no pancreatobiliary malunion.

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Type V cysts: If multiple cysts are confined to one side of the liver, hepatic lobectomy may be curative. Recurrent cholangitis and stone formation are common if multiple cysts are distributed throughout the liver. Antibiotics and drainage procedures are helpful in such cases, but liver transplantation should be considered in progressive cases.

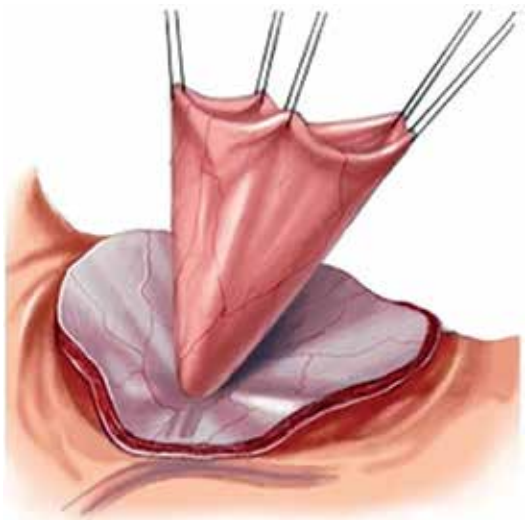

Figure 3. Mucosectomy of distal portion of choledochal cyst.

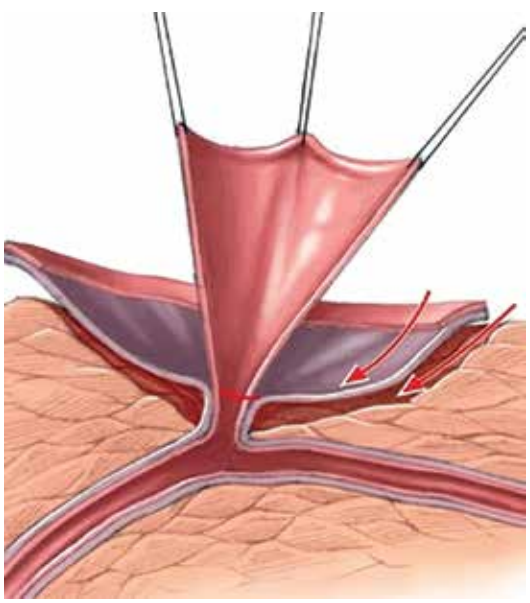

Figure 4. Intrapancreatic dissection of terminal bile duct.

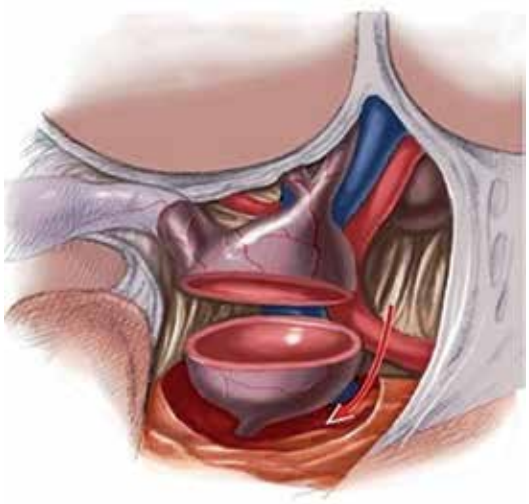

Figure 5. The common hepatic duct is transected at the level of distinct caliber change.

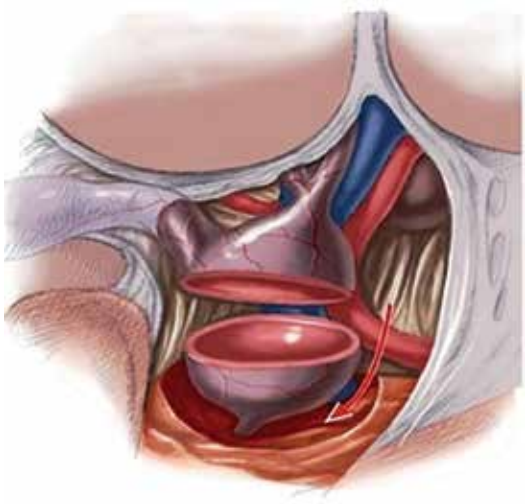

Figure 6. Roux-en-Y (RY) hepaticojejunostomy at the time of cyst excision.

The prognosis of choledochal cyst is excellent if the diagnosis is made expediently prior to the development of irreversible liver disease or malignancy. The common late complications are cholangitis, obstructive jaundice, pancreatitis, stone formation, and portal hypertension [37]. Long-term outcomes after excision and hepaticojejunostomy reconstruction for choledochal cysts have been reported in different series. Most of these show that with standard treatment of excision and drainage, these patients will have no significant sequelae from this treatment.

The congenital hepatic fibrosis coexistent in patients with type V CCD, it predisposes patient to portal hypertension. The incidence of cholelithiasis due to bile stasis is around 37.5–74%.

Hepatolithiasis is most often associated with type IV-A CCD and is related to the presence of membranous or septal stenosis [38]. Total cyst excision reduces the risk of malignancy. However, sporadic malignancy has been reported after the excision of cysts. Cholangiocarcinoma developing after total resection of choledochal cysts after 10 to 34 years has been previously reported [39].

Biliary tract malignant tumor were associated in 80 patients (9.9%); 40 had bile duct cancer (50.0%), 35 had gallbladder cancer (43.8%), 3 had periampullary cancer, synchronous gallbladder and bile duct cancer was found in 2 patients. With a median follow-up duration of 51.8 months, 26.3% had a recurrence [40].

Incidence of hepato-biliary cancer in TYPE I, TYPE III, Type Iva, unknown was reported to be 71,1.3, 22.5 and 5%. Significantly more patients classified with type IVa had bile duct cancer and significantly more patients classified with type I had gallbladder cancer (P = .03) [41].

In a review of 200 children who had cyst excision. Primary cyst excision was performed in 176, 19 had cyst excision converted from other biliary surgery. The mean follow-up period was 10.9 years. In 188 patients Roux-en-Y hepaticojejunostomy was performed, 11 had standard hepaticoduodenostomy, and one had a jejunal interposition hepaticojejunostomy. There was no operative mortality. Eighteen (9.0%) patients had complications including cholangitis choledochus calculi, pancreatitis, and small bowel obstruction. Fifteen of the 18 children required surgical interventions such as revision of the hepaticoenterostomy. There was no occurrence of malignancy [42].

8. Conclusion

CDC is a congenital anomaly of hepatobiliary ducts. Various theories have been proposed including congenital origin, APBDJ, and defects in canalization during embryogenesis. CDC has been divided into five types depending on location of cyst. Choledochal cysts can have variable presentations ranging from infantile Cholestasis to pain abdomen jaundice and abdominal lump in adults. MRCP is the main investigation for diagnosis early diagnosis and treatment avoids possible late complications of cholangitis, cirrhosis, hepaticolithiasis and spontaneous perforation. Excision of the cyst with Roux-N Y hepaticojejunostomy is the best approach.

Author details

Raashid Hamid[1]*, Nisar A. Bhat[2], Mansoor Ahmad[3] and Balvinder Singh[4]

*Address all correspondence to: drraashidhamid@gmail.com

1 Department of Paediatric Surgery Govt Medical College Srinagar, Srinagar, Jammu and Kashmir, India

2 Department of Paediatric and Neonatal Surgery Skims, Srinagar, Jammu and Kashmir, India

3 Department of Surgery Govt Medical College Srinagar, Srinagar, Jammu and Kashmir, India

4 Government Medical College, Srinagar, Jammu and Kashmir, India

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Chapter 4

Diverticular Disease

Can Konca, Suleyman Utku Celik and Cihangir Akyol

Additional information is available at the end of the chapter

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Abstract

Diverticulosis is a common problem, especially in industrialized countries. The main risk factors for the development of diverticular disease are physical inactivity and consumption of a low-fiber diet. Among the population with diverticulosis, only 10–25% of the patients develop diverticulitis. Computed tomography (CT) scans are very helpful for diagnosis and deciding the treatment strategy. Patients with acute diverticulitis usually have a good response to conservative therapy. However, some of the patients present with complications such as perforation, fistula, abscess, stricture, and obstruction. Depending on disease severity, they commonly require surgical or radiologic intervention. Despite lots of contradictory results on treatment approaches, recent guidelines tend to be less invasive than the ones in the past. As a result, less invasive treatment protocols, including nonsurgical follow-up, percutaneous drainage, minimally invasive surgery and resection with primary anastomosis, are more commonly used than the more invasive Hartmann procedure. In this chapter, we discuss the clinical characteristics, diagnostic workup and different treatment approaches in the management of diverticular diseases.

Keywords: diverticular diseases, diverticulitis, diverticulosis, epidemiology, management

1. Introduction

Diverticulosis is a common medical problem, most frequently in industrialized countries. It is defined as saccular outpouchings of the bowel wall and is usually located at the sigmoid colon. Diverticulosis is not a disease per se but a condition, and thus, it is usually asymptomatic. When these saccular outpouchings become obliterated, inflammation in bowel wall and hence diverticulitis develops. There are many types of diverticular disease with respect

to its clinical presentation. Usually, it presents as a mild and medically treatable uncomplicated diverticulitis. However, complicated diverticulitis such as abscess, perforation, fistula or obstruction can be the first presentation as well. Diverticular hemorrhage is another complication of diverticulosis, but inflammation is not a factor in its pathophysiology and it is a different clinical condition apart from diverticulitis. As a result, diverticular hemorrhage will not be discussed in this chapter.

As its prevalence rises with industrialization, numerous efforts have been made to find the best treatment option. Although some debates are still ongoing, minimally invasive treatments become more common, and necessity of high morbidity-related procedures like the Hartmann procedure is more questionable nowadays.

2. Incidence

In Western countries, the prevalence depends on age. The incidence increases with age, and nearly 70% of the 80-year-old population has diverticulosis [1]. Among the population with diverticulosis, only 10–25% of the patients develop diverticulitis, 10–20% of those patients with diverticulitis will be hospitalized for treatment and surgical therapy will be reserved only for 20–50% of these patients [2].

The left-sided diverticular disease is more common in western countries; on the other hand, the right-sided diverticular disease is more common in eastern countries. In the United States, the localization of diverticular disease involves sigmoid and left colon in 95% of the patients, and 95% of the surgical candidates for diverticular disease have sigmoid colon diverticulosis [3].

Recent studies have estimated that symptomatic diverticulitis under the age of 65 tends to have a male predominance and have more severe CT findings. Additionally, diverticular bleeding is more common in men, whereas obstructions are more common in women [4, 5].

3. Pathophysiology and etiology

The saccular outpouching in diverticulosis is not a true diverticula. They do not contain all layers of the bowel wall; instead, they are formed by the herniation of mucosal and submucosal layers of the bowel wall through the muscular layer. Thus, they are called ‘false’ or ‘pulsion’ diverticula. Diverticular disease tends to occur at the weakest points of the colon wall where the vasa recta penetrate the circular muscle. As a result, diverticula are localized at each side of the mesenteric taenia and on the mesenteric border of the two antimesenteric taenias [6]. Also, the structure of the colon wall contains differences from normal colon wall such as thickened circular muscle, narrow lumen and shortened taenia [7]. Besides the structural changes in the colonic wall, alterations in colonic motility have a role in the development of diverticular disease. Increased colonic motility causes enhanced longitudinal haustral contractions

and temporary isolation of a segment of colon, a process called segmentation. As a result, segmentation generates a pulsion force causing visible distension of the local diverticula [7].

Moreover, the imbalance of the neurotransmitter spectrum reported in diverticular disease involves both excitatory agents, such as acetylcholine and substance P, and inhibitory agents, such as nitric oxide and vasoactive intestinal polypeptide (VIP) released by enteric nerve cells [8, 9].

On microscopic examination, the structure of the taenia contains more elastin, which is increased over 200% compared to controls, and colonic collagen changes are similar to the ones that occur with aging [7–9]. These structural changes are similar to connective tissue disorders such as Marfan syndrome or Ehler-Danlos syndrome in which diverticulosis tends to occur earlier than the normal population [10].

The localization of the colonic segment of diverticular disease and complications, such as diverticulitis, microperforation and abscess, depends on the intraluminal pressure of the colonic segment. As a result, sigmoid colon is the most common localization for the disease since it has the highest intraluminal pressure and increased motility index with regard to its smaller diameter [3].

4. Risk factors

The main risk factors for the development of diverticular disease are physical inactivity and consumption of a low-fiber diet [11–13]. Fiber from fruits and vegetables has the most protective effect against diverticulosis development while higher consumption of red meat and fat increases the incidence [11, 14]. Thus, the incidence of diverticulosis increases with a Western-style diet [11, 15]. On the other side, diverticulosis is less common among vegetarians [16]. As the fiber intake increases, the stool becomes more bulky and lesser segmentation forms in the colon and diameter of the sigmoid colon increases. By that way, transportation of the stool becomes easier with lower intracolonic pressures obtained [3].

Other identified risk factors for the development of complicated diverticular disease are smoking (three times higher risk of developing complications), NSAID use, steroid use, renal failure, and organ transplantation [17, 18].

Several studies have been evaluated the role of age in diverticular disease and diverticulitis. The incidence of diverticular disease increases with age. At the age of 40, its incidence is 5%, whereas at the age of 80 the incidence rises up to 80% [19]. As the age gets older, diverticula are more proximally located and increased in number. On the other hand, diverticulitis at younger ages is more likely to develop complications [20, 21].

Recent studies demonstrated that obesity and higher body mass index are also associated with an increased incidence of diverticulitis, especially patients under the age of 40 years [21–24]. Additionally, an association between increased cross-sectional visceral fat area and complicated diverticulitis had been demonstrated [25].

5. Signs and symptoms

The degree of inflammation and existing complications are the two main factors determining the clinical presentation of diverticular disease.

In acute diverticulitis, the most common complaint is abdominal pain. Since sigmoid colon is the most common localization of diverticulitis in adults, the pain is usually located in the left lower quadrant. Variable localizations can occur depending on the anatomy of the sigmoid colon such as right lower quadrant or suprapubic pain. Especially in Asian populations, cecal diverticulitis may present as right lower quadrant pain [26–28].

About 50% of the patients with acute diverticulitis have constipation, while 25–35% are accompanied by diarrhea [29].

The degree and radiation of pain vary according to the severity and extent of inflammation. Early in the presentation, a localized left lower quadrant sensitivity can be observed while acute abdomen due to peritoneal irritation develops after perforation. Dysuria and urinary urgency may occur as well due to the presence of inflammation which is in close proximity to the bladder [30]. The persistent abdominal pain can be based on increased pain-mediating neurotransmitters (e.g. galanin, neuropeptide K) and enteric nerve fiber remodeling most likely due to postinflammatory reactions—similar to irritable bowel syndrome [7].

Nausea and vomiting can be present due to peritoneal irritation or the development of complications such as bowel obstruction [30].

6. Laboratory findings

In patients with acute diverticulitis, inflammation-related leukocytosis and elevated C-reactive protein (CRP) may be detected. Nevertheless, in uncomplicated patients, leukocyte levels may remain within the normal range of up to 45% of patients [31]. Serum amylase levels may be increased in patients with perforation and colonic flora may contaminate urine cultures if colovesical fistula develops.

7. Imaging

Abdominal X-rays may detect subdiaphragmatic free air due to a perforation in patients with acute diverticulitis. However, direct X-rays have no diagnostic value in patients with uncomplicated diverticulitis.

Abdominal ultrasonography is a preferred method of imaging since it is cheap and noninvasive. However, it is an operator-dependent method and has an inferior sufficiency in the evaluation of luminal organs and ruling out other causes of abdominal pain. Hypoechoic peridiverticular inflammatory reaction, detection of a peridiverticular or mural abscess,

thickening of the intestinal wall more than 4 mm in the area of abdominal sensitivity and presence of diverticula in other segments of bowel are among the ultrasonographic findings that support a diagnosis of acute diverticulitis [32].

CT is the most useful imaging technique for diagnosing acute diverticulitis with a sensitivity of 94% and a specificity of 99% [33]. Additionally, it allows assessment of the complications and other causes of abdominal pain. CT findings that support the diagnosis of acute diverticulitis are the presence of diverticula in the bowel, pericolic fat stranding, colonic wall thickening that is more than 4 mm and abscess formation (**Figure 1**) [34].

It is a fast and reliable test and also serves as a guide for percutaneous drainage. It can also be used to determine the severity and extent of the disease. Ambrosetti et al. was first to classify the disease severity according to the CT findings [31]. They divided acute diverticulitis into two groups as mild and severe according to the CT findings (**Table 1**). Surgical intervention was more frequently needed in patients who had severe disease. Similarly, in people who had

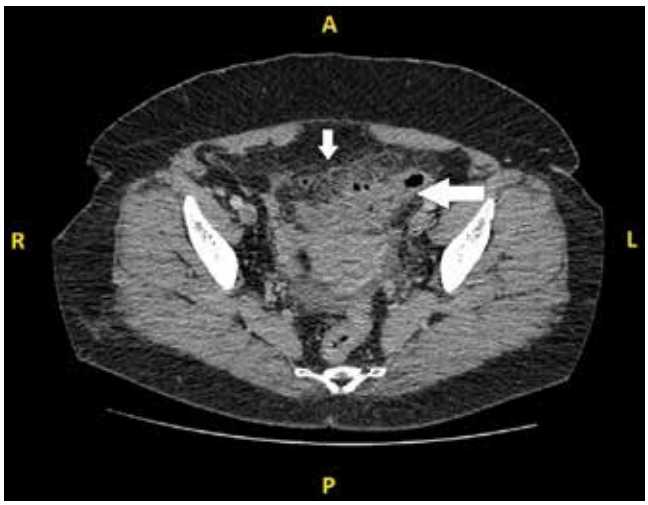

Figure 1. Computed tomography scan demonstrates infiltration of the fat surrounding the sigmoid colon (small arrow) whose wall is thickened and irregular (big arrow).

Mild diverticulitis	**Wall thickening (>5 mm)** **Pericolic fat stranding**
Severe diverticulitis	Mild diverticulitis findings and at least one of the followings: • Abscess • Extraluminal air • Extraluminal contrast

Table 1. Ambrosetti CT criteria for diverticulitis severity.

severe disease under the age of 50 years, recurrences and complications were more frequent [31]. According to another study, the markers of nonoperative treatment failure were defined as the presence of abscess formation or extraluminal air >5 mm in diameter [35].

A modified Hinchey classification system was defined by the addition of preoperative CT findings to the parameters of Hinchey classification used in the evaluation of acute diverticulitis (**Table 2**) [36–38]. In the modified system, stage I was divided into stage Ia characterized by the presence of pericolic inflammation and phlegmon and stage Ib with pericolic abscess (**Figure 2**). While BT can provide sufficient discrimination in stages 0, I and II, it is insufficient in distinguishing stages III and IV, which are purulent and feculent peritonitis, respectively [36].

Stage	Findings
0	Mild clinical diverticulitis
Ia	Confined pericolic inflammation phlegmon
Ib	Confined pericolic abscess within sigmoid mesocolon
II	Pelvic, distant intraperitoneal abscess
III	Generalized purulent peritonitis
IV	Feculent peritonitis

Table 2. Modified Hinchey classification system for acute diverticulitis.

Figure 2. Coronal view of the inflamed sigmoid colon with characteristic findings of diverticular abscess.

Another method that can be used for diagnosis is MRI. However, it is slower, more expensive and less accessible than CT and thus still not routinely used. It may be useful in situations where CT is insufficient such as colovesical or colovaginal fistulas.

8. Differential diagnosis

The differential diagnosis of acute diverticulitis includes other causes of lower abdominal pain. Colorectal cancer; acute appendicitis; inflammatory bowel disease; infectious colitis; ischemic colitis; bowel obstruction; irritable bowel syndrome; gynecologic causes like tubo-ovarian abscess, ectopic pregnancy and ovarian torsion and urologic causes like urolithiasis, cystitis and pyelonephritis should be excluded before establishing the diagnosis of acute diverticulitis. Many of these entities can be ruled out by history, physical examination, laboratory studies and imaging.

Colorectal cancer (CRC) is probably the most important and challenging condition in the diagnostic evaluation since it can mimic the clinical features and CT findings of acute diverticulitis such as bowel wall thickening. The findings that are suggestive for acute diverticulitis, in that case, are the presence of pericolonic and mesenteric inflammation, colonic segment involvement of more than 10 cm and absence of metastatic mesenteric lymph nodes [39, 40]. In almost 10–20% of the cases, CRC and acute diverticulitis differentiation cannot be clearly established and endoscopic evaluation needs to be scheduled after the resolution of inflammatory process [41].

9. Role of endoscopy

In acute diverticulitis, endoscopic evaluation of the colon is not recommended because of the risk of free perforation [42]. But in order to exclude underlying malignancy, colonoscopic evaluation is recommended after at least 6 weeks from the resolution of clinical findings (**Figure 3**) [42–44]. The incidence of finding CRC after an acute diverticulitis episode is between 2.8 and 3.4% [45, 46].

10. Treatment of acute diverticulitis

In acute diverticulitis, treatment protocol depends on the severity of the disease. Generally, mild diverticulitis can be treated in outpatient settings. On the other hand, complicated diverticulitis usually requires hospitalization and surgical intervention.

10.1. Treatment of uncomplicated diverticulitis

In mild cases without fever and marked peritonitis, outpatient treatment is recommended [47]. Routine antibiotic usage is still contradictory in the guidelines [47–50]. If antibiotic treatment

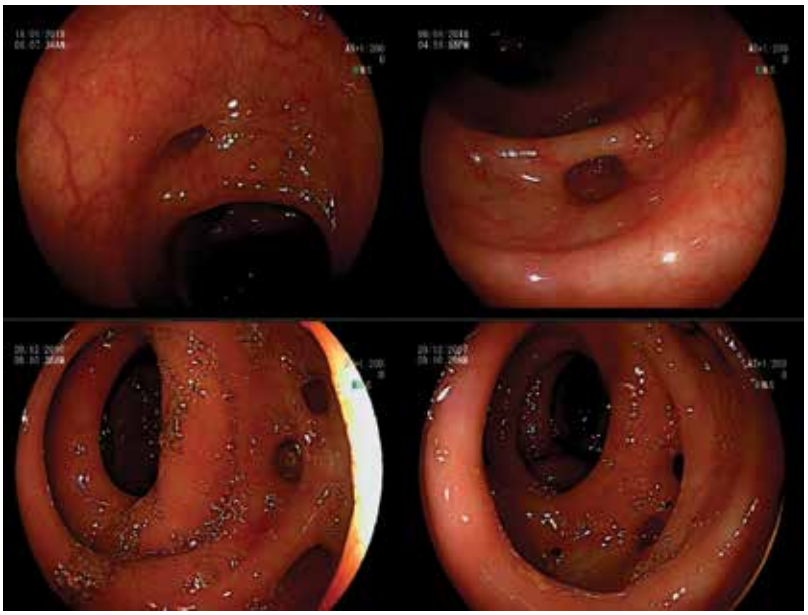

Figure 3. Endoscopic visualization of diverticulosis.

is planned, the coverage of the therapy should include Gram-negative rods, Gram-positive rods and especially the anaerobic flora of the colon [47, 51]. Most common microorganisms are *Escherichia coli* and *Bacteroides fragilis* [52, 53]. There is no clear recommendation for dietary restriction for outpatient treatment. A diet rich in fiber (20–30 g/daily) is recommended for the patients with diverticulosis to lower the risk of developing diverticulitis [11, 54]. Recent studies demonstrated that combination of mesalamine use with antibiotics lowers symptom severity and prevents disease recurrence [55–57]. Probiotic use is another topic under investigation in the management of acute diverticulitis [58–60].

Patients with fever, immunosuppression, sepsis, severe abdominal pain or diffuse peritonitis, those who failed outpatient treatment and intolerant of oral intake, and those with significant comorbidities or older age should be treated as an inpatient. Restriction of oral intake until the resolution of the symptoms and intravenous antibiotics are recommended [61–63].

Traditional teaching for the treatment of recurrent uncomplicated diverticulitis used to be planning an elective operation after the second acute episode [64]. But recent studies showed that in patients followed up with a nonoperative management protocol for uncomplicated diverticulitis, only 5.5% of them required emergency operations [65, 66]. As a result, waiting until third or even fourth episode before deciding for an elective operation has been defined as a more cost-effective management plan with less morbidity [47, 67]. Also, it is found that the probability of surgery after the first hospitalized attack was the same after three attacks [66].

Today, it is thought that after a conservatively managed episode, diverticular disease usually follows a rather benign clinical course and that complications develop mostly at first

presentation [33]. Therefore, elective sigmoid resections should be restricted for use in treating complicated disease, such as symptomatic stenosis, fistulas to an adjacent organ or recurrent diverticular bleeding [33, 64–66].

10.2. Treatment of complicated diverticular disease

Complications of diverticulitis are perforation, fistula, abscess, stricture and obstruction. Depending on disease severity, they usually require surgical or radiologic intervention. While parenteral antibiotics and bowel rest could be adequate for the treatment of mild cases, exploratory laparotomy could be needed for patients with severe clinical findings [65].

10.3. Diverticular abscess

In acute diverticulitis, diverticular abscess occurs between 16 and 56% of the patients and can be localized in pericolic, pelvic, hepatic or retroperitoneal areas [38, 68]. CT is the most effective tool for diagnosis since it can identify the size, localization, and surrounding structures that preclude percutaneous drainage (**Figure 4**). The size of the abscess is essential for the treatment plan, as abscesses less than 4 cm usually resolve with parenteral antibiotics. On the other hand, larger abscesses require percutaneous drainage or surgical drainage if they are not suitable for percutaneous access (**Figure 5**) [38, 63, 69]. Transabdominal route is the preferred method for percutaneous drainage if possible [70]. But percutaneous drainage is

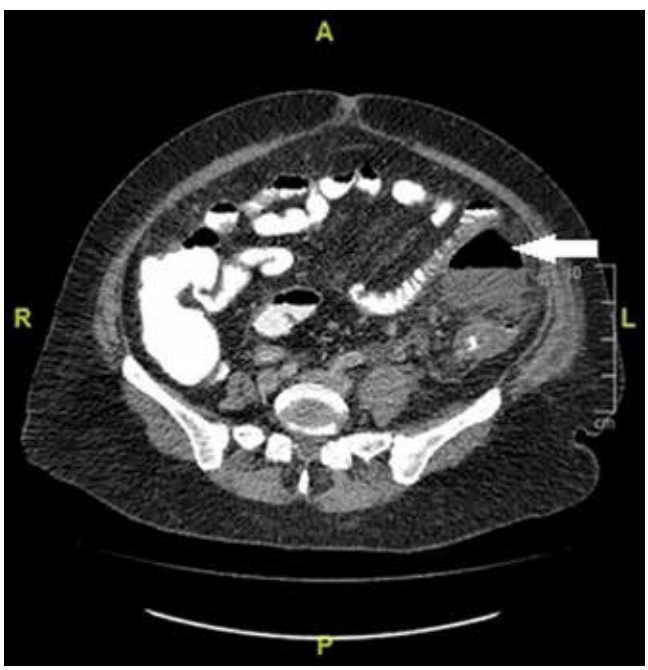

Figure 4. Computed tomography revealed a modified Hinchey stage II diverticulitis.

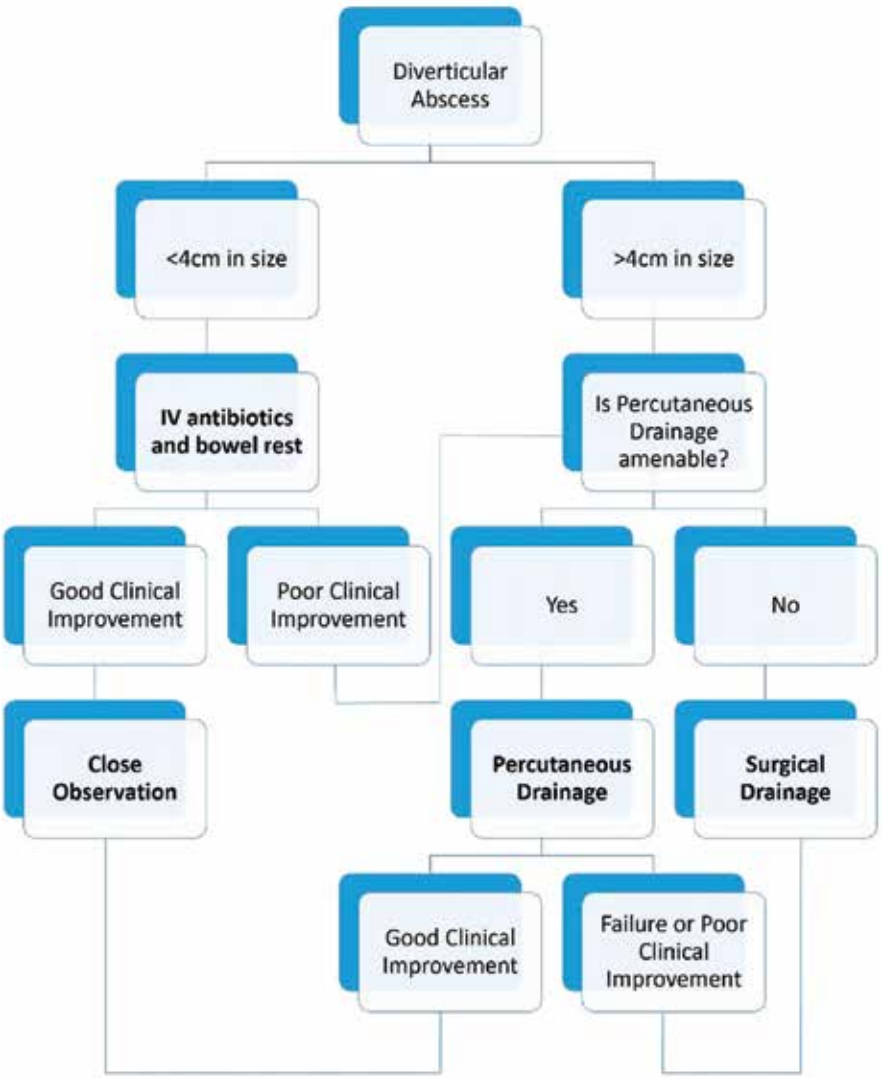

Figure 5. A management for diverticular abscess.

amenable in 20–30% of diverticular abscesses with a 20–30% failure rate [71]. In multilocular and complex abscesses, the failure rate is higher than simple unilocular abscesses [70].

Percutaneous drainage does not negate the need for surgery, but in 60–80% of the patients, surgery can be performed in a single stage and electively [47, 72]. Traditionally, patients with diverticular abscess referred for surgery because of the high risk of recurrent sepsis [37]. With recent studies showing asymptomatic follow-up of the patients treated with successful percutaneous or surgical drainage, the need for elective surgery becomes questionable [38, 73, 74]. As a result, recent guidelines do not recommend routine elective resections after successful nonsurgical treatment of diverticular abscess [47]. On the other hand, symptomatic or immunocompromised patients should be referred for elective surgery [47, 72].

10.4. Perforated diverticulitis

Only 1–2% of the patients with acute diverticulitis presents with free perforation. There are two types of perforation in acute diverticulitis: purulent peritonitis and feculent peritonitis. The differential diagnosis of these conditions is difficult with CT and often requires exploratory laparoscopy or laparotomy. Usually, patients have a fever, acute abdominal findings on examination and significant leukocytosis. Free perforation of acute diverticulitis usually occurs on the first attack and presents with abdominal distention with diffuse tenderness, rigidity and rebound tenderness. The condition can lead to sepsis and septic shock if not treated with a rapid intervention and the mortality rates approach 20% [75, 76].

The goal of the treatment is to eliminate the septic focus. Traditionally, the Hartmann procedure was the choice of treatment, but it has a high morbidity and mortality rate and requires a second major abdominal surgery for reversal colostomy. Studies have shown that nearly one-third of the patients could not undergo the second reversal operation and have permanent colostomy, especially in the elderly population [77]. As a result, resection with primary anastomosis has been studied as an alternative method for the treatment of perforated diverticulitis. Several studies have shown superior results with that procedure compared to the Hartmann procedure depending on the patient's condition [76, 78]. Recent guidelines recommend open or laparoscopic resection with primary anastomosis in hemodynamically stable patients [47]. The factors affecting the choice of treatment are hemodynamic instability, the severity of diffuse peritonitis, ischemia or edema of the bowel at the anastomotic segment, immunocompromised state and malnutrition.

Recent studies investigated laparoscopic lavage for the definitive treatment of Hinchey III diverticulitis and considered it as a safe approach for selected patients [47, 79]. On the other hand, there are conflicting results in the literature against laparoscopic lavage [80–82]. Further trials will be needed for the standardization of this technique.

10.5. Fistulas

Approximately 2% of the patients with acute diverticulitis will develop fistula formation to the adjacent structures [83]. Fistula formation is a result of spontaneous rupture and decompression of an abscess to an adjacent structure like urinary bladder, vagina, colon, small intestine, uterus or abdominal wall and skin. They usually do not require emergency surgery. Colovesical fistula can be seen in 65% of the cases and is the most common type of fistula [84–86]. Because of the anatomic blockage of uterus and vagina in women, colovesical fistulas are more common in men. Patients with colovesical fistulas present with polymicrobial urinary infections, pneumaturia, and fecaluria. Air or contrast in the bladder can be seen on CT scans. Cystoscopy and colonoscopy should be done in those patients to exclude bladder or colon cancer involvement.

In women who have undergone prior hysterectomy, colovaginal fistulas are more common. Fecal vaginal discharge and passage of air per vagina can be seen in these patients.

Surgery is indicated when fistula formation diagnosed. Resection of the colonic segment and suture repair of the affected structure with interpositioning of the omentum between anastomosis and the repair site is the treatment of choice [87, 88].

10.6. Diverticular stricture/obstruction

Recurrent attacks of diverticulitis can lead to sigmoid stricture and less commonly obstruction. Because obstructing colon cancer is far more common than diverticular stricture, the differential diagnosis should be focused to exclude malignancy.

The treatment plan depends on the severity of the obstruction. Patients with partial obstruction can be treated in elective settings; on the other hand, patients with complete obstruction will require emergency surgery. Options for surgery include the Hartmann procedure, resection and primary anastomosis with or without on-table lavage [89, 90].

11. Prognosis

Among patients with diverticulosis, only 4% will develop acute diverticulitis and 15% of these patients will require surgical treatment [91, 92]. Although the incidence is as low as 16% below 45 years of age, it has been proposed that younger individuals have the more severe disease but require lesser surgical intervention [31].

Mortality rates of the patients with peritonitis vary between 0 and 36% depending on the patients' characteristics. On the other hand, elective colectomy has a low rate of mortality rate around 1% [93]. The anastomotic leakage rate is also higher in Hinchey III or IV diverticulitis (8–22%) than elective colectomy (1–3%) [76, 93–95]. On the other hand, Hartmann reversal rates are between 20 and 50% depending on the patients' comorbidities and condition [96–98].

Recurrent diverticulitis or its symptoms develop at a rate of 3–13% after elective resection [99, 100]. The most important determinant is the level of the anastomosis [100]. When anastomosis is established with the distal sigmoid colon, the incidence of recurrence is 12.5% while the incidence is 6.7% for the anastomosis with the proximal rectum [101]. Thus, resection of the sigmoid colon entirely and anastomosis to the proximal rectum is recommended. It is not necessary to resect all the diverticular segments more proximal than sigmoid colon but the proximal resection margin should be soft pliable bowel [63].

Immunocompromised patients usually present with severe and complicated disease. Studies have shown that approximately 40% of them had free perforation and emergency surgery required in 60% of the patients. As a result, they have higher postoperative morbidity and mortality rates as 65 and 40% accordingly [102–104].

12. Conclusion

Diverticular disease is a common condition in developed countries. In order to lower the rising incidence, population-based dietary modifications should be considered. Recent treatment guideline recommendations are focused on less invasive and elective solutions. As a result, a shift to nonsurgical follow-up or elective minimally invasive surgery from high morbidity-related Hartmann procedure should be done whenever possible, depending on the patients' condition, to achieve lesser morbidity and mortality rates.

Conflict of interest

The authors declare that they have no conflict of interest.

Author details

Can Konca[1], Suleyman Utku Celik[2] and Cihangir Akyol[1]*

*Address all correspondence to: cihangirakyol@gmail.com

1 Department of General Surgery, Ankara University School of Medicine, Ankara, Turkey

2 Clinic of General Surgery, Gulhane Training and Research Hospital, Ankara, Turkey

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Chapter 5

Gastrointestinal Stromal Tumors (GIST)

Rahman G. Barry, Thao T. Wolbert and
David A. Denning

Additional information is available at the end of the chapter

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, occurring predominantly in the stomach and small intestine. These tumors account for up to 3% of all gastrointestinal malignancies, with a reported annual incidence of 10–15 cases per million population. GISTs are thought to originate from interstitial cells of Cajal (ICC) or ICC precursor cells, and are characterized by activating mutations in the KIT (CD117) and platelet-derived growth factor receptor alpha (PDGFRα) proto-oncogenes in 85–95% of all cases. The clinical presentation and tumor biology of GISTs are widely variable, with several advances being made over the past two decades in the understanding of GIST tumor biology and pathophysiology. This has led to a paradigm shift in management from the purely surgical approach of the past, to a multi-modality treatment strategy with a greater role for targeted therapies in the form of tyrosine kinase inhibitors, resulting in significantly improved patient outcomes.

Keywords: gastrointestinal stromal tumor (GIST), stromal tumors, gastric tumors, KIT mutation, imatinib

1. Introduction

Gastrointestinal stromal tumors (GIST) represents the most common mesenchymal tumor of the gastrointestinal (GI) tract, accounting for up to 3% of all GI malignancies [1, 2]. The history of GIST dates back several decades, with early classifications including GI schwannomas, leiomyomas, leiomyoblastomas and leiomyosarcomas based on the histological findings and variable differentiation associated with these tumors. With advances in immunohistochemical staining techniques and improvements in microscopic structural imaging, GISTs became recognized as a distinct entity. Although the term GIST was originally coined in 1983 by Mazur

and Clark, it was not until 1998 that Hirota et al. discovered a gain-of-function mutation in the KIT proto-oncogene associated with GISTs [3, 4]. This finding led to a greater understanding of these tumors, and an eventual reclassification of GI sarcomas.

The reported annual incidence of GIST is 10–15 cases per million population, with over 5000 new cases being diagnosed each year within the United States [5–8]. GISTs can occur at any age, however, more than 80% have been reported in individuals over 50, with the median age of presentation at 63 years old [9, 10]. Most studies have reported no significant gender predilection, with a few studies identifying a slight male predominance [7, 8, 11]. While GISTs can occur anywhere along the GI tract, they are most commonly found in the stomach (50%), followed by small intestine (36%), colon (7%), rectum (5%) and esophagus (1%) [12–14]. In rare instances, primary GISTs are identified outside of the GI tract, including the omentum, retroperitoneum and mesentery. These account for <5% of all GISTs and are termed extra-gastrointestinal stromal tumors (E-GIST), and could represent metastasis from an undetected primary tumor [13, 15].

Immunophenotypically, GISTs have a close resemblance to the interstitial cells of Cajal (ICC), the pacemaker cells of the intestine, suggesting that they either originate from ICC or from ICC precursor cells, both of which express type III tyrosine kinase receptors [14]. Activating mutations in the KIT (CD117) and platelet-derived growth factor receptor alpha (PDGFRα) proto-oncogenes are responsible for 85–95% of all GISTs [15]. The vast majority of GISTs occur sporadically, with approximately 5% occurring in the setting of syndromes, most commonly Neurofibromatosis type 1 [16]. Less frequently associated syndromes include Carney triad and Carney-Stratakis syndrome, as well as an association with desmoid tumors. Tumor biology and behavior occur along a spectrum from benign spindle cell nodules to aggressive sarcomas, however, most GISTs, particularly gastric GISTs, are benign.

2. Pathobiology

2.1. Histopathology

From a histologic standpoint, GISTs can be divided into three main subtypes based on their microscopic appearance. The most common subtype is spindle cell (70%), followed by epithelioid (20%), and mixed (10%) subtypes [15]. The spindle cell subtype demonstrates KIT or PDGFRα proto-oncogene mutations in the vast majority of cases, and most commonly affects individuals in their fifth and sixth decades of life [15, 17]. Due to these molecular expressions, the spindle cell subtype responds well to treatment with Imatinib mesylate (Gleevec ®), resulting in a better overall prognosis. The epithelioid subtype is less common, and often seen in a younger, predominantly female population, and more commonly arises from the stomach [15, 18]. In addition, this subtype often lacks KIT and PDGFRα proto-oncogene mutations, and often demonstrated lymphatic metastases, resulting in a poorer prognosis when compared to the spindle cell subtype. It is critical to assess the number of mitoses per 50 high-power fields (HPF) during microscopic analysis as it is an important prognostic indicator, along with tumor size.

2.2. Molecular biology

The identification of the KIT proto-oncogene by Hirota et al. in 1998 led to significant advances in the understanding of GIST molecular pathogenesis and set the stage to allow for breakthroughs in the treatment of this disease. A major revolution in the treatment of GISTs began with the introduction of imatinib mesylate (Gleevec®), a tyrosine kinase inhibitor (TKI) with activity against both KIT and PDGFRα proto-oncogene mutations. Before the advent of TKI therapy, GISTs were generally thought to be resistant to drug therapy, due to the ineffectiveness of traditional chemotherapy regimens.

Over the past decade, with more frequent use of imatinib therapy in GISTs, medication resistance in KIT-mutated GISTs is being more frequently encountered. This resistance is classified as either primary or secondary depending on whether they have been on treatment for less than 6 months or greater than 6 months, respectively. Different types of KIT proto-oncogene mutations have been identified, and determination of the specific mutation has been shown to predict the tumor response to tyrosine kinase inhibitor therapy. Most KIT proto-oncogene mutations involve exon 11 (75%), and portend a better prognosis due to a favorable response to tyrosine kinase inhibitor therapy [8, 19]. The majority of familial cases of GIST also tend to have exon 11 mutations. Another subset of patients harbor mutations involving exon 9, and is characterized by poor responsiveness to tyrosine kinase inhibition therapy, a shorter progression-free interval, and decreased overall survival. This subset is most frequently seen in non-gastric GISTs, and while traditional imatinib therapy shows limited efficacy, high-dose imatinib or sunitinib malate (Sutent®), a multiple tyrosine kinase receptor inhibitor, has had significant treatment success [20]. The exon 18 D842V mutation is the most common PDGFRα proto-oncogene mutation, and demonstrates resistance to tyrosine kinase inhibitor therapy, portending a poor prognosis.

Approximately 75–80% of GISTs harbor mutations in the KIT proto-oncogene, and approximately 10% of GISTs have a gain-of-function mutation in the PDGFRα tyrosine kinase receptor (**Table 1**) [21]. While the vast majority of GISTs demonstrate mutations in KIT or PDGFRα, the remaining 10–15% do not have mutations in these exons, and are known as wild-type (WT) genotypes. These WT genotypes are characteristically very resistant to tyrosine kinase inhibition therapy. Almost 10% of WT GISTs harbor a BRAF V600E mutation on exon 15, and are more commonly seen in small intestine GISTs [22]. Secondary resistance in patients who have been on imatinib therapy for over 6 months commonly occurs due to secondary KIT proto-oncogene mutations involving exon 13 and 14, or from mutations involving other tyrosine kinases [23]. These secondary mutations are more frequently encountered with epithelioid or mixed histology and have a predilection for lymphatic metastasis, portending a poor prognosis [15, 24, 25]. More recent studies on WT GISTs have revealed defects in the Krebs cycle enzyme succinate dehydrogenase (SDH), due to either a mutation or abnormal gene methylation, with WT GISTs now commonly being referred to as SDH-deficient GISTs [26, 27].

Numerous receptors and markers have been found to be associated with GISTs. KIT and PDGFRα mutations occur in up to 95% of cases, followed by expression of CD34 (60–70%), smooth muscle actin (ACAT2-30–40%), S100 (5%), desmin (DES-1–2%) and keratin (1–2%) [28–30]. More recently, gene microarray analyses have identified additional markers for

Genetic Type	Distribution	Imatinib Response	Features
KIT mutations			
-Exon 9	SB/Colon	High-dose imatinib	Biologically aggressive
-Exon 11	All sites	Responsive	Longer event-free and overall survival;
			Common in Familial GISTs; Deletions associated with malignant course
			Duplications favorable
-Exon 13	All sites	Responsive	Spindle cell subtype; More common in SB
-Exon 17	All sites	Responsive	Spindle cell subtype;
PDGFRα mutations			
-Exon 12	All sites	Responsive	Epithelioid subtype; Indolent course; More common in stomach
-Exon 14	Stomach	Responsive	
-Exon 18 D842V	Stomach, E-GIST	Resistant	-Exon 18 (non-D842V) occurs in all sites

Table 1. Molecular classification of GISTs.

GIST. The most notable of these is the DOG1 (Discovered on GIST-1) gene, which has been identified in 97% of all GISTs, and expresses a calcium-gated protein known as anoctinin-1 [31]. When used along with KIT, DOG1 has allowed up to 100% sensitivity in GIST detection and has also been found to be highly specific for GISTs [32].

2.3. Gross pathology

GISTs show significant size variation, ranging from millimeters in size to well over 20 cm [33]. The tumors originate from muscle rather than epithelium, and are often friable. Tumors are typically well-circumscribed with intact overlying mucosa, but may be nodular or ulcerated, and may occasionally have a pseudocapsule. As the tumor increases in size, it may outgrow its blood supply and demonstrate necrosis, cystic degeneration or hemorrhagic foci. It is necessary to clearly delineate tumor size, as it is a critical anatomic prognostic indication, along with the number of mitoses per 50 HPF [16, 27]. A size greater than 5 cm and a mitotic index greater than 5 per 50 HPF correlates with aggressive tumor behavior and a poorer prognosis. A risk assessment scheme based on several large series published by Miettinen et al. demonstrates that for gastric GISTs with a mitotic index 5 per 50 HPF or lower, tumor sizes of 2–5, 5–10 and >10 cm resulted in metastasis or tumor-related death in 1.9, 3.6 and 10% of patients, respectively. Similarly, for gastric GISTs with a mitotic index of more than 5 per 50 HPF, tumor sizes of 2–5, 5–10 and >10 cm resulted in metastasis or tumor-related death in 16, 55 and 86% of patients, respectively [34, 35].

2.4. Micro-GIST

As imaging techniques improve and newer modalities such as endoscopic ultrasound (EUS) are utilized more frequently, small asymptomatic GISTs are being identified in the stomach wall, and are often under 1 cm in size. The term micro-GIST as described by Scherubl et al.

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has been found to be pathobiologically different from GISTs that become clinically significant. They have a very low proliferative rate and have different KIT mutations than those typically seen on larger tumors, with no reported progression of these tumors [36–38].

3. Diagnosis

The majority of GIST cases present with vague, non-specific symptoms, with up to 25% being diagnosed incidentally on imaging studies performed or other abdominal pathologies or trauma [39]. Specific symptoms often depend on the location of the tumor, tumor size, and presence of metastatic disease. The most common symptoms are GI bleeding, vague abdominal discomfort, and an abdominal mass, with other symptoms including abdominal pain, nausea, vomiting anorexia and early satiety. GISTs tend to displace adjacent structures rather than invade them, and because of their submucosal origin, they can reach comparatively larger sizes before becoming symptomatic. GISTs with high mitotic rates tend to quickly outgrow their blood supply, and can develop a necrotic core, increasing the risk of rupture, fistulization, and intraperitoneal hemorrhage. Specific to their location, GISTs can result in dysphagia in esophageal cases, gastric outlet obstruction with gastric cases, obstructive jaundice in tumors of duodenal origin, and can act as a lead point for intussusception and small bowel obstruction [40–42]. A high index of suspicion remains paramount for accurate preoperative diagnosis given the rarity of this condition.

Multiple diagnostic and treatment guidelines have been published on GIST, including the National Comprehensive Cancer Network (NCCN) and the European Society of Medical Oncology (ESMO) guidelines. A GIST is suspected whenever a well-circumscribed mural or extramural, submucosal mass of any size is identified in the distal esophagus, stomach or small intestine, whether through imaging studies, at the time of surgery, during endoscopy, or on pathology analysis. It is critical to keep GIST in the differential diagnosis of any mass found in the alimentary canal from esophagus to rectum. GISTs remain the most common mesenchymal tumors of all sections of the GI tract with the exceptions of the esophagus, colon, and rectum, where leiomyomas are more common.

The imaging study of choice for initial evaluation of a GIST is a computed tomography (CT) scan of the abdomen and pelvis using oral and intravenous contrast enhancement, with arterial and venous phases. GISTs will typically appear as a well-circumscribed, enhancing mass arising from the gastric or intestinal lumen. Large GISTs, which have outgrown their blood supply and have areas of necrosis, may appear as heterogeneously enhancing masses on CT imaging. It should be noted that CT Imaging in the setting of inadequate gastric distension can make it difficult to identify small GISTs. Even in patients with prior endoscopic imaging, a baseline CT scan is still necessary to determine full tumor extent and to evaluate for liver and peritoneal metastatic disease.

Routine magnetic resonance imaging (MRI) is inferior to CT imaging for the initial evaluation of a GIST due to the constant movement of the stomach, small bowel, and surrounding tissues. Results using MRI with diffusion-weighted imaging (DWI), however, may be comparable to PET/CT imaging [43]. MRI is indicated in evaluation of peri-ampullary and rectal

GISTs, and to further evaluate for metastatic liver disease, as lesions are occasionally isodense to liver parenchyma on CT. Neither MRI nor CT has been shown to reliably predict tumor invasion into surrounding structures.

Positron Emission Tomography combined by CT imaging (PET/CT) plays a role in GIST diagnosis and management, as these tumors tend to show significant metabolic activity, and therefore lend themselves well to functional imaging with PET using ^{18}F–fluorodeoxyglucose [44]. It is often used for assessment of metastatic disease and early metabolic changes, especially in response to tyrosine kinase inhibitor therapy, which may be informative in the setting of neoadjuvant therapy. PET imaging may also be beneficial in detecting small omental metastases, which may not easily be identified on CT scans, as ^{18}F–fluorodeoxyglucose is not taken up to any significant degree by normal small intestine or omentum. Recently, a large percentage of GISTs have been found to express somatostatin receptors, SSTR1 and SSTR2. This has created a role for somatostatin receptor scintigraphy in evaluation of GISTs, similar to its role in GI and pancreatic neuroendocrine tumors [45].

Endoscopy plays a significant role in the evaluation of GISTs, and provides a means of tissue sampling for pathologic analysis. Upper GI endoscopy is used to evaluate tumors in the esophagus, stomach and duodenum, while colonoscopy is used to evaluate rectal and colon masses. For distal duodenal and jejunoileal masses, which are poorly accessible by traditional endoscopic techniques, there is a role for capsule endoscopy and for double-balloon enteroscopy in evaluating these lesions. Endoscopic ultrasound (EUS) has also been used in the evaluation of suspected GISTs. They are visualized as circumscribed hypodense lesions deep to the mucosa. Tumors with irregular borders, size greater than 4 cm, as well as significant echogenic foci and cystic spaces have been found to correlate with malignant behavior [46].

Endoscopy and EUS offer the advantage of being able to perform a tissue biopsy at the time of the procedure. Unfortunately, endoscopic mucosal biopsies are successful in only 20–30% of cases, even in GISTs which involve the mucosa or the superficial submucosa. EUS-guided fine-needle aspiration cytology, however, has demonstrated more favorable results, with a diagnostic yield of 76%, and EUS-guided core biopsies with a yield of 97% [47, 48]. While there is a role for percutaneous biopsies, particularly in large tumors, many institutions have demonstrated superior yields from EUS-guided biopsies [49, 50]. It should be noted, however, that if imaging studies are strongly suggestive of a mesenchymal tumor which appears to be resectable, it is usually not necessary to obtain a tissue diagnosis preoperatively. Conversely, if metastatic disease is evident, or if resectability is questionable, a tissue diagnosis is required to plan for immunohistochemical analysis and targeted molecular therapy.

The pathologic diagnosis of GIST is defined by the morphology, ultrastructure and immunohistochemistry findings. These tumors are mesenchymal in origin and have spindle cell, epithelioid cell or mixed histology with variable mitotic activity, which along with tumor size are of prognostic significance. Immunohistologically, up to 95% of GISTs stain positive for KIT (CD117). Additional staining for markers such as PDGFRα, PI3K, CDKN2A and DOG1 can also be performed. In addition to tumor size and mitotic activity, several pathologic and immunohistochemical findings have been shown to affect prognosis and predict recurrence, including Ki67 proliferation index, presence of diffuse mucosal involvement, tumor rupture, tumor location, completeness of resection, aneuploidy, and telomerase expression [42, 51–57].

4. Management

4.1. Primary GIST

Definitive surgical resection in patients with primary, localized GISTs remains the only chance for cure [58]. The surgical approach to GISTs takes into consideration the typical tumor growth patterns and tends to follow the general principles of management of sarcomas. It is uncommon for GISTs to have lymph node spread, and they usually do not demonstrate significant intramural extension. Given the somewhat predictable pattern of growth and the infrequency of lymph node involvement, extensive tumor resection and lymph node dissections can usually be avoided unless there is gross lymphadenopathy present. Surgical management typically involves a wedge resection of the stomach, or a segmental small bowel resection for small bowel GISTs.

The best long-term results were traditionally thought to be achieved after complete resection with microscopically negative margins (R0 resection), typically via resections with 1–2 cm margins. Although the goal of surgical resection should always be to obtain an R0 resection, recent studies have demonstrated that tumor size and inherent biologic status play a greater role in predicting survival than do microscopic margins. It is now generally accepted that grossly negative margins (R1) do not lead to significant differences in recurrence-free survival(RFS) when compared to R0 resections, irrespective of the use of adjuvant therapy [11, 59]. Gross resection to negative margins is generally achievable in 85% of localized, primary GISTs, with cases of adjacent organ involvement surgically approached with en bloc resection. The American College of Surgeons Oncology Group (ACOSOG) Z9000 and Z9001 studies, in addition to demonstrating no difference in RFS between R0 and R1 resections, demonstrated that surgical resection of tumors ≥3 cm was curative in 70% of patients at long-term follow-up, underscoring the pivotal role of surgical resection with curative intent in medically fit patients. The NCCN guidelines reflect these results, with recommendations to resect all GISTs with a size over 2 cm.

GISTs involving the colon and small intestine tend to be more aggressive, and warrant resection regardless of size, whereas for gastric GISTs smaller than 2 cm, endoscopic surveillance or serial imaging seems to be a reasonable option. A 2011 study by Kim et al. looking retrospectively at 989 patients with small subepithelial gastric tumors less than 3 cm in size demonstrated that only 8.5% of tumors had significant growth at median follow-up of 24 months. Twenty-five patients underwent tumor resection due to concerning growth or finding on imaging, of which 19 were GISTs, and only 3 of these were considered high-risk, with 4 classified as intermediate-risk [60]. The high incidence of small gastric GISTs is reflected in autopsy series where the incidence of subcentimeter gastric GISTs was as high as 22.5% in persons over 50 years old in a German study, and the incidence of microscopic GISTs was as high as 35% in gastric resection specimens for gastric cancer in a Japanese study [61, 62].

Gross resection margins of 2–3 cm for small bowel GISTs, and a microscopically free margin of only several millimeters in gastric GIST wedge resections is generally considered adequate. Greater gastric resections, including partial or total gastrectomy, are usually reserved for larger GISTs, or those which preclude wedge resection based on location [63].

Rectal GISTs remain uncommon, however consideration may be given to endoscopic resection based on size, extent, and anatomic relationships. While not common practice, laparoscopic resection of small GISTs, particularly those which are gastric in origin, has been described with good outcomes [64, 65].

Incomplete (R2) resections of GISTs are generally reserved for surgery with palliative intent to alleviate symptoms related to pain, bleeding, or mass effect. Despite the high rate of successful complete gross tumor resection, there has been a historically high recurrence rate of over 50%, with an associated 5-year mortality rate of approximately 50% [11, 42, 53]. The median time to recurrence after an adequate R0 resection has been found to be between 19 and 25 months, with recurrences typically involving the liver and peritoneum, and is usually not amenable to a repeat resection [11, 53, 66]. GISTs are usually very vascular with a fragile pseudocapsule. Careful intraoperative handling of the tumor is therefore essential to minimize the risk of tumor rupture, which often results in peritoneal recurrence [53].

Open resection of gastric and small intestine GISTs has been the traditional approach to operative management, however, minimally invasive approaches are now being utilized with good outcomes. Laparoscopic resection of gastric and some small intestine GISTs is being attempted with increased frequency, and allows for many of the benefits of laparoscopic surgery, including decreased postoperative pain, a shorter hospital length-of-stay, faster return to work and functional independence, and a better cosmetic outcome [67–71]. In addition to open surgical options for colon and rectal GISTs, endoscopic resection in cases of small rectal GISTs may also be considered. More recently, laparoscopic and endoscopic cooperative surgery (LECS) has been employed in resection of gastric GISTs, where the mucosal dissection of tumors that protrude intraluminally is performed endoscopically [72].

4.2. Advanced GIST

Despite adequate surgical resection of localized GISTs, not all operations are curative. Many studies have reported high recurrence rates, up to 50%, after complete tumor resection [11, 40]. The initial sites of recurrence are most frequently the liver (50%), peritoneum (50%), or both (20%), with bone and lung metastases often occurring later [73]. Both liver and peritoneal involvement in this setting tend to be diffuse and multifocal, with surgery playing a very limited role in the face of recurrent or metastatic disease. Historically, conventional chemotherapy and radiotherapy regimens have been ineffective in treating advanced GISTs [74]. The advent of targeted molecular therapy has revolutionized the treatment of GISTs, with tyrosine kinase inhibitors such as imatinib playing a pivotal role in management.

The clinical value of imatinib for high-risk patients and those with advanced disease was established in the ACOSOG Z9000 and Z9001 trials. The ACOSOG Z9000 trial demonstrated a remarkable improvement in the survival rate of high-risk patients (tumor size ≥10 cm, tumor rupture or <5 peritoneal metastases) who had undergone complete surgical resection of KIT-positive GISTs [75]. The ACOSOG Z9001 trial was a randomized trial comparing the use of imatinib to a placebo in moderate risk GISTs (tumor size ≥3 cm). There was a significant increase in RFS in the imatinib group, though overall survival was no different in the short-term [76].

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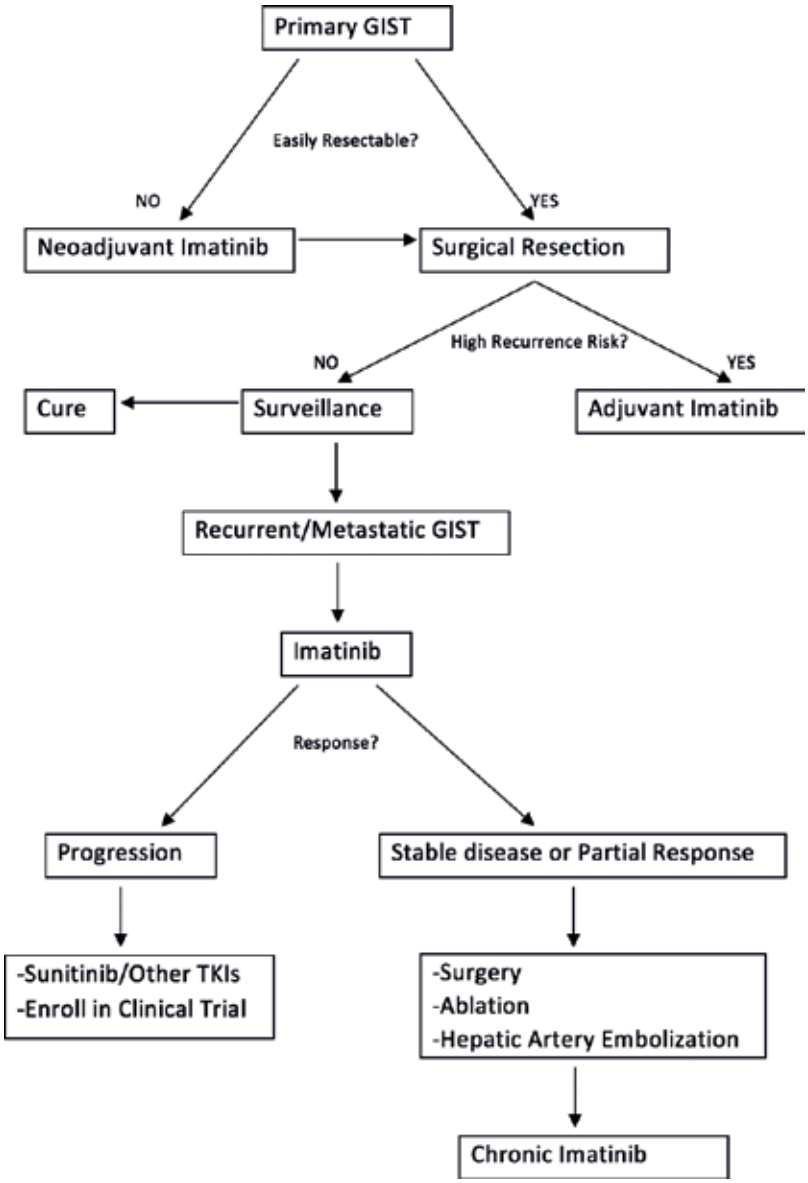

Figure 1. A schematic overview of the approach to management of gastrointestinal stromal Tumors (GISTs). (Adopted from [40]).

Patients receiving imatinib therapy show changes in metabolic activity on PET scans within hours, however, a decrease in tumor size often takes several weeks to months, and tumors may even increase in size initially. For these reasons, the traditional World Health Organization (WHO) and Response Evaluation Criteria in Solid Tumors (RECIST) criteria are not ideal in evaluating response to imatinib therapy in GIST. This response to imatinib therapy is better evaluated by contrast-enhanced CT scans using the Choi criteria, which evaluates for both a decrease in tumor size as well as the tumor density [77, 78]. The use of PET scans have also

been shown to be very sensitive in evaluating tumor response, given the early changes in tumor metabolic activity [79]. The tumor response to imatinib therapy at day 8 on PET scans have been shown to correlate with 1-year prognosis in unresectable GISTs [79, 80]. Imatinib use in the neoadjuvant setting has not been studied as extensively as adjuvant therapy, but remains very useful in locally advanced or borderline resectable tumors, and tumors in locations where tumor downsizing may allow for a less morbid operation.

Resistance to imatinib therapy unfortunately occurs, and may be of two types as mentioned earlier. Primary resistance occurs in patients who either never had an initial response, or who show disease progression within 6 months of initiating therapy, while secondary resistance occurs in those who show disease progression after 6 months of therapy. This latter group often acquires mutations in KIT or PDGFRα that interfere with imatinib activity [81, 82]. Sunitinib and regorafenib are both newer FDA approved agents which block multiple tyrosine kinase receptors for use in GIST patients with disease progression or intolerance to imatinib. Several other tyrosine kinase inhibitors, including nilotinib, masatinib, dasatinib and sorafenib have been used in cases of resistance to imatinib and sunitinib or in patients with intolerance, however, their role in the management of GISTs continues to be investigated. A schematic overview of the approach to management of GISTs is shown in **Figure 1** [40].

5. Surveillance

Long-term follow-up is necessary in all patients with GISTs, due to their unpredictable biological behavior. Most recurrences tend to occur within the first 3–5 years, and surveillance recommendations take this into account. Recommendations by the NCCN include performing a history, physical examination, and a contrast-enhanced CT scan of the abdomen and pelvis every 3–6 months for 3–5 years, and then annually thereafter [8]. Recommendations from the European Society of Medical Oncology (ESMO) are based on tumor size and mitotic activity [83]. High-risk tumors (size ≥5 cm and mitoses ≥5/50 HPF) require a CT scan of the abdomen and pelvis every 3–4 months for 3 years then every 6 months for 2 years thereafter, while tumors <5 cm in size with a mitotic rate of <5/50 HPF should have a CT scan of the abdomen and pelvis every 6 months for 5 years.

Conflict of interest

The authors have no conflicts of interest to disclose.

Author details

Rahman G. Barry*, Thao T. Wolbert and David A. Denning

*Address all correspondence to: rahmanbarry@gmail.com

Department of Surgery, Marshall University, Huntington, WV, USA

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