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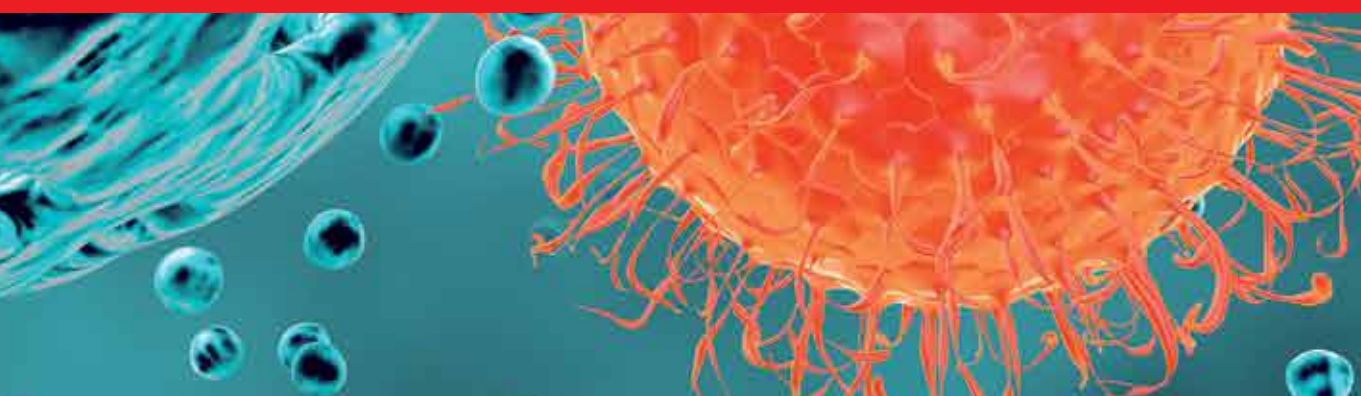
Gastric Cancer

An Update

Edited by Hajime Orita,
Hiroshi Maekawa and Michael Gibson



GASTRIC CANCER - AN UPDATE

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Meet the editors

Hajime Orita is an associate professor at the Department of Surgery, Juntendo University School of Medicine, Shizuoka Hospital. He specialized in surgery of the esophagus and stomach, laparoscopic surgery of the esophagus and stomach (LADG, LTG), endoscopic diagnosis and therapy (upper gastrointestinal tract), endoscopic surgery of esophagus and stomach (ESD), and chemotherapy for esophageal and stomach cancer patients. Dr. Orita's research focuses on cancer metabolism, Fatty Acid Synthase (FAS) as a cancer treatment, diagnosis and cancer prevention, cancer metabolism, the relationship between cancer and diabetes, chemoresistance research related to CHFR methylation in esophageal and gastric cancer, new cancer suppressor gene (GASDERMIN), working with the National Institute of Genetics, new prognostic predictors for gastrointestinal stromal tumors (GIST), Pfetin by use of proteomics technology, and working with the National Cancer Center Research Institute.

Dr. Hiroshi Maekawa graduated from Gunma University School of Medicine in 1991. After that he was with Juntendo University School of Medicine, Department of Surgery, from 1991 until 1999 when he switched to Juntendo University, Shizuoka Hospital, Department of Surgery where he still works. He was appointed associate professor, Juntendo University Faculty of Health Science and Nursing from 2011 and assistant professor at the Department of Coloproctological Surgery, Shizuoka Hospital from 2012. His research interests are in the field of pancreatic surgery and fat metabolism in biliary and pancreatic cancer.

Dr. Gibson is an Associate Professor of Medicine at the Vanderbilt University, Vanderbilt-Ingram Cancer Center, where he is Director of Translational Research for Head and Neck Oncology. After obtaining his MD from Johns Hopkins, he completed an Osler Medical Residency and Medical Oncology Fellowship at Johns Hopkins Hospital while concurrently earning a PhD in clinical investigation from the Johns Hopkins Bloomberg School of Public Health. He currently leads local and national therapeutic trials for aero-digestive cancers, all with translational laboratory components. The overall goals of his research efforts are to bring novel therapeutics to the treatment of aero-digestive cancers based on rational pre-clinical investigation and in the setting of a focus on patient safety and outcomes.

Contents

Preface

This book is a collection of reviewed and relevant research chapters, concerning the developments within the gastric cancer field of study.

The book includes scholarly contributions by various authors and is edited by a group of experts in gastric cancer therapy. Each contribution comes as a separate chapter complete in itself but directly related to the book's topics and objectives.

The book is divided in three sections: Operation, Chemotherapy, and GIST.

Section 1 includes the following chapters: Reconstructive Procedures after Total Gastrectomy for Gastric Cancer; Laparoscopic Endoscopic Cooperative Surgery: Current Status and Perspective and Reconstruction after Laparoscopic Distal Gastrectomy.

Section 2 includes a chapter focusing on Adjuvant Chemotherapy of Gastric Cancer.

Section 3 includes a chapter on Gastric GIST.

The target audience comprises scholars and specialists in the field.

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Operation

Chapter 1

Reconstructive Procedures after Total Gastrectomy for Gastric Cancer

Nebojsa S. Ignjatovic, Tomislav D. Randjelovic, Miroslav P. Stojanovic, Goran Z. Stanojevic and Miodrag N. Djordjevic

Additional information is available at the end of the chapter

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Abstract

Till this day, there are more than 60 described surgical procedures of the intestinal reconstructions after a total gastrectomy. In 1897, Schlatter reconstructed the digestive tract by creating a termino-lateral esophagojejunostomies that was the first successful total gastrectomy. Many of the total gastrectomy pioneers did the reconstruction by esophagoduodenostomy or by forming a loop esophagojejunostomy. The main reconstruction modalities after a total gastrectomy are a restitution of the intestinal continuity, without a preservation of the duodenal food passage (esophagojejunostomy with a Roux-en-Y configuration) and a restitution of the intestinal continuity with a preservation of the duodenal passage (esophagojejunostomy with Roux-en-Y configuration and forming of the lateral-terminal jejunoduodenal anastomosis double tract and jejunal interposition by Longmire). The surgeries in these categories can be combined with forming of an enteral pouch or a stomach reservoir which would simulate a reservoir of a normal intact stomach. The ideal reconstruction procedure after total gastrectomy should replace all lost functions of the stomach. Preservation of duodenal transit with replacement of the jejunal segment, the so-called physiological route, is now believed to be preferential for postoperative nutritional condition, prevents persistent postgastrectomy syndrome, and improves the quality of life. Reconstructive procedures which allow duodenal passage should be regarded as a key to physiological reconstruction.

Keywords: gastric cancer, total gastrectomy, reconstructive procedures, nutritive status, quality of life

1. Introduction

1.1. Background and history

The development of stomach surgery is one of the most fascinating chapters in the history of surgery. The era of surgical treatment of gastric cancer (GC) began with the first successfully performed distal subtotal gastrectomy in 1881 by Theodor Billroth. The first total gastrectomy (TG) was probably carried out by Conner in 1887 in Cincinnati, but the patient died [1]. The first successful TG due to GC was performed by Carl Schlatter in Switzerland in 1897 [2]. The patient was a 56-year-old woman who lived less than 14 months and died from secondary metastatic deposits in the liver. Krönlein first introduced the term TG in 1898. Charles Brigham of San Francisco in the same year performed the first successful TG in the United States to create an esophagoduodenal anastomosis, using the Murphy button [3]. The high postoperative mortality in TG performed in the 1940s, was reduced by the introduction of antibiotics, the use of blood transfusions, and the improvement of anesthetics and surgical techniques. During this period TG was proposed as a routine surgical treatment for all resectable GC. This approach was later abandoned due to inability to improve the survival rate, high operative mortality, and increased incidence of undesirable postoperative effects after TG [4]. By 1980, TG was rarely performed and was only applied in highly selective cases [5]. The contribution of these and many other authors during the nineteenth century provided a basis for modern surgical treatment of patients with GC. From the beginning of the 1940s, radical resection, including regional lymphadenectomy for all GC, was recommended [6]. Operations of such extensions, at that time, were burdened with unacceptable morbidity and mortality. To date, efforts have been made to define the optimal extent of resection, lymphadenectomy, and reconstruction.

Digestive tract reconstruction after TG was mostly performed initially by creating a direct anastomosis of the esophagus with a duodenum or with a jejunum loop. The inevitable problem of billiard regurgitation was solved in 1909 by adopting the creation of the Roux-en-Y (RY) type of esophagojejunostomy configuration [7]. A large number of surgeons continued to perform jejunum loop reconstruction until 1947, when Orr promoted the concept of end-to-end anastomosis using the RY-type configuration of esophagojejunostomy, which is now a standard procedure for reconstruction after TG [8].

2. Reconstructive procedures after total gastrectomy

2.1. Concept of reconstructive procedures after total gastrectomy

During the first successful TG in 1897, Schlatter reconstructed the digestive tract by creating end-to-side esophagojejunostomy [2]. Many of the pioneers of TG performed reconstruction with esophagoduodenostomy or formed loop esophagojejunostomy [7, 9]. High operational risk and frequent malnutrition observed during the postoperative period gave TG an unfavorable reputation. The loop esophagojejunostomy technique was modified by Hoffman in 1922.

He added a small side-to-side jejunojejunostomy between two ends of the jejunum loop [10]. This provided partial bypass to the duodenal content and reduced the frequency of alkaline reflux esophagitis. The major immediate postoperative problem after TG concerned the integrity of anastomosis on the esophagus. Later postoperative problems were associated with reconstruction and nutritional status and quality of life that is more affected by the aspects of reconstruction than the anastomosis on the esophagus itself.

To date, more than 60 different reconstructive procedures (RP) of intestinal reconstructions have been described after TG which were, and are now, in use in surgical institutions [11, 12]. The main modalities of reconstruction after TG are restoration of intestinal continuity, without preserving duodenal passage (DP) of food (esophagojejunostomy with RY configuration) and restoration of intestinal continuity with the preservation of DP (esophagojejunostomy with RY configuration and formation of side-to-end jejunoduodenostomy double tract (DT) and Longmire's longitudinal interposition). Operations in these categories can be combined with the formation of an enteral pouch or a gastric reservoir that simulates the function of the reservoir of the normal intact stomach. The RP with pouch and neo-stomach formation have been developed to provide food tanks, with the goal of preserving duodenal transit and providing the anatomy and physiology of the digestive tract. Advantages and disadvantages of these RP continue to be the subject of discussion due to the existence of contradictory results from various studies.

2.2. Reconstructive procedures without duodenal passage preservation after total gastrectomy

2.2.1. Esophagojejunostomy Roux-en-Y configuration

The RY configuration of esophagojejunostomy has become the most widely used method of reconstructing intestinal continuity around the world [13, 14]. This precious intestinal configuration is now used in reconstruction and drainage of the stomach, esophagus, and pancreatic-biliary tree, as well as in bariatric surgery [15].

The procedure was inaugurated by César Roux (1857–1934), a Swiss surgeon and professor, in 1893 [16]. Initially, after TG, the jejunum loop was placed in a retrocolonic fashion. RY configuration of esophagojejunostomy immediately became objectionable due to a recurrent complication, that is, the potential formation of ulceration on the jejunal anastomosis [7]. The idea of using the RY configuration for reconstruction after TG was introduced early, in 1909 [9]. Despite Reid's 1925 report on the use of this RP, most of the surgeons of that time continued to prefer loop esophagojejunostomy with an anastomosis between two jejunum loops, thereby preventing the alkaline reflux of duodenal content and consecutive esophagitis [17]. In 1940, several papers again drew attention to the Roux-en-Y intestinal configuration, and in 1947, Orr reintroduces end-to-side esophagojejunostomy in creating a RY configuration (**Figures 1–3**) [8].

The primary factor in creating RY is the preservation of adequate vascularization. Jejunum vascularization comes from superior mesenteric artery, aorte abdominalis' branch. Superior mesenteric artery branches for vascularization of the intestinum are formed on its left side, and their number is variable 13–21, for vascularization of jejunum 3–7 (average 5) and 8–17 (average 11) for the ileum. Intestinal arteries branch in the mesenterium, and through the

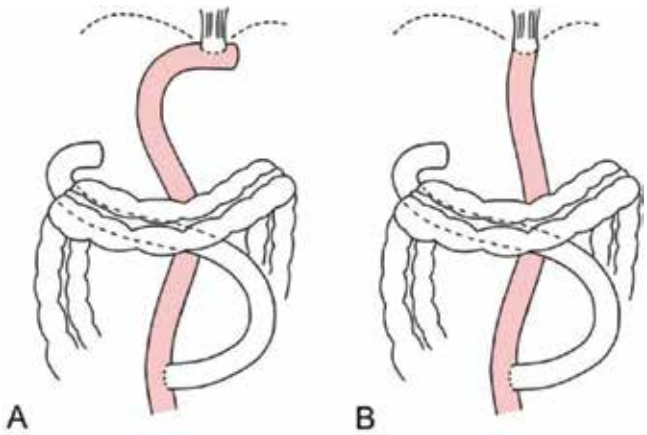

Figure 1. Schematic representation of reconstruction after TG without DP with a standard RY configuration with the creation of (A) end-to-side or (B) end-to-end esophagojejunostomy.

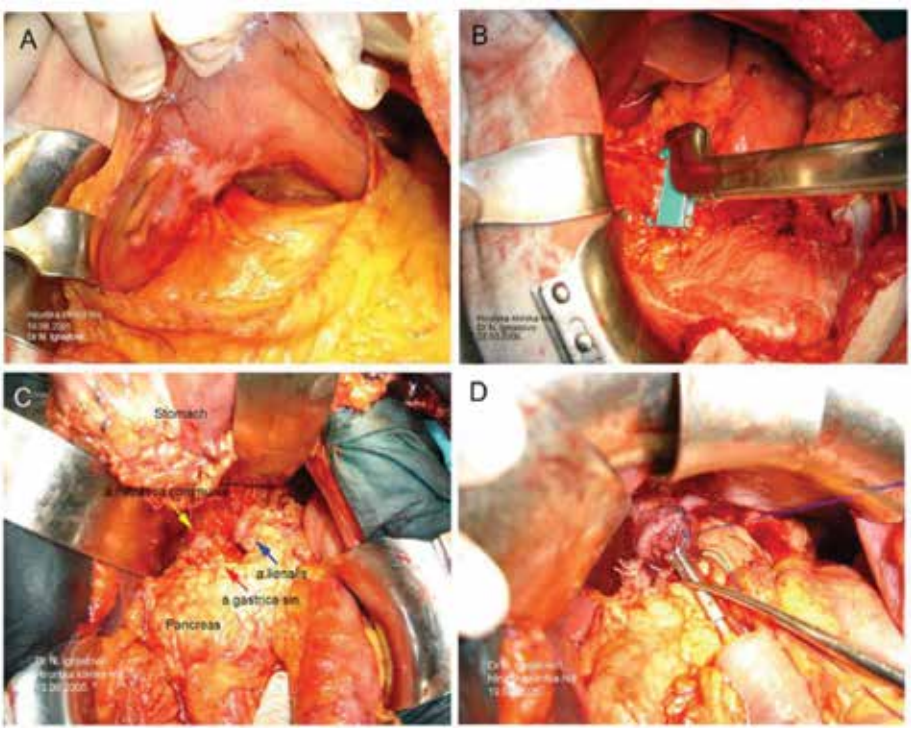

Figure 2. A representation of the operative reconstructive technique after TG without the preservation of DP by the RY configuration on the material of the author of this chapter: (A) diffuse GC of the antropyloric region of the stomach; (B) closure of the duodenal residue using a linear stapler TA 30; (C) lymphovascular dissection of the plexus coeliacus, a.hepaticae communis (yellow arrow), a.gastricae sin. (red arrow), and a.lienalis (blue arrow); (D) bringing the jejunum loop to the approximation with distal esophagus and forming end-to-end esophagojejunostomy with circular stapler CEEA Ø25 mm.

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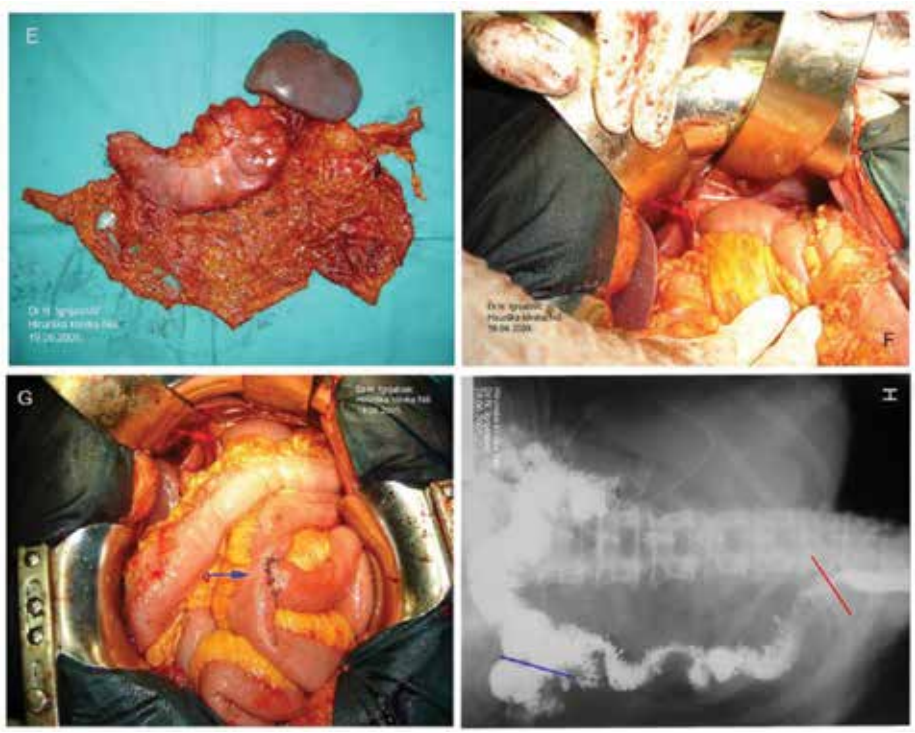

Figure 3. A representation of the operative reconstructive technique after TG without the preservation of DP by the RY configuration on the material of the author of this chapter: (E) specimen of the stomach, spleen, and large omentum, (F) formed end-to-end esophagojejunostomy (red arrow), (G) formed end-to-side jejunojejunostomy with Roux Y anastomosis (blue arrow), (H) contrast radiography: sufficient anastomosis of esophagojejunostomy (red line) and end-to-side jejunojejunostomy with Roux-en-Y anastomosis (blue line).

vascular arcades of the I–IV orders, they connect to one another before the separation of terminal vasa recta entering the small intestine on the mesenteric edge. Arcades are more developed in the proximal part of the intestinum. They are arranged in three rows, so that arcades allow good vascularization and formation of isolated segments. Vasa recta are terminal type, and each such blood vessel vascularizes about 0.5 cm of the intestinal wall [18]. There are long and short arteriolae rectae. The long arteriole recta are divided into two branches, anterior and posterior. Entering the jejunum wall, each of those branches vascularizes specific area of the jejunum wall and they anastomose on the antimesenteric edge. The antimesenteric edge has the weakest vascularization and therefore is susceptible to the occurrence of dehiscence after the creation of anastomosis. Short arteriolae rectae, which can directly originate from the paraintestinal arterial arcades, or from other arterioles, are intended for the vascularization of the mesenteric intestine [19]. The regularly firmed distal end of the RY jejunum loop was mobilized by dividing two vasa recta [7].

The main goal in choosing the reconstruction of the esophago-intestinal continuity RY configuration after TG without preserving DP is to prevent the formation of biliary reflux into the esophagus. Biliary contents can cause damage to the esophagus mucous membranes, or

alkaline esophagitis [20]. In 1924, the proposed RY loop length was only 7.5 cm, but it increased steadily and significantly over time. Wells proposed in 1956 a length of 20–25 cm. The smallest length of the RY loop of 35 cm proved to be capable of preventing the formation of alkaline biliary reflux [21]. The vast majority of experienced surgeons today use RY loop length of 40–60 cm. The wide application of the RP RY configuration is attributed to its simplicity because it uses a minimum number of anastomosis.

In order to adequately replace the stomach and increase the reservoir of the jejunal substituent, the RP RY configuration was modified by Hunt and later by Lawrence by creating a jejunal pouch [22, 23]. Several modalities of the reconstruction of the jejunal pouch include forming formations J-pouch, Ω-pouch, S-pouch, and an aboral pouch [22–25].

Forming the Hunt-Lawrence pouch, the jejunum in length is brought up posterior to the transverse colon. The distal portion of the divided afferent limb, with approximate length of 15–20 cm, is placed posterior to the transverse colon, plicated to the proximal efferent limb and retained by traction sutures. A small stab wound is formed at the midportion of each limb of plicated loops, and a linear stapler is introduced through it, while side-to-side anastomoses are created upward and down along the antimesenteric borders. Following the inspection of the anastomotic lines for complete hemostasis, a circular stapler (stapler CEEA) is introduced through the central hole of the pouch for the esophagojejunostomy.

The hole is closed transversely with a running suture following the withdrawal of the circular stapler. Intestinal continuity is then reestablished by hand in RY fashion, about 20–30 cm below the pouch (**Figures 4** and **5**) [26–28].

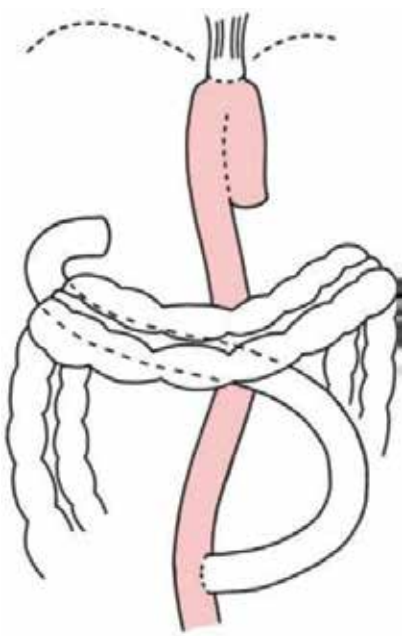

Figure 4. Schematic representation of reconstruction after TG without DP with a the Hunt-Lawrence pouch.

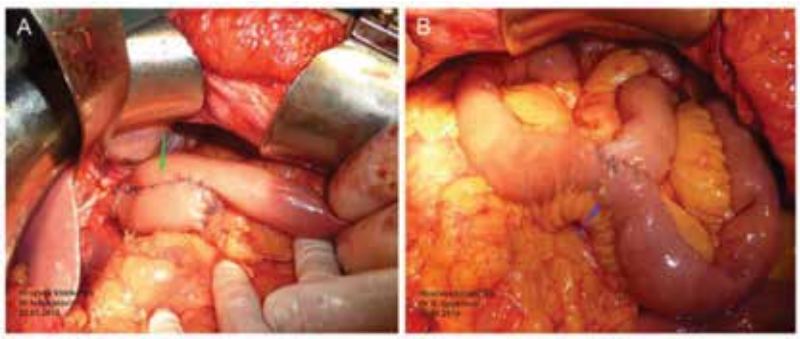

Figure 5. A representation of operative reconstructive technique after TG without DP preservation by the pouch configuration on the material of the author of this chapter: (A) end-to-side esophagojejunostomy is formed (red arrow) and longitudinal side-to-side jejunojejunostomy (green arrow); (B) end-to-side jejunojejunostomy is created with Roux-en-Y anastomosis (blue arrow).

The use of pouch reconstruction provides a reduction in the occurrence of dumping syndrome, postoperative weight development, regurgitation of bile, and insufficient size of indigested meals [27].

2.3. Reconstructive procedure with duodenal passage preservation after total gastrectomy

2.3.1. Esophagojejunostomy Roux-en-Y double tract configuration

The RP using the jejunum after TG with the preservation of DP is the esophagus RY configuration of the DT in the establishment of esophagoduodenal continuity. The description of operational technique was first provided in 1965 by Japanese authors Kajitani and Sato [29]. In this RP after TG, the duodenum in the first act remains open, and after the creation of an esophagojejunal anastomosis according to the principles of the operational technique of carrying RY configurations with a duodenum duct, an additional distal end-to-side jejunoduodenal anastomosis is established at about 20 cm distal from created esophagojejunal anastomosis [30]. Today's modification of the originally described technique is the creation of end-to-end duodenal anastomosis at 35–40 cm distal from esophagojejunal anastomosis [31]. Creation of distal termino-lateral jejunojejunal anastomosis is performed according to the principles of the original RY configuration of esophagojejunostomy at about 60 cm from end-to-side or end-to-end esophagojejunal anastomosis (**Figure 6**). Creation of esophagojejunal anastomosis is performed by a manual two-layer suture technique or the use of the CEEA circular surgical stapler, while the creation of jejunoduodenal and jejunojejunal anastomosis is performed by a manual two-layer suture technique (**Figure 7**) [31, 32]. The RY configuration of the DT is now applied in some institutions in Japan.

2.3.2. Esophagojejunostomy with the interposition of the jejunal segment by Longmire

RP using the jejunum after TG with the preservation of DP is the interposition to isoperistaltics free jejunal segment according to the Longmire method in establishing esophagoduodenal

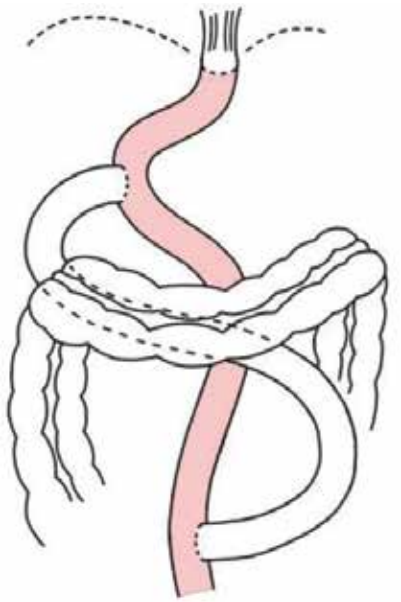

Figure 6. Schematic representation of reconstruction after TG with DP with a RY configuration of DT with the creation of end-to-end esophagojejunostomy and side-to-end jejunoduodenostomy.

continuity. After Seo's first attempt in 1941, the inauguration of this RP after TG was performed by Longmire in 1951, even though the idea was proposed 3 years earlier by Saccharow [33–36].

Hays interposed a triple jejunal pouch between the esophagus and duodenum in 1953 [37]. Gütgemann recommended the interposition of a very long jejunum loop of at least 30 cm in length to increase the reservoir function of the inserted jejunal pouch [38]. Poth in 1966 favored the interposition of an antiperistaltic jejunal pouch in various combinations [39]. In 1972, Schrader and Koslowski interposed an additional 10 cm shorter antiperistaltic jejuna segment, which anastomosed distally from Longmire's reconstruction [40]. They favored the view that a short anisoperistaltic interposition of the neuromuscular segment could slow down the gastric emptying and simulate neopylorus [40, 41]. In 1982, Cuschieri created a large jejunum pouch interposed between the esophagus and the duodenum [42]. Nakane and Schwarz recommended Hunt-Lawrence Shaped pouch in 1990, interposed between the esophagus and duodenum [27, 43]. The reconstruction of the ileocecal interposition described by Lee and Hunnicutt is also in use with the basic idea of replacing the ileocecal valve as a substitute for the cardiac sphincter [44, 45]. This reconstruction provides anatomic barrier between the neo-stomach and the esophagus to prevent biliopancreatic reflux.

The original RP after TG by Longmire implies the establishment of an esophagoduodenal continuity using a previously fully mobilized intestinal segment on a free vascular sponge ante- or in a retrocolonic fashion by using an isolated first jejunal segment of 15 cm in length (**Figure 8**) [34].

This type of reconstruction is also known as the Beal-Longmire operation. Today, after the mobilization of the first segment of the jejunum in the length of at least 25–35 cm and with a longer

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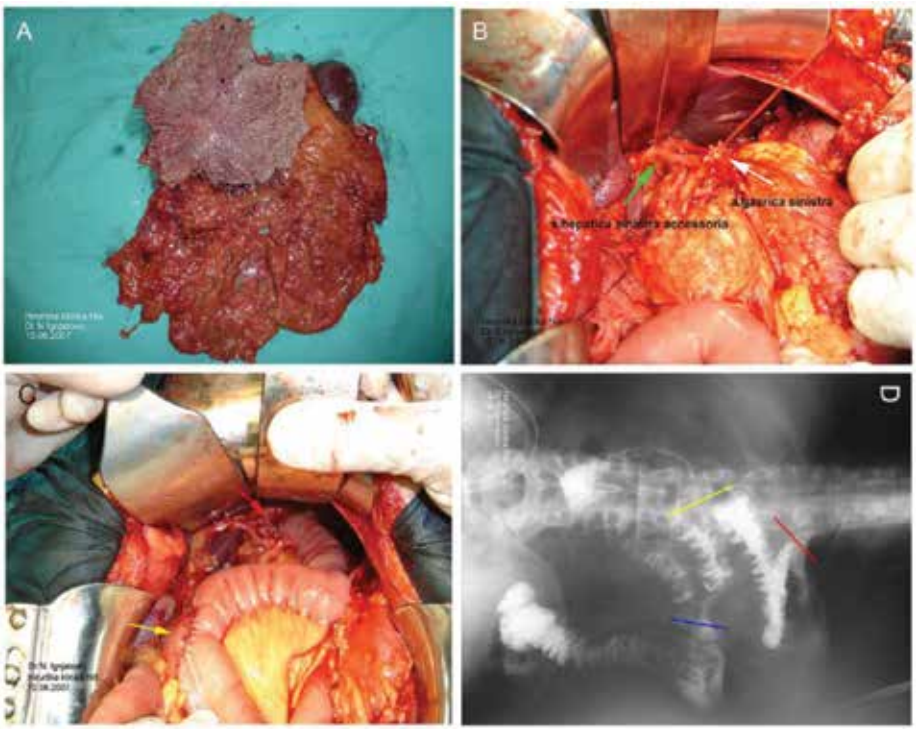

Figure 7. A representation of the operative reconstructive technique after TG with the preservation of DP by the RY configuration on the material of the author of this chapter: (A) specimen of the stomach (stomach open by large curvature), spleen, and large omentum, (B) arterial variation of branching a.hepaticae sinistrae accessoriae (yellow arrow) from a.gastricae sinistrae (white arrow), (C) formed end-to-end esophagojejunostomy (red arrow) and side-to-end jejunoduodenostomy (yellow arrow), (D) contrast radiography: sufficient anastomosis of esophagojejunostomy (red line), jejunoduodenostomy (yellow line), and jejunojejunostomy with Roux-en-Y anastomosis (blue line).

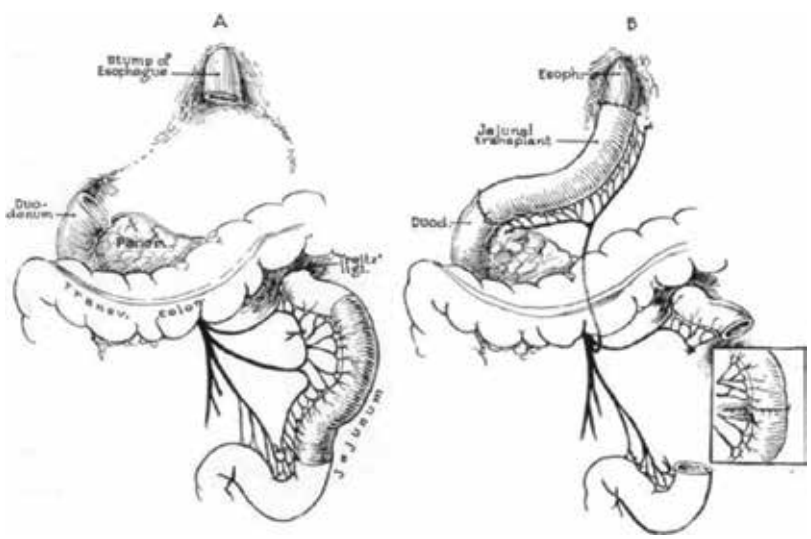

Figure 8. Original schematic representation of reconstruction after TG with DP by Longmire [34].

mesentery, both of these structures have retrocolonic transmesocolic position and they make anastomosis with the esophagus and duodenum in the isoperistaltic position. Modification by Schreiber and Gütgemann uses the jejunum segment in a length of 40 cm [38, 46]. Creating a proximal termino-lateral or end-to-end esophagojejunostomy is performed by a manual dual-layer technique or the use of a circular stapler (stapler CEEA), while a distal end-to-end jejuno-duodenostomy is performed by a manual two-layer mint technique. It is very important that the torsion and tension of the mesenterium be avoided in creating an isolated jejunum segment. The continuity of the resected proximal end of the first segment and the second segment of the jejunum with the application of a two-layer manual knot tying technique is established with end-to-end jejunojejunostomy (**Figures 9** and **10**).

In 1952, Longmire and Beal stated that all patients with reconstructed isolated jejunal segment after 4 months of follow-up were able to restore regular nutrition and preoperative body weight. In all patients, there was no early onset of pyrosis and epigastric pain [34]. Longmire also states that after adequate mobilization of the duodenum and avoidance of tension on the esophageal and jejunoduodenal anastomosis itself and the normalization of food passage through the duodenal segment, the benefits of interposition with the jejunal segment have been achieved: increasing the capacity of the isolated jejunal segment with the dilatation of the intestinal wall itself and the smaller regurgitation of biliary and intestinal contents [34]. Longmire points out that with this RP, there was no significant increase in operative risk during the performance of total gastrectomy, that is, the risks of vascular ischemia that are present in the transposition of the ileum and ascendant colon were eliminated. The reconstruction

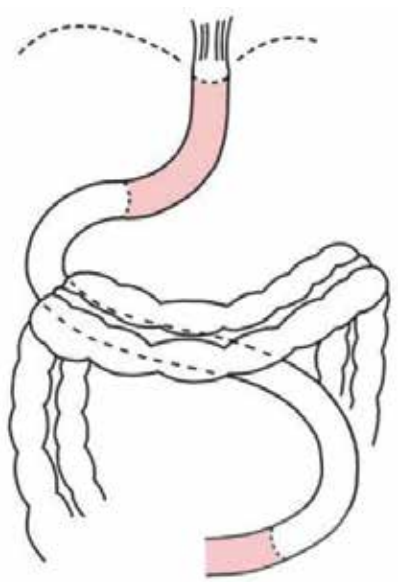

Figure 9. Schematic representation of reconstruction after TG with DP by Longmire, by interposition of jejunal segment with the creation of end-to-end esophagojejunostomy and end-to-end jejunoduodenostomy.

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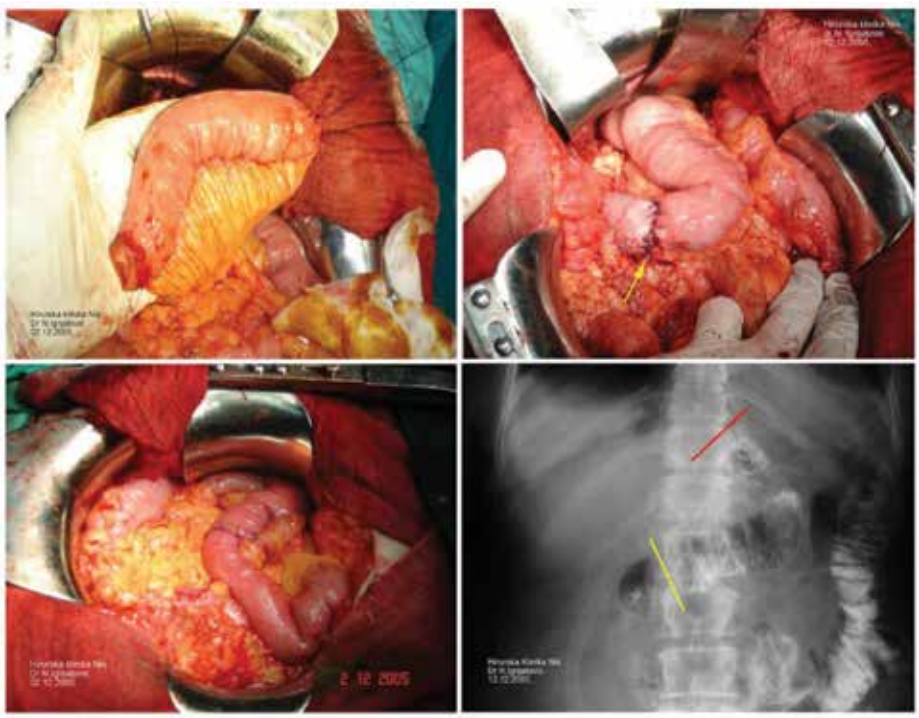

Figure 10. A representation of the operative reconstructive technique after TG with the preservation of DP by Longmire on the material of the author of this chapter: (A) isolated free jejunal segment on the vascular retina placed in a retrocolonic fashion, (B) formed end-to-end esophagojejunostomy (red arrow) and end-to-end jejunoduodenostomy (yellow arrow), (C) formed end-to-end jejunojejunostomy, (D) contrast radiography: sufficient anastomosis of esophagojejunostomy (red line) and jejunoduodenal anastomosis (yellow line).

of the intestinal continuity with the Longmire's jejunal interposition provides theoretical advantages over the reconstruction of the RY configuration [31].

3. Advantages of reconstructive procedures with preservation duodenal passage after total gastrectomy

The survival rate after TG in GC has been improved thanks to early diagnostics and advanced operating techniques. Many reconstructive techniques after TG have been developed in efforts to prevent postgastrectomy syndrome and preserve the physiological nutritional status of patients and rapid return to normal daily preoperative activities [47]. At the same time, the procedure for gastric reconstruction should be technically easily performed with minimal postoperative complications. RP that meet these requirements are those with the preservation of DP RY configuration of DT, Longmire procedure for the esophagus interposition of the jejunal segment, as well as the procedure of interposition with the jejunal pouch (e.g., Hunt-Lawrence pouch) [31].

Following a RP, the RY configuration of DT, food on the intestinal digestive pathway passes the duodenum and makes the intestinal wall distension by stimulating the ganglion cells of the myenteric and submucosal plexus, thereby leading to an adequate regulation of intestinal motility. This physical contact with the intestinal mucosa stimulates a large number of cells to produce peptides with hormonal, paracrine, and neurocrine effects. Chymus entering the duodenum primarily stimulates secretion: secretin, cholecystokinin, cholecystokinin-pancreozymin, enteroglucagon, vasoesthetic peptide, motilin, somatostatin, gastric inhibitory peptide, intestinal gastrin, serotonin, insulin, insulin glucagon, P substance, neurotensin, and enkephalin. These numerous polypeptides have a complex initial and stimulating regulatory role in the food digestion phase: bile release, gallbladder contact stimulation, Oddi sphincter relaxation, pancreatic juice secretion, vasodilation of the blood vessels of the mesentery of the intestinum and portal vein, intestinal secretion and peristalsis, absorption of food, secretion of insulin, and inhibitory effects in the interdigestive phase [48]. Kelly and authors suggest an explanation of the cause of the secondary deficiency of pancreatic secretion, inadequate stimulation, insufficient microvasculus of the heme and pancreatic enzymes, and weakened dietary fat assimilation in the new conditions of the absence of DP after TG [49]. Some non-randomized, retrospective studies have demonstrated the superiority of the performance of the jejunal interposition on the RY configuration of esophagojejunostomy when it comes to nutrition and the ability of postoperative rehabilitation [50–52]. However, due to a terminal vascular stem, the interposition of the jejunal segment as a free intestinal transplant between the esophagus and the duodenum is considered a high-risk procedure compared to other RP [53].

The nutritional status of patients after TG is changed. In many patients, calorie intake is inadequate, thus making it impossible to regain preoperative body weight. The causes of nutritional status disorders are the lack of appetite or problems caused by abnormal food passage. In order to maintain an ideal nutritional status, i.e., to preserve the integrity of the tissue and the function of the cells of the organism, nutrition requires essential nutrients and energy materials, regularity of food intake, regularity of passage and digestion, adequate resorption, and utilization of nutrients. Loss of body weight after TG is temporary and represents a significant postoperative problem in asthenic patients with GC. The mechanism of body weight loss includes malabsorption, malnutrition, and the consumption of material elements due to tissue restitution. It is known that the state of nutrition of the patient correlates with morbidity and mortality. Malnutrition usually manifests itself as a weight loss (15–24% of preoperative weight), which many authors cite in their studies in patients after TG [54]. If ingested food does not pass through the duodenum, an adequate mixture of the chymus with gallbladder and pancreatic enzymes is not formed. Therefore, the mixing of chymus and gallbladder and pancreatic contents is delayed beyond the time required for proper digestion in the distal parts of the jejunal Roux loop beneath the anastomosis with a jejunum in reconstruction without DP. Relative pancreatic insufficiency may also lead to malabsorption of patients in whom reconstruction excludes the passage of food through the duodenum [54]. Studies have shown that patients with TG who have undergone DP prevention have less loss of body weight and body mass index and have fewer symptoms as consequences of RP [55–58]. Fat and protein malabsorption occurs in over 50% of patients after total gastrectomy. In most patients, malabsorption of fat after TG is of doubtful clinical significance. The cause of steatorrhea after gastrectomy is most likely multifactorial: loss of digestive enzymes of the stomach, reduced

stimulation of pancreatic and bile secretions, inappropriate or inadequate mixing of food with bile and pancreatic juice, increased bowel motility, and excessive bacterial colonization of the small intestine. Carbohydrate absorption can be reduced by excessive bacterial colonization and the use of nonmalignant carbohydrates [57].

Postgastrectomy sideropenia anemia is caused by iron-induced malabsorption that occurs after reconstruction with the circumvention of the duodenal segment in which its resorption normally occurs. The iron resorption disorder in patients following TG is due to gastric acid deficiencies that allow the passage of nonabsorptive Fe^{2+} into the absorbent Fe^{3+} form and the removal of the duodenum as the main site of absorption of iron from the passage of the chymus [55].

In a study by Bae and authors, there were very serious deficiencies of vitamin B_{12} in patients after TG. This indicates that parenteral substitution of vitamin B_{12} in gastrectomized patients is necessary due to inadequate absorption in the intestines. The serum level of vitamin B_{12} was significantly reduced after TG and is believed to be due to its deficiency in absorption. Bae also pointed out that anemia due to deficiency of vitamin B_{12} is a process that develops within a few years [54].

The term postgastrectomy bone disease describes bone disease after TG. It can occur as an osteomalacia or osteoporosis that is more pronounced than in normal physiological aging. Postgastrectomy bone disease is probably due to RP after TG in which the duodenum and proximal jejunum from food passage are excluded, since they are the major sites for the absorption of calcium in physiological conditions [59]. Calcium absorption is primarily performed in the duodenum and jejunum and depends on the level of vitamin D [60]. Accelerated transit of food through the intestinum also reduces calcium absorption time, while the presence of steatorrhea leads to the formation of insoluble calcium soaps that can contribute to calcium malabsorption [59].

Liedman reported in his study that a significant increase in alkaline phosphatase levels in patients after 3–10 years after TG, in a group of patients with a RY RP [61]. Heiskanen and authors have reported that the serum level of alkaline phosphatase has been used to detect postgastrectomic osteomalacia. In other prospective studies after partial gastrectomy and TG, normal and elevated serum levels of alkaline phosphatase were observed [62]. In a group of patients with reconstructed RY configurations in the study of Iivonen and authors, serum alkaline phosphatase activity increased significantly over the course of 3 postoperative years with a tendency to be higher than the group of patients with DP preservation [63].

Bassotti and authors were probably the first to examine the intestinal motility of the Roux loop after a complete gastrectomy by manometric route and concluded that patients with reconstruction of the Roux-en-Y configuration had significant motor abnormality in the Roux loop [64]. Sun and authors in their study claimed that the continuity of the gastrointestinal tract plays a key role in the coordination of intestinal motility [65]. Studies have shown that surgical manipulation of the gastrointestinal tract, in the form of resection followed by reanastomosis, results in intestinal motility disturbance [47, 64]. In support of this assertion, several studies suggest that the interruption of motility due to gastrointestinal resection is actually due to damage to the pacemaker for the gastrointestinal tract, i.e., interstitial cell of Cajal (ICC). The ICC is responsible for the creation and propagation of slow electrical waves that coordinate the stages of contraction of the intestine [65]. The entire problem of postgastrectomy symptoms

may be attributed to accelerated intestinal transit. Fast transit results in accelerated glucose uptake, which causes increased insulin secretion. Accelerated transport of peptides and lipids gives an unusually large incentive to the secretion of cholecystokinin and stimulation of feedback regulation. In the end, there are abnormally high levels of gastrointestinal hormones and increased production of somatostatin. Excreted somatostatin has an inhibitory effect on GUT hormones, but this further reduces bowel motility and digestive juice production. This entire phenomenon becomes less significant in time due to the adaptation of the intestine [66].

Several studies have shown that the presence of postprandial hyperglycemia following TG reconstruction can indicate an abnormal glucose metabolism, possibly representing intolerance to glucose or diabetes at an early stage [43]. In relation to the type of RP, Schwarz and authors have found significantly higher levels of glucose in a patient with RY reconstruction, when there was no DP preservation in patients with pouch, as opposed to patients undergoing a RP in which DP was preserved. There was no development of pathological glucose tolerance in patients with established DP prevention [43]. Kalmár and authors have published significantly higher levels of postprandial glucose in patients with exclusion of DP RY reconstruction than the control group, thus supporting the hypothesis that the exclusion of DP disrupts homeostasis of glucose more than reconstruction with the preservation of DP [66]. Observing duodenal preservation, the glucose homeostasis disorder was significantly higher in patients with RY procedure [65].

With the standardization of TG performance due to GC, the survival period of operative patients has significantly increased and hence the possibility of postgastrectomy syndrome. The causes of the postgastrectomy syndrome can be hypocaloric food intake, exclusion of duodenal passage, loss of absorption surface, lack of peptic digestion, excessive bacterial colonization, and the occurrence of exocrine and endocrine pancreatic insufficiency [57]. Symptoms related to food intake due to abnormal transit reported in several studies relate to the onset of early and late dumping syndrome, alkaline reflux, pyrosis, loss of appetite, feeling of satiety and fullness, epigastric pain, meteorism, dysphagia, and diarrhea [67]. Schwarz and authors, as well as Zherlov and authors, have shown in their studies that reconstruction in which DP is preserved has a lower incidence of postgastrectomy symptoms [43, 68]. Persistent postprandial discomfort and fullness may be to some extent due to poor receptive adaptation of the proximal part of the small intestine. In addition to poor receptive adaptation of the proximal part of the small intestine, the distal end of the Roux loop can also act as a functional obstruction, which leads to Roux-stasis syndrome, which is characterized by epigastric pain, nausea, and vomiting, and is most likely due to the lack of motor function in the distal region Roux loop [57, 69].

The lack of gastric acid after TG and altered intestinal motility in reconstruction with RY configuration with or without pouch seems to lead to bacterial colonization, which may be one of the main causes of malnutrition after TG. Excessive bacterial growth leads to the formation of damage to the mycelium and decongestion of bile salts. Several mechanisms blame for malabsorption of fat: loss of gastric emulsification of triglycerides, rapid food passage, and pancreatic stimulation disorder [63].

The overall impact of many symptoms after a RP can be summarized in the health quality of life. The quality of life is a multidimensional approach that consists of functional, emotional,

physical, and social aspects, as well as from subjective disease symptoms and adverse effects of therapy. Controlling gastrointestinal symptoms seems important in an attempt to reduce damage to quality of life [70]. In their study, Hoksch and authors confirmed that reconstruction with the preservation of DP is the most optimal procedure in improving the quality of life of patients after TG [58].

4. Conclusion

TG is widely used as a major surgical treatment for GC. TG results in risk of postgastrectomy syndrome, such as weight loss, dumping syndrome, biliary reflux esophagitis, and a reduction in the quality of life [3, 4]. The ideal RP after TG should replace all lost functions of the stomach, provide an optimal enough reservoir that can accommodate to the size of the meal, prevent reflux, ensure strong propulsion of equal-sized boluses of chyme entering the duodenum, and respond properly to the changing levels of gastrointestinal hormones and neural information [7]. The choice of RP should ensure good digestive function to prevent persistent postgastrectomy syndrome. Preservation of duodenal transit with replacement of the jejunal segment, the so-called physiological route, is now believed to be preferential for postoperative nutritional condition. RP which allow DP should be regarded as a key to physiological reconstruction.

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Conflict of interest

The authors declare no conflict of interest.

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Chapter 2

Laparoscopic Endoscopic Cooperative Surgery: Current Status and Perspective

Shunsuke Sakuraba

Additional information is available at the end of the chapter

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Abstract

Laparoscopic endoscopic cooperative surgery (LECS) is now performed worldwide as a result of the invention of new operative techniques. It is seromuscular resection by laparoscopy for gastric submucosal tumors such as gastrointestinal stromal tumors (GISTs). Endoscopic dissection of the mucosal to the submucosal layer determines the appropriate incision line, resects the tumor, and closes the visceral wall defect. Various minimally invasive LECS techniques are now well established. LECS-associated techniques, adaptation of them, and challenges for the future are reviewed in this chapter.

Keywords: LECS, SMT, GIST

1. Introduction

In the last decade, LECS has been performed all over the world in association with the invention of new operative techniques. Approaches are grouped into three major categories: laparoscopy-assisted endoscopic resection (LAER) in which resection is performed primarily by the endoscopic team under laparoscopic control; endoscope-assisted laparoscopic resection (EALR), where the laparoscopic teams perform the resection under endoscopic monitoring; and combined laparoscopic endoscopic resection (CLER), which is performed by the laparoscopic and the endoscopic teams. Description of these approaches and the details about CLER, especially LECS, nonexposed endoscopic wall-inversion surgery (NEWS), and a combination of laparoscopic endoscopic approaches to neoplasia with a nonexposure technique (CLEAN-NET) are described in the following chapters. Various LECS techniques for GIST are recently established, and the application of this approach to early stage gastric cancer, which is difficult to resect with the ESD technique because of severe scars or ulcers, is described. LECS for other

organs such as the duodenum or colorectum is also being attempted, but only with expert technique and specialist knowledge. LECS plus biopsy of sentinel lymph node for early gastric cancer is planned as a clinical trial.

1.1. Laparoscopy-assisted endoscopic resection

Endoscopic resection is performed under laparoscopic control [1–3]. The endoscopist performs an endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) with laparoscopic assistance (**Figure 1**). Laparoscopic support has many advantages. First, when accidental complications such as perforation or massive bleeding occur during the endoscopic resection, laparoscopic surgeons can treat them immediately. Second, if the endoscopist has difficulty in resecting the tumor as a result of tumor location, the laparoscopic team can reposition the stomach with manipulation of the serosal side. Although laparoscopy-assisted endoscopic resection (LAER) requires a laparoscopic team and general anesthesia in addition to endoscopy, the advantage is greater safety; therefore, perforation risk is high in ESD because of massive tumor or duodenal location, LAER is preferred. Irino et al. reported LECS for duodenal tumors in three patients using LAER, demonstrating feasibility of this approach [4]. A unique point of their method is that the laparoscopist places seromuscular sutures to reinforce the thinned duodenal wall in order to prevent postoperative perforation or bleeding. Seromuscular reinforcement is performed for all cases. As such, these techniques can be grouped into the CLER. The perforation rate for duodenal-ESD is still much higher than for gastric-ESD, esophageal-ESD and colorectal-ESD [5–10], so LAER or CLER are good alternatives.

1.1.1. Endoscope-assisted laparoscopic resection

In this category, laparoscopic surgeons mainly resect the tumor with endoscopic support as follows:

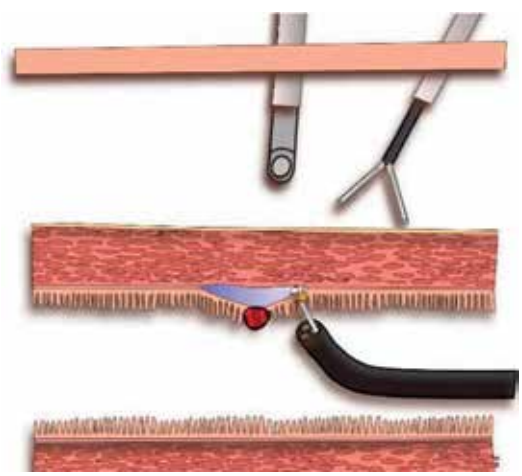


Figure 1. The endoscopist performs an endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) with laparoscopic assistance.

1. Endoscope-assisted wedge resection:

Under endoscopic monitoring, tumor location is confirmed, and blood vessels in the excision area around the tumor are prepared and if necessary the omentum is dissected, and the greater curvature of the stomach is mobilized by the laparoscopist. Several seromuscular sutures are placed around the lesion (**Figure 2**) and by pulling the stitches upward with laparoscopic forceps (**Figure 3**), the tumor is removed with laparoscopic linear stapling devices (**Figures 4** and **5**). According to laparoscopic surgeons, the staple line can be reinforced with a hand sewing suturing. The abovementioned technique is the most commonly combined surgery in the world, with more than 500 cases published [11–17]. Although the complication rate is 0–3% [11], the main problem can be excessive gastric resection by the laparoscopic linear stapling devices resulting in transformation or stenosis.

2. Endoscope-assisted laparoscopic transluminal (transgastric) surgery:

When the tumor is located along the posterior gastric wall, it is difficult for the laparoscopist to obtain a visual field, so a transgastric technique is often used. Under endoscopic monitoring, the laparoscopic surgeons make an incision in the anterior abdominal wall (**Figures 6** and **7**). The laparoscopic team directly confirms the lesion and removes it with

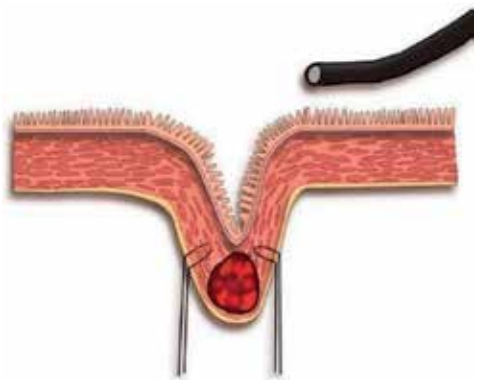


Figure 2. Several seromuscular sutures are placed around the lesion.

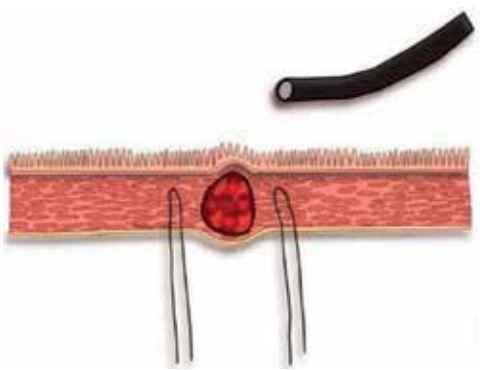


Figure 3. Surgeons pull the stitches upward with laparoscopic forceps.

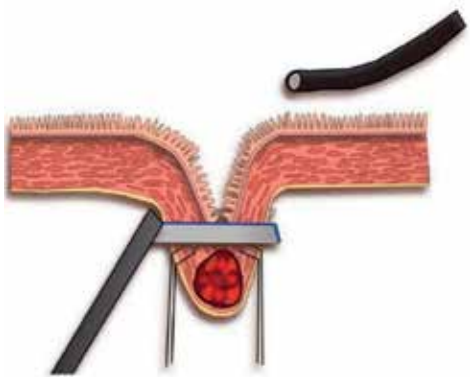


Figure 4. The appropriate incision line is determined under endoscopic monitoring.

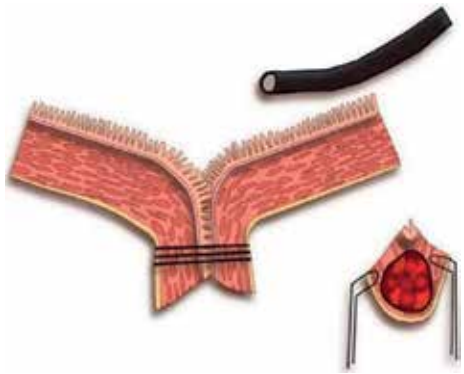


Figure 5. The tumor is removed with laparoscopic linear stapling devices.

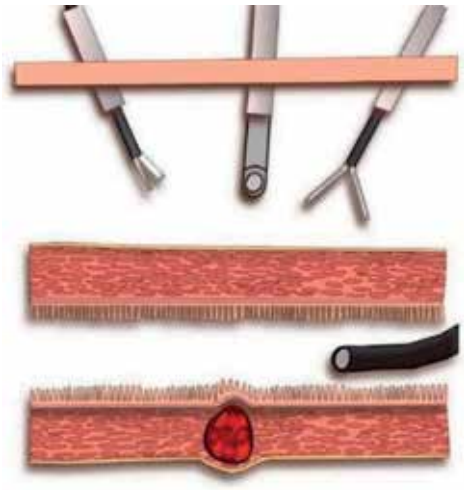


Figure 6. The tumor is located along the posterior gastric wall.

an inverted wedge resection using laparoscopic stapling devices. The opened gastric wall is closed with laparoscopic staplers or hand sewing sutures.

3. Endoscope-assisted laparoscopic intraluminal (intragastric) surgery:

Indication for this technique is the same as for transgastric surgery approaching the posterior gastric wall. This technique was first reported by Ohashi et al. in [18], and a modified procedure was described by Dong et al. in [19]. All laparoscopic trocars are placed in the gastric cavity, penetrating both the abdominal and stomach walls. All trocars are fixed with balloon inflation of the stomach and the abdominal wall (**Figures 8** and **9**). The laparoscopist secures a visual field in the gastric lumen, and the tumor is removed by full-thickness resection or laparoscopic stapling devices. The trocar holes are closed with sutures or clips. **Figures 1–9** are excerpted from Dimitrios's report.

Figure 7. The laparoscopic surgeons make an incision in the anterior abdominal wall.

Figure 8. It is difficult for laparoscopist to approach the tumor.

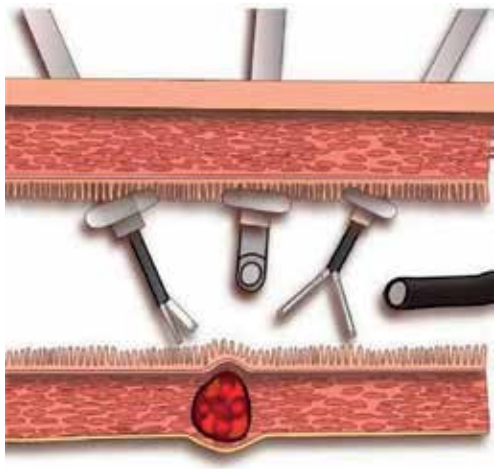


Figure 9. All laparoscopic trocars are placed in the gastric cavity, penetrating both the abdominal and stomach walls. All trocars are fixed with balloon inflation of the stomach and the abdominal wall. The **Figures 1-9** are excerpted from Dimitrios's report.

2. History of the LECS technique

Although surgical local resection with laparotomy or laparoscopic surgery is performed for gastric submucosal tumor (SMT), it is difficult when tumors are small or have an intramural growth pattern. It is difficult to determine the appropriate incision line from the abdominal cavity side, so excessive gastric resection might result in transformation or stenosis. LECS is a newly developed technique, first reported by Hiki et al. in [20] for local resection of GIST. This procedure is further categorized into CLER, which is an approach that combines ESD and laparoscopic gastric resection to determine the incision line, to resect the tumor and to close the stomach wall. As LECS can minimize the resected region and preserve the function of the stomach after surgery, the procedure was added to the national insurance list in Japan in 2014, and subsequently rapidly diffused throughout the surgical community [21–24]. Further applications of LECS then developed, so the first version is named classical LECS to distinguish it from subsequent modified LECS techniques. Classical LECS involves whole layer resection using laparoscopy and endoscopy. However, this technique may lead to contamination of and seeding of tumor cells into the peritoneal cavity, especially when the tumor is associated with an ulcer or epithelial lesion. To prevent peritoneal spread, modified LECS procedures now include inverted LECS with crown method [25], nonexposed endoscopic wall-inversion surgery (NEWS) [26] and a combination of laparoscopic endoscopic approaches to neoplasia with a nonexposure technique (CLEAN-NET) [27].

3. Classical LECS

Hiki et al. first reported classical LECS in 2006 [20] for local resection of GISTS in order to prevent excessive gastric resection followed by transformation, stenosis or stasis of food after surgery. In classical LECS, the incision line is determined by the endoscopist, and an

endoscopic mucosal incision is made. Artificial perforation is performed by endoscopic forceps, and the seromuscular layer is dissected using laparoscopic and endoscopic forceps. The gastric wall defect is closed with laparoscopic stapling devices. Hiki described his LECS procedure in detail, and the following are excerpted from his writing.

1. "Tumor location was confirmed by intraluminal endoscopy." (**Figure 10**)
2. "Blood vessels in the excision area around the tumor were prepared by laparoscopy." (**Figure 11**)
3. "Endoscopic submucosal resection around the tumor and artificial perforation was performed." (**Figure 12**)
4. "Operation device was inserted into the perforation hole, and seromuscular dissection began by laparoscopy." (**Figure 13**)

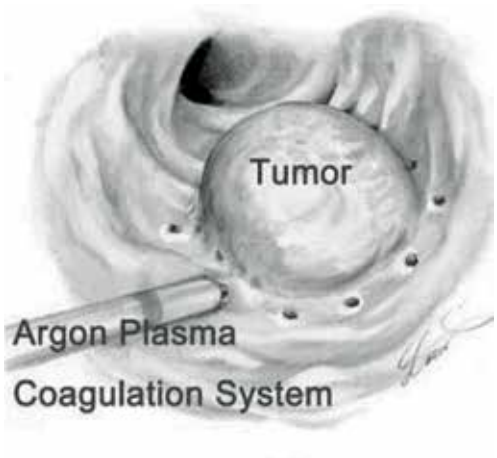


Figure 10. Tumor location was confirmed by intraluminal endoscopy.

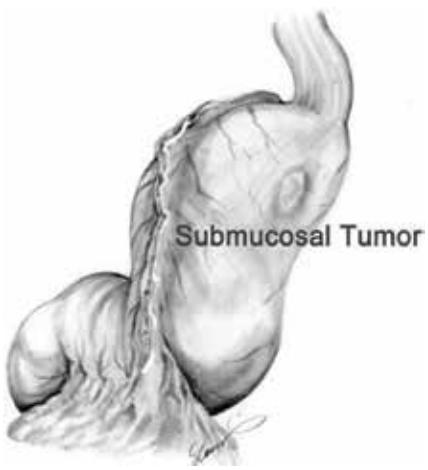


Figure 11. Blood vessels in the excision area around the tumor were prepared by laparoscopy.

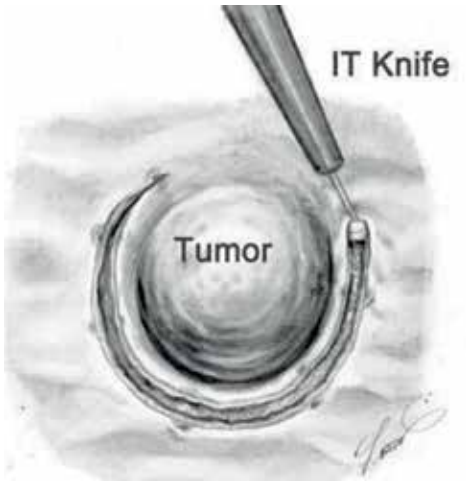


Figure 12. Endoscopic submucosal resection around the tumor and artificial perforation was performed.

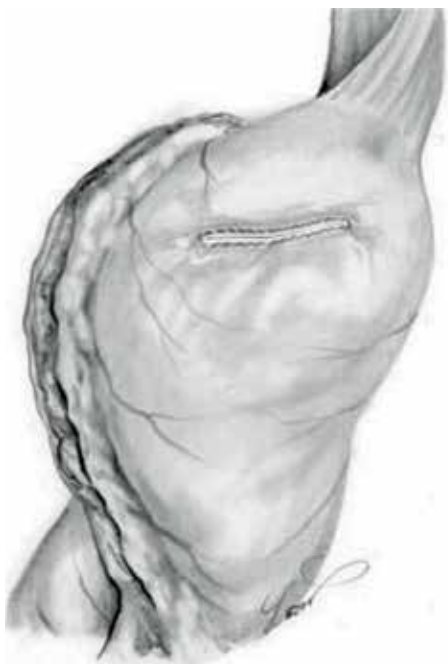


Figure 13. Operation device was inserted into the perforation hole, and seromuscular dissection began by laparoscopy.

5. "After resecting the tumor, the incision line was closed using laparoscopic stapling devices." (**Figures 14** and **15**). **Figures 10–15** are excerpted from Hiki's report.

Although modified LECS techniques are used, the Hiki procedure is a basic concept that is employed throughout low invasive surgery for GISTs. By minimizing the resected region,

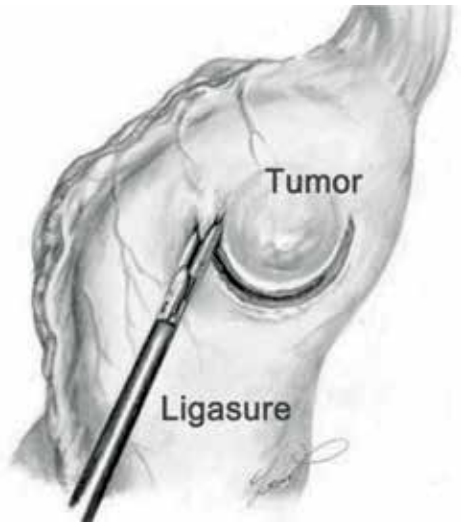


Figure 14. After resecting the tumor, the incision line was closed using laparoscopic stapling devices.

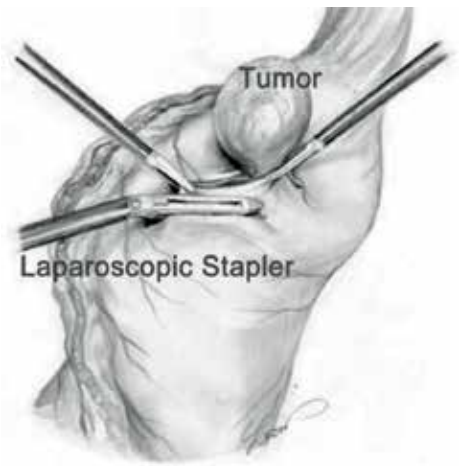


Figure 15. LECS technique can minimize the resected region. The **Figures 10-15** are excerpted from Hiki's report.

LECS makes it possible to preserve the postoperative function of the stomach. Hiki maintains that removal of the tumor must be performed carefully with a specimen retrieval bag in order to prevent peritoneal and port-site dissemination of tumor.

4. LECS with crown method

In order to reduce the transmural communication during the operation, Nunobe et al. reported the crown method and inverted LECS [25]. By pulling up the incision line of the stomach with

several stitches, abdominal cavity contamination is prevented. This technique was named crown method because pulled-up stomach wall looks like a crown (**Figure 16**). Using the traction of the stitch, the resected specimen is inverted to the intragastric cavity. This technique

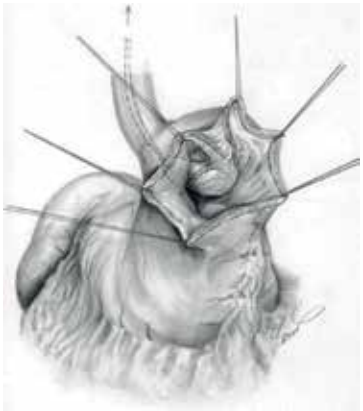


Figure 16. Surgeons pull up the incision line of the stomach with several stitches and pulled up stomach wall looks like a crown.

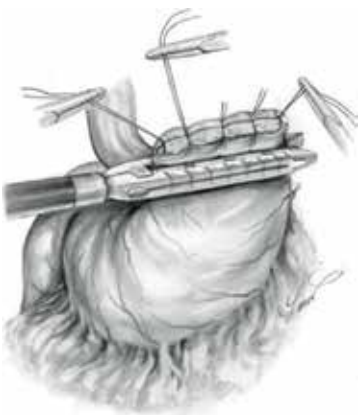


Figure 17. The stitches are also used as a supporting tool when the incision line is closed with a laparoscopic stapling device. The **Figures 16** and **17** are excerpted from Nunobe's report.

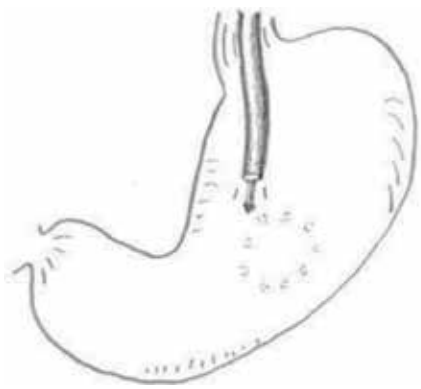
was named inverted LECS. Inverted LECS with crown method is not only useful for preventing tumor seeding into peritoneal cavity, but also for securing the visual field during the operation. The stitches are also used as a supporting tool when the incision line is closed with a laparoscopic stapling device (**Figure 17**). Although nonexposed endoscopic wall-inversion surgery (NEWS) [26] and a combination of laparoscopic endoscopic approaches to neoplasia with a nonexposure technique (CLEAN-NET) [27] are described later as nonexposure procedures, inverted LECS with crown method has few limitations such as tumor size or tumor location in comparison with NEWS or CLEAN-NET. As such, it can make it possible

to remove the tumor without the contamination of abdominal cavity. **Figures 16** and **17** are excerpted from Nunobe's report.

5. NEWS

Classical LECS with crown method is an improved technique that reduces the risk of cancer cell dissemination. However, it can be difficult to completely prevent the contamination because of transmural communication during the procedure. Nonexposed endoscopic wall-inversion surgery (NEWS) was first reported by Goto et al. in 2011 with the goal of minimizing transmural communication during the operation [26]. They performed NEWS in an *ex vivo* porcine model and described the usefulness of this procedure. By inverting the tumor into the inside of the stomach without opening the gastric lumen, complete resection with nonexposure was achieved. The procedure is as follows:

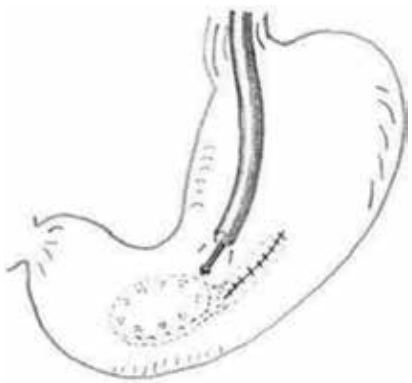
1. "Markings around a model lesion are made with electrocautery knife."



2. "A circumferential seromuscular incision is made from the outside."

3. "The muscle layer is linearly sutured at approximately 5 mm intervals with the lesion inverted into the inside."

4. "A circumferential mucosubmucosal incision is performed from inside with electrocautery knife guided by the endoscope." These figures are excerpted from Goto's report.

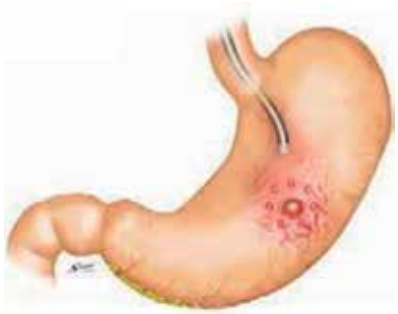


He reported NEWS for three lesions (one anterior wall, one lesser curve and one posterior wall of the gastric body) using porcine stomach, and complete resection was achieved for all lesions safely and without perforation or air leakage. Nonexposure techniques such as NEWS and CLEAN-NET are adequate for SMT without ulceration as well as SMT with ulceration or even early gastric cancer. In his report, the maximal specimen size was 50 mm; however, there is a limit of removable tumor size. Because the resected tumor is removed through the pharynx by the endoscope, solid tumor such as GIST over 30 mm is thought to be difficult to retrieve.

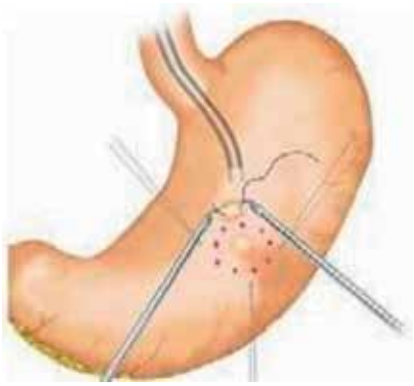
6. CLEAN-NET

A combination of laparoscopic endoscopic approaches to neoplasia with a nonexposure technique (CLEAN-NET) was first reported by Inoue et al. in [27]. This procedure also involves a nonexposure technique like NEWS, but with a difference. By preserving the continuity of the mucosa, the mucosa works as a barrier (a clean net), to prevent abdominal cavity contamination and seeding of tumor cells into the peritoneal cavity. The specimen is lifted from the peritoneal cavity, so it is retrieved laparoscopically. Inoue actively performs endoscopic and laparoscopic full-thickness resection for not only GISTs but also for early gastric cancer. The procedures are described below.

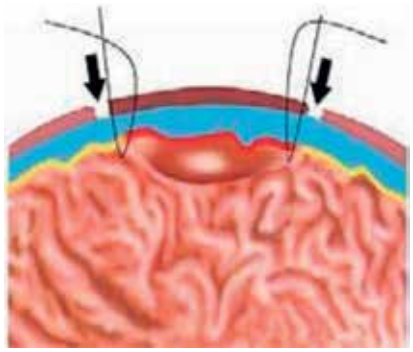
1. "Endoscopic markings are placed on the surrounding mucosa of the lesion with electrocautery knife."



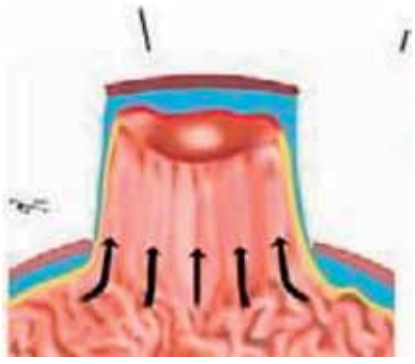
2. "The mucosal layer is fixed onto the seromuscular layer using four stay sutures."



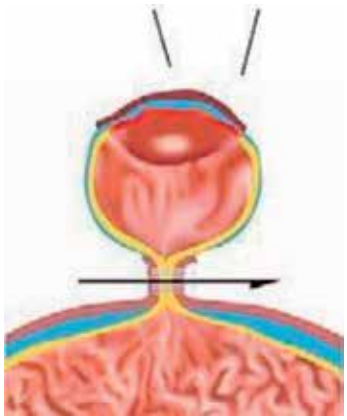
3. "By pulling four stitches upward with laparoscopic forceps, selective seromuscular dissection outside the four stiches is performed using a laparoscopic electrocautery knife."



4. "A full-layer specimen is lifted by four stay sutures. This process allows a wider cancer-free margin around a full-thickness lesion."



5. "A full-layer resection using a mechanical stapler is performed and the resected tumor is removed from abdominal cavity side." These figures are excerpted from Inoue's report.



The abovementioned procedure with nonexposure technique is advantageous for epithelial tumor and GIST with ulceration. CLEAN-NET also makes it possible to secure a sufficient margin around the tumor and to resect lymph nodes together with the tumor if it is located at either the lesser or greater curvature of the stomach. Because the CLEAN-NET procedure needs the process that the mucosal layer stretches without breaking apart, a large tumor is thought to be difficult to resect.

7. Laparoscopy-assisted endoscopic full-thickness resection

This technique was reported by Abe et al. in [28]. The same procedure as LECS technique is applied; however, the endoscopist plays an important role in resecting the tumor. The endoscopic team starts full-thickness resection around the tumor, and after two-thirds of the resection is performed, the laparoscopic team finishes the full-thickness resection with laparoscopic devices.

7.1. LECS for duodenal tumors

There are some limitations with LECS for removal of duodenal tumors. First, anatomical elements such as the pyloric ring, Vater's papilla and the third to fourth portion make it difficult to perform. Second, there are a few reports of lymph node metastasis from submucosal invading duodenal cancers or carcinoids, so partial resection is controversial. Small submucosal tumors, duodenal adenomas, or intramucosal carcinomas at duodenal bulb or the opposite side of the papilla are indications for LECS. The basic concept of gastric LECS also applies to duodenum LECS [4, 29]. The difficulty in mobilizing organs and closing the defected walls needs to be advanced.

7.2. LECS for colorectal tumors

LECS for colorectal tumors is not often used. We rarely experience GISTs in the colorectum, and in many cases the laparoscopist must achieve adequate mobilization which may be difficult in colorectal-LECS. Some researchers have reported the laparoscopy-assisted endoscopic resection (LAER) for colorectal tumors [30–32], and as the combined laparoscopic endoscopic resection (CLER). Fukunaga et al. reported LECS for laterally spreading colorectal tumors, which are difficult to resect by the ESD technique because of submucosal fibrosis or multiple surrounding diverticula [33] (**Figures 18** and **19**). He suggested several concerns about his technique: limitation for tumors located on the mesenteric side, strictures after surgery, and contamination of the abdominal cavity by bowel contents. He proposed several adjustments in his report. Indications for colorectal LECS are the same as for colorectal ESD. Tumors that would be difficult to resect endoscopically are good indications for both. **Figures 18** and **19** are excerpted from Fukunaga's report.

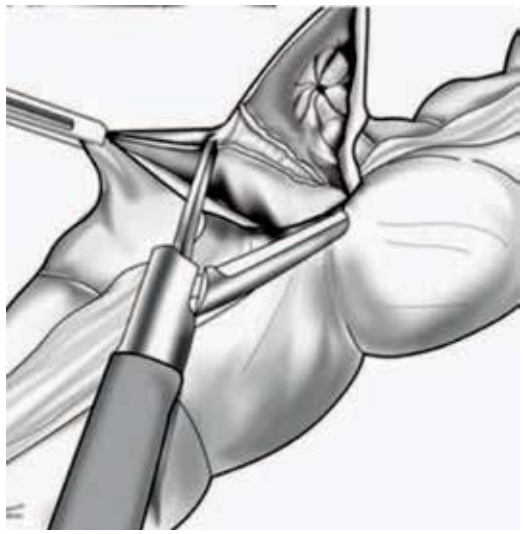


Figure 18. A laparoscopic coagulating system is used to dissect the full thickness of the colon wall along the submucosal line created by endoscopic dissection.

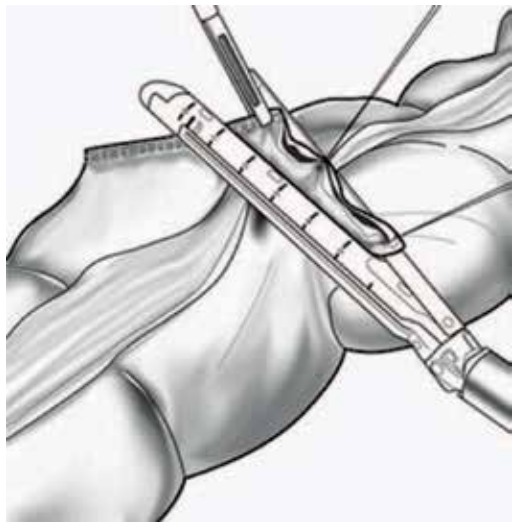


Figure 19. The incision line was closed using laparoscopic stapline devices. The **Figures 18** and **19** are excerpted from Fukunaga's report.

7.3. LECS plus biopsy to sentinel lymph node for early gastric cancer

The application LECS has progressed from resection of gastric submucosal tumors to early stage gastric cancer. The current therapeutic adaptation is for removal of low-risk lymph node metastases. Further, there still remains the possibility of lymph node metastasis in treating

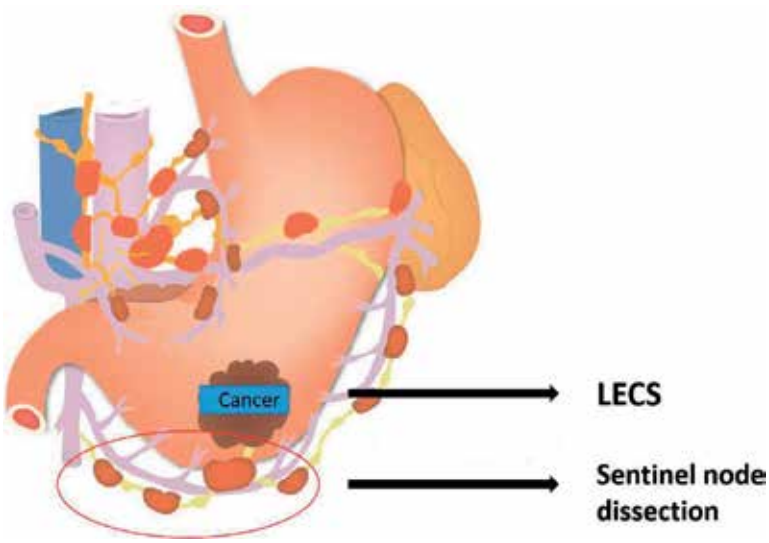


Figure 20. By combining LECS technique and sentinel node biopsy, LECS with lymph node dissection might become possible in the future.

gastric cancer. On the other hand, some researchers reported the utility of sentinel node biopsy in patients with gastric cancer [34–36]. Although gastric lymphatic drainage is often complicated, by using the dual tracer method with radiolabeled tin colloid and blue dye, Kitagawa reported that the sentinel node detection rate was 97.5% (387 of 397) and the accuracy of nodal evaluation for metastasis was 99% (383 of 387) in cT1 and tumors <4 cm [36]. These facts implicate that by combining LECS technique and sentinel node biopsy, LECS with lymph node dissection might become possible in the future (**Figure 20**). More research and clinical trials about LECS and biopsy to sentinel lymph node for early gastric cancer are expected.

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Chapter 3

Reconstruction after Laparoscopic Distal Gastrectomy

Satoshi Kanda and Tetsu Fukunaga

Additional information is available at the end of the chapter

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Abstract

Laparoscopy-assisted distal gastrectomy (LADG) has advanced much in the past 10 years in the eastern countries, due to the high gastric cancer incidences. Reconstruction is the major hurdle for perfect laparoscopic distal gastrectomy (LDG). Initially, hand-associated or small incisional open laparotomy reconstruction, the so-called associated operation, was performed. A full laparoscopic operation is much better for the patient—small wound, less pain, and quick recovery. Several reconstruction methods have been developed by experts during more than 10 years. The question of what method is the best after distal gastrectomy is still controversial. This chapter focuses on the reconstruction methods in the total laparoscopy distal gastrectomy (LDG) operation, explains the merits and demerits of several methods, and introduces our original method, named augmented rectangle technique (ART).

Keywords: LDG, Billroth I and II, R-Y, delta, ART

1. Introduction

Gastric cancer operations have the most impact on food intake and body weight loss, resulting in more changes in patient's circumstances than any other surgery [1–3]. Its morbidity and mortality are, respectively, ranked fifth and third in the world—with the incidence in China, Japan, and Korea, the highest in the world. Even now, with chemotherapy and immunotherapy well progressed, surgery is still required for the curable treatment for that cancer [4, 5].

Laparoscopy-assisted distal gastrectomy (LADG) with gastroduodenostomy for early gastric cancer was first reported in 1994 by professor Kitano. Initially, hand-associated or small incisional open laparotomy reconstruction, the so-called associated operation, was performed. Full laparoscopic operation is much better for the patients, due to small wound, less pain, and quick recovery. According to the 12th Nationwide Survey of Endoscopic Surgery in Japan, in

2013, 52.7% of patients who underwent distal gastrectomy underwent laparoscopic surgery [1]. After distal gastrectomy, several reconstruction methods are available, and the choice of reconstruction is usually dependent on surgeons or institutions. There are three famous reconstruction methods, Billroth I and II and Roux-en-Y. Studies comparing gastroduodenostomy with gastrojejunostomy are still lacking and inconsistent; therefore, controversy remains regarding which method is the best after distal gastrectomy.

Billroth I gastroduodenostomy is one of most common reconstruction methods, and it offers advantages such as the following: (1) it is the only way to preserve the physiological root of the food passing through the duodenum, (2) it has technical simplicity during open surgery, and (3) it confers a lower incidence of internal hernia or adhesions. However, the risk of anastomotic failure is higher, and the laparoscopic gastrointestinal anastomosis involves a high degree of difficulty. Of course, if the size of gastric remnant is too small, Billroth I reconstruction cannot be done. These methods for total laparoscopic operation are the most difficult and have developed by experts during more than 10 years.

Billroth II gastrojejunostomy shares some pros and cons with the Billroth I and Roux-en-Y methods. It enables a wide stomach resection without anastomotic tension and is relatively easy during laparoscopic surgery. However, postoperative bile reflux into the remnant stomach is more frequent, and, although rare, afferent loop syndrome can develop.

Roux-en-Y gastrojejunostomy prevents bile reflux [1]. Other advantages over Billroth I are as follows. It is acceptable if the gastric remnant is too small to perform Billroth I, and there is less anastomotic tension. However, the high incidence of Roux stasis syndrome is one of its major drawbacks and, although rare, leakage of duodenal stump is a severe complication.

2. Billroth I

Billroth I is the most common and physiological reconstruction method after distal gastrectomy. For laparoscopy-assisted distal gastrectomy (LADG), Billroth I reconstruction can be performed by an extracorporeal or intracorporeal method. Initially, hand-associated or small incisional open laparotomy reconstruction, so-called associated operation, was performed. Due to an increasing number of laparoscopic gastrectomies, the laparoscopic technique has become possible for total laparoscopic distal gastrectomy (TLDG). This portion describes old extra-methods and new intra-methods.

2.1. Extracorporeal Billroth I anastomosis

Extracorporeal Billroth I anastomosis has several merits when compared to intracorporeal anastomosis. Tumor location is identified by palpitation. It is easily and rapidly performed like conventional open surgery, and it uses fewer staples than the intracorporeal anastomosis. For the problem of the cost, extracorporeal Billroth I is still the most common reconstruction method for LADG. Additionally, extracorporeal anastomosis is a procedure that should be considered as the first choice in view of safety in the inexperienced facility learning laparoscopic gastrectomy.

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2.1.1. Extracorporeal hemi-double stapling technique

After lymph node dissection, a 4–6 cm minilaparotomy is made at the upper midline (**Figure 1**) [6]. The stomach is pulled out of the peritoneal cavity through the small incision, which is applied by a wound retractor (**Figure 2**). A purse-string instrument is applied to the duodenum distal to the resection line. A Lister forceps is applied just proximal to the purse-string clamp, and the duodenum is transected between the two clamps (**Figure 3**). The duodenal stump is unclamped and held by Alice forceps equally at three points. An anvil is inserted into the duodenal stump, and a purse-string suture is tied over the anvil (**Figure 4**). Then, the duodenal stump is returned to the abdominal cavity; at this time, the purse-string suture thread is clamped without cutting it, leaving the clamp outside of the abdominal cavity. The greater curvature side of the proximal resection margin is transited with an 80-mm linear stapler (**Figure 5**). Thereafter, an entry hole is made along the lesser curvature side of the previous staple line at the disbanded of 3 cm to the lesser curvature; the shaft of the circular stapler is introduced into the gastric remnant through the gastrostomy (**Figure 6**). The shaft is rotated toward the duodenum with the distal stomach, and then the trocar is advanced to penetrate the corner of the stapling line at the greater curvature (**Figure 7**). The trocar is connected to the anvil placed in the duodenum. The instrument is closed and fired, completing the end-to-end gastroduodenostomy. After checking for bleeding at the anastomotic line, the lesser curvature side of proximal resection margin is transected with another linear stapler (**Figure 8**).

2.1.2. Extracorporeal end-to-side posterior wall method

The distal gastrectomy procedure is the same as for the abovementioned method [6]. For resection of the proximal margin, the stomach is transected 5 cm from the greater curvature to the middle of the planned resection line using two clamps, and the remaining proximal resection is done using an 80-mm linear stapler. After distal gastrectomy, the head of the circular stapler is inserted into the remnant stomach through the opening of the greater curvature side of the proximal resection, which was temporarily clamped. The trocar is advanced

Figure 1. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 1.

to pass through the posterior wall of the remnant stomach and then coupled on the anvil placed in the duodenum. The device is closed and fired, completing the end-to-side gastro-duodenostomy. Finally, the opening in the remnant stomach is shuttered using an additional linear stapler.

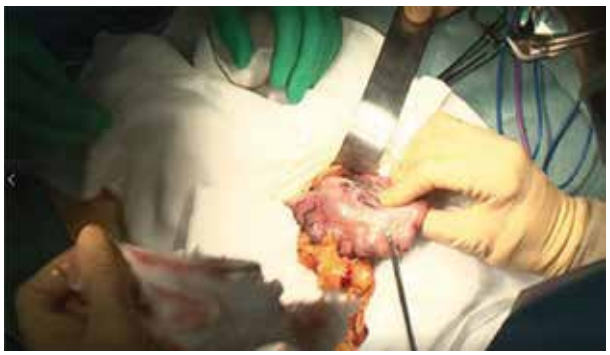

Figure 2. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 2.

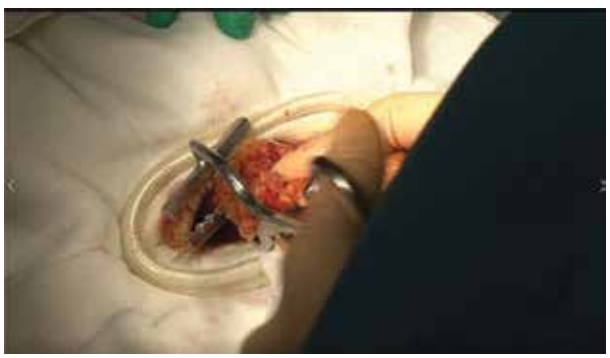

Figure 3. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 3.

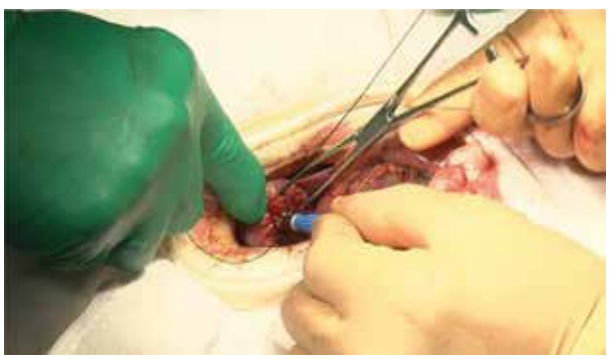

Figure 4. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 4.

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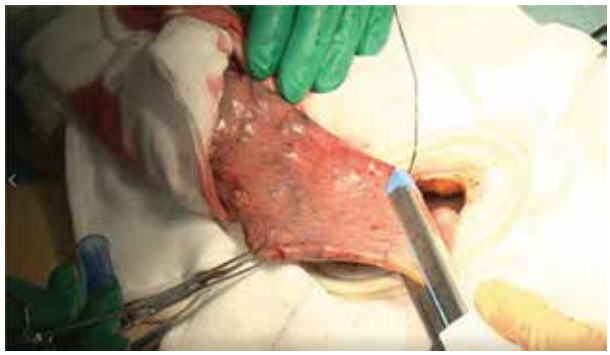

Figure 5. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 5.

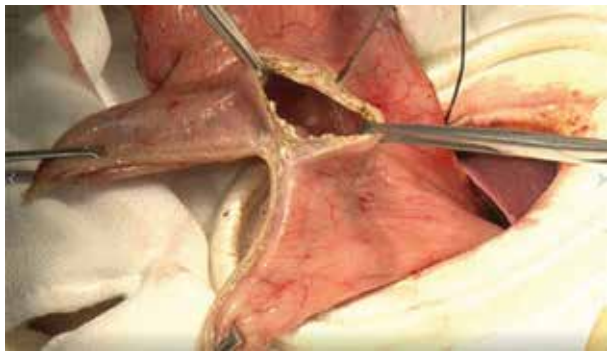

Figure 6. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 6.

Figure 7. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 7.

In this method, there is no overlap between the liner stapler and circular stapler, which is said to be likely to cause anastomotic leakage in general, but the possibility of an ischemic area remaining between the liner stapler and the circular stapler is considered a problem. In order to avoid this complication, it is said to set the place to puncture the back wall ten from liner stapler, but then the "dog's ear" deformation remains widely.

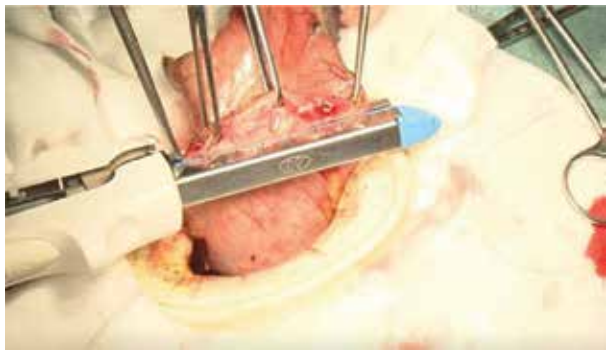

Figure 8. Extracorporeal hemi-double stapling technique – depiction of procedure as described in the text, step 8.

2.2. Intracorporeal Billroth I anastomosis

2.2.1. Delta-shaped anastomosis

The delta-shaped anastomosis originally created by Professor Kanaya is a functional end-to-end gastroduodenostomy technique using endoscopic linear staplers [7].

For the duodenal bulbus resection, the direction of the stapling is more vertical than the mesenteric-antimesenteric direction. End-to-end anastomosis is done vertically to maintain an enough blood supply to the anastomosis and to preserve a space for the jaw of 45-mm linear stapler to be inserted into the entry hole. Before stapler firing, the staple line on the remnant stomach is rotated to the left side, and the staple line on the duodenal stump is rotated to the right side to form a side-to-side gastroduodenostomy between the posterior wall of the remnant stomach and the posterior wall of the duodenum. After firing the stapler, a relatively large entry hole is made, and the operator checks for anastomotic bleeding through this hole. After transient approximation of the entry hole with clips, the hole is closed by two consecutive firings of a 45-mm liner stapler.

2.2.2. Intracorporeal triangular anastomotic technique (INTACT)

The other intracorporeal anastomosis method, novel intracorporeal triangular anastomotic technique, was reported by Omori et al. [8].

After all dissection of lymph nodes is finished, the stomach and duodenal bulb are staple-transected parallelly, and the resected stomach with dissected LNs is retrieved through the umbilical incision. Small entry holes are made on the greater curvature side, for each of the remnant stomach and the duodenal bulb, leaving a space almost 1 cm away from each stapling line. The cartridge side of the linear stapler (45-mm articulating medium/thick cartridge) is inserted to the transection line of the stomach. Then, the linear stapler fork side is carefully inserted into the bulb via the hole parallelly. This process makes The cartridge side is inserted parallel to the transection line of the stomach. The posterior walls, so-call V-shaped anastomosis, of both the gastric remnant and the bulbs, the dorsal side of the posterior suture line of the Billroth I. After arresting hemorrhage of the suture line, the entry hole is sutured by 2–3 points temporarily, avoiding slipping the liner staple. Finally, the entry hole is closed by a 45-mm linear stapler suture and created completing the anterior half of the anastomosis. The almost

60° anastomotic angle between the second anastomotic line and the first suture line is best designed for passing the food. This second anastomotic line length should be approximately 30 mm without the ventral staple lines. Thirdly, the linear staple with a 60-mm articulating medium/thick cartridge is placed in the direction toward the posterior wall and also placed almost perpendicular to the transection line of the stomach for resecting the blood less area. Those three staplers created the triangular anastomosis and simultaneously removed three staple lines of the duodenal transection line, the ventral line of the first anastomosis, the end of gastric transection line, and the ischemic tissues in between these staple lines. This technique yielded an end-to-end anastomosis of a triangular orifice [9].

2.2.3. Augmented rectangle technique

We have reported that laparoscopy-assisted distal gastrectomy (LADG) with extended lymph node dissection for gastric cancer was technically feasible and had favorable oncologic outcomes compared to the open gastrectomy [1, 10]. Unlike the extracorporeal anastomosis performed during the LADG, a standardized reconstruction method has not been established for the Billroth I (BI) gastroduodenostomy in the totally laparoscopic distal gastrectomy (LDG). A triangle anastomosis or a delta-shaped anastomosis is reported for the LDG without associated laparotomy. However, these two methods seem complicated for the LDG because of the need for stay sutures and further have the risks of ischemia or stenosis postoperatively. Therefore, we have developed an "augmented rectangle technique (ART)" as a new BI anastomosis performed during the LDG. The ART does not need stay sutures and therefore facilitates the LDG.

A 12-mm trocar for the laparoscope is inserted into the umbilicus. A 12-mm trocar is introduced into the left premaxillary line 1 cm below the costal margin. A second 12-mm trocar is inserted into the left midclavicular line 2 cm above the umbilicus. A 5-mm trocar is inserted into the right premaxillary line 1 cm below the costal margin. A third 12-mm trocar is placed by the camera assistant between the patient's legs (**Figure 9**).

Duodenal resection is performed with the surgeon's right hand using a 60-mm endoscopic linear stapler (ELS) from the greater curvature side of duodenum to lesser curvature side. The duodenum is transected just below the pyloric ring because it is necessary to preserve a long duodenum for anastomosis (**Figure 10**).

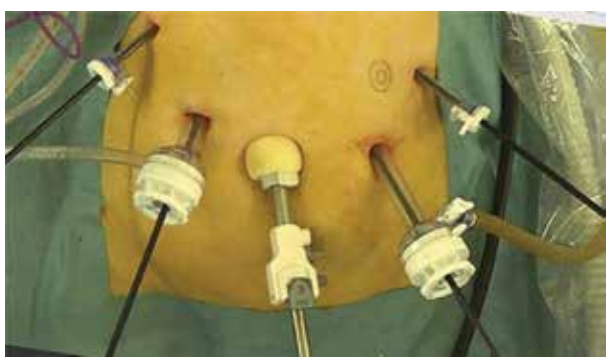

Figure 9. Augmented rectangle technique – depiction of procedure as described in the text, step 1.

Gastric resection is also done using two 60-mm ELS through the 12-mm trocar of the left lower quadrant from greater curvature to lesser curvature (**Figure 11**).

The superior duodenal vessels along the lesser curvature are transected to mobilize the duodenum (**Figure 12**).

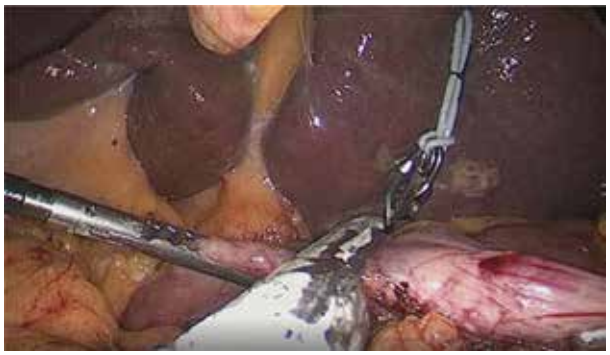

Figure 10. Augmented rectangle technique – depiction of procedure as described in the text, step 2.

Figure 11. Augmented rectangle technique – depiction of procedure as described in the text, step 3.

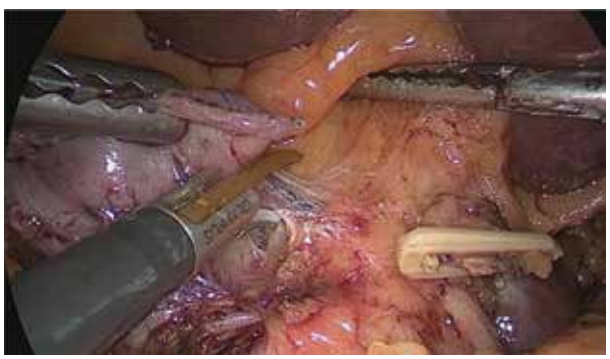

Figure 12. Augmented rectangle technique – depiction of procedure as described in the text, step 4.

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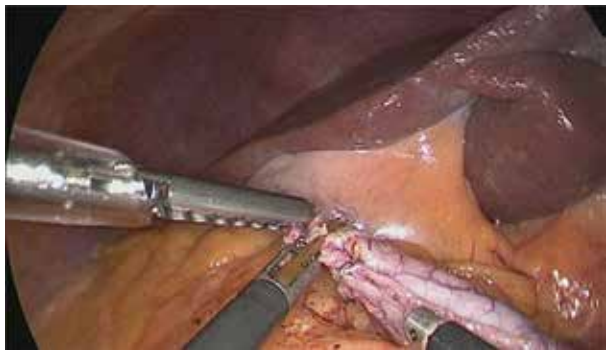

Figure 13. Augmented rectangle technique – depiction of procedure as described in the text, step 5.

An entry hole is made on the tip of the greater curvature side of the duodenal stump. The surgeon holds the tip of greater curvature side of the duodenal stump by his left hand located upside, and the assistant holds the tip of lesser curvature side of the duodenal stump by her right hand. Also, an assistant holds a suction by her left hand to prevent contamination by digestive tract contents in the abdominal cavity. A 5-mm incision is created in the previous stapled line at the greater curvature side of duodenal stump (**Figure 13**). Also, an entry hole is made on the tip of greater curvature side of remnant stomach (**Figure 14**).

The thicker cartridge fork of the 60-mm ELS is inserted into the stomach through the 12-mm trocar of the left lower quadrant. At this time, the tip of the ELS is pressed against the posterior gastric wall 2 cm away from the gastric resection margin, and the ELS is used to grasp the tissue close to the suture line near the ELS entry hole (**Figure 15**).

An ELS gently holding the posterior wall of the remnant stomach is rotated clockwise to the duodenal side, which is then ready for the gastroduodenostomy. The surgeon, who is standing on the patient's right, opens the ELS and moves its thinner jaw to cover the duodenum. The margin of resection at the lesser curvature end of the duodenum is rotated externally by 90° (**Figure 16**). The entire length of the ELS is inserted, and the device is then closed and

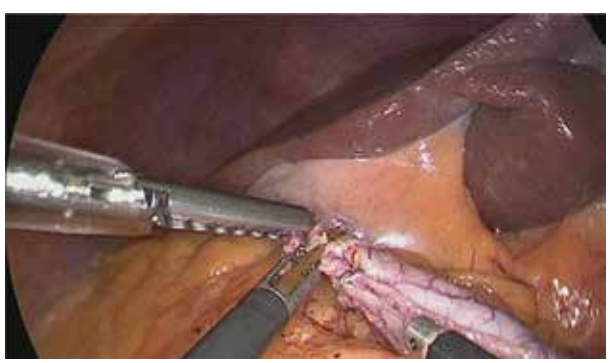

Figure 14. Augmented rectangle technique – depiction of procedure as described in the text, step 6.

fired. The ELS is withdrawn, the lumen is examined to confirm the absence of hemorrhage, and the residual duodenum and stomach are once again placed under adequate traction (**Figure 17**).

Figure 15. Augmented rectangle technique – depiction of procedure as described in the text, step 7.

Figure 16. Augmented rectangle technique – depiction of procedure as described in the text, step 8.

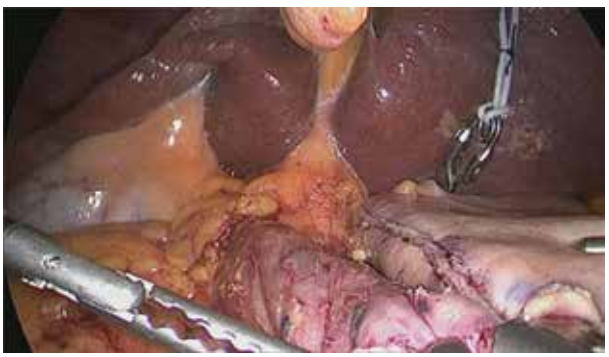

Figure 17. Augmented rectangle technique – depiction of procedure as described in the text, step 9.

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Next, the insertion hole is closed, and a margin is created with the use of a 30-mm ELS. This margin is closed on this side to avoid the need for stapling the transected duodenal margin (**Figure 18**). The surgeon grasps the cranial ends of a V-shaped suture line created with the first ELS, and care is taken to ensure that the gastric and duodenal resection margins remain

Figure 18. Augmented rectangle technique – depiction of procedure as described in the text, step 10.

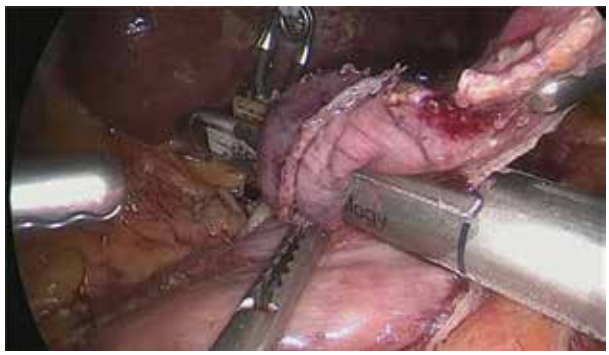

Figure 19. Augmented rectangle technique – depiction of procedure as described in the text, step 11.

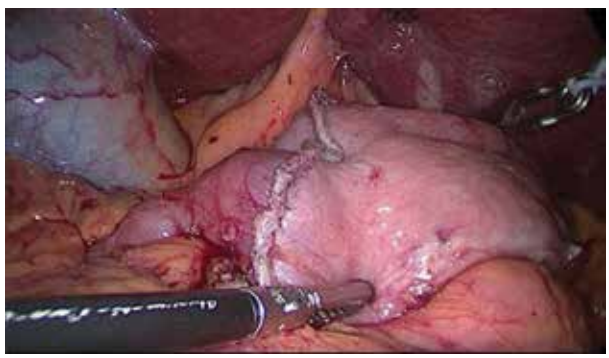

Figure 20. Augmented rectangle technique – depiction of procedure as described in the text, step 12.

close together. This creates the third side of a rectangle. Next, a 60-mm ELS is used to create the fourth side of the rectangle, while the entire stapled duodenal stump is being removed. The surgeon places caudolateral traction on the duodenal stump. Meanwhile, the assistant adjusts the position of the ELS to ensure overlap between the two suture lines, the first being along the second staple line and the second being along the gastric stump (**Figure 19**). With this suturing, the end-to-end anastomosis with an augmented rectangular gastroduodenal anastomotic stoma is complete (**Figure 20**).

3. Roux-en-Y reconstruction (RY)

Roux-en-Y reconstruction is one of the standard options after distal gastrectomy. In 1995, Kitano et al. used an extracorporeal gastrojejunostomy with manual suturing as a reconstruction procedure for distal gastrectomy. The improvements in stapling devices contributed to easy access to the site of operation. The advantage and disadvantage of RY reconstruction compared with Billroth I are as follows: prevention of bile reflex and reduction in incidence of anastomotic leakage.

3.1. Antecolic isoperistaltic RY reconstruction

A 12-mm trocar is inserted through the umbilical region by the open procedure, and then CO_2 pneumoperitoneum is established. A 12-mm trocar is introduced into the left pre-axillary line 1 cm below the costal margin. A 5-mm trocar is inserted into the left midclavicular line 2 cm above the umbilicus. The second 5-mm trocar is inserted into the right pre-axillary line 1 cm below the costal margin. Another 12-mm trocar is placed by the camera assistant between the patient's legs.

Laparoscopic mobilization of the stomach and lymph node dissection are carried out in a conventional procedure. The duodenum is divided distal to the pylorus with a 60-mm ELS; then, the stomach is divided with two ELSs. The specimen is removed through an extended 4-cm incision in the umbilical port. Following re-establishment of the pneumoperitoneum, the jejunum 20 cm distal to the ligament of Treitz is prepared for Roux limb, and the mesentery of this jejunum is divided for a distance of 8 cm. The prepared jejunum is then divided with an ELS to ensure a gastrojejunostomy without tension. A side-side jejunojejunostomy is fashioned 25 cm distal to the planed gastrojejunostomy using an ELS under direct vision through the umbilical incision. The jejunojejunostomy defect is closed with absorbable suture in an intermittent fashion. Following re-pneumoperitoneum, the jejunal limb is brought to the gastric remnant through an antecolic route. A right-oriented Roux limb is created such that the cut end of the Roux limb faces the greater curvature of remnant stomach. The jejunal limb is anastomosed to the greater curvature of remnant stomach side to side with an ELS; then, the site of entry hole is closed using an absorbable barbed suture. The duodenal stump is embedded with seromuscular suture and then fixed with the alimentary limb on the duodenal stump in a proper radian.

3.2. Antecolic antiperistaltic RY reconstruction

The duodenum and stomach are divided distal to the pylorus with three 60-mm ELSs. The specimen is removed through an extended 4-cm incision in the umbilical port. After

re-pneumoperitoneum, the proximal jejunum is identified and divided 25 cm distal to the Treitz ligament, and the mesentery of the jejunum is divided. The jejunum is divided with a 60-mm ELS. Small holes are made at the tips of linear stapler of the greater curvature side of the remnant stomach and distal side of jejunal stump. The gastrojejunostomy is performed between the posterior wall of remnant stomach and antimesenteric border of the distal jejunum with a 60-mm ELS. The common entry hole is closed with a 60-mm ELS. The jejunojejunostomy is performed through an umbilical minilaparotomy with a 60-mm ELS and hand-sewn suture.

4. Billroth II anastomosis

A Billroth II gastrojejunostomy enables wide stomach resection without anastomotic tension and is relatively easy during laparoscopic surgery. However, postoperative bile reflex into the remnant stomach is bothersome, and although rare, afferent loop syndrome can develop. So, Billroth II is rarely performed in Japan, but according to a nationwide survey conducted in 2014 in Korea, Billroth II was the adopted reconstruction after distal gastrectomy in 35.8% of cases [2].

4.1. Surgical procedure of Billroth II gastrojejunostomy

Herein, a laparoscopy-assisted uncut Roux-en-Y operation after distal gastrectomy as reported by Uyama et al. is described [11].

A laparoscopic mobilization of the stomach and en bloc lymph node dissection is performed, with a 4-cm long minilaparotomy made on the upper abdomen, through which the en bloc mobilized stomach and lymph nodes were delivered and the stomach is transected.

Laparoscopy-assisted reconstruction is then started. First, the transverse colon is retracted cephalad to expose the ligament of Treitz, and the jejunum 25 cm distal to this ligament is delivered via the minilaparotomy. The position of the gastrojejunostomy, whose length is 4 cm, is determined. Next, a Braun anastomosis is created extracorporeally. A stapler without a blade is placed across the afferent jejunal limb just distal to the created Braun anastomosis. This stapler is closed and fired extracorporeally, which enables occlusion of the afferent jejunal lumen without division of the jejunum. Seromuscular sutures are placed on this staple line, and delivered jejunum is replaced into the abdominal cavity. The operation turns again to a laparoscopic procedure. The gastrojejunostomy is started while observing the created Braun anastomosis and stapling across the jejunum laparoscopically. The corner of the greater curvature of the stomach stump is cut, and a small hole is made on the site of the planned gastrojejunostomy, using laparoscopic coagulating shears.

One jaw of the endoscopic linear stapler is inserted into the jejunum and the other into the stomach. The device is closed and fired, creating a gastrojejunostomy. The firing of the stapler converts the two holes into one common entry hole, which is closed by a laparoscopic hand-sewn technique. Two seromuscular sutures are placed between the afferent loop and lesser curvature of the gastric remnant to lift up the afferent loop, with the aim of preventing food flowing into the afferent loop. Finally, the seromuscular suture between the stomach and efferent loop is placed on the top of created V-shaped anastomosis, because this is the weakest point, due to the remaining tension.

5. Discussion

Our policy of reconstruction after distal gastrectomy is as follows. The first choice is Billroth I reconstruction. If the remnant stomach is too small for Billroth I reconstruction, we perform isoperistaltic RY reconstruction.

To date, we have used ART in 160 patients who underwent laparoscopic distal gastrectomy for stomach cancer between December 2013 and August 2017. These included 50 women and 110 men, with a mean age of 69.5 years and a mean body mass index (BMI) of 21.8. D1+ lymphadenectomy was performed in 81 patients, and D2 lymphadenectomy in 79 patients. The mean operation time was 227 minutes, and the mean blood loss volume was 47.3 mL. There were no intraoperative complications associated with reconstruction of the gastrointestinal tract, and none of the patients required conversion to open surgery. There were also no postoperative complications, such as anastomotic leakage or stenosis, associated with the reconstruction, and the mean postoperative hospital stay was 12 days (**Table 1**). Postoperative endoscopic examinations typically confirmed a large, elliptical anastomotic stoma (**Figure 21**).

Sex
Age
Body mass index
Operation time
Intraoperative blood loss
Extent of lymph node dissection
D1+/D2
Clinical stage
I/II/III/IV
Conversion to open surgery
Postoperative complications
Anastomosis-related complications
Anastomotic leakage
Anastomotic hemorrhage
Delayed gastric emptying
Non-anastomosis-related complications
Pancreatic fistula
Intra-abdominal infection
Intraperitoneal hemorrhage
Surgical site infection
Time to oral intake
Postoperative hospital stay

Table 1. Characteristics of patients in whom ART-based anastomosis was performed (***n*** = 160).

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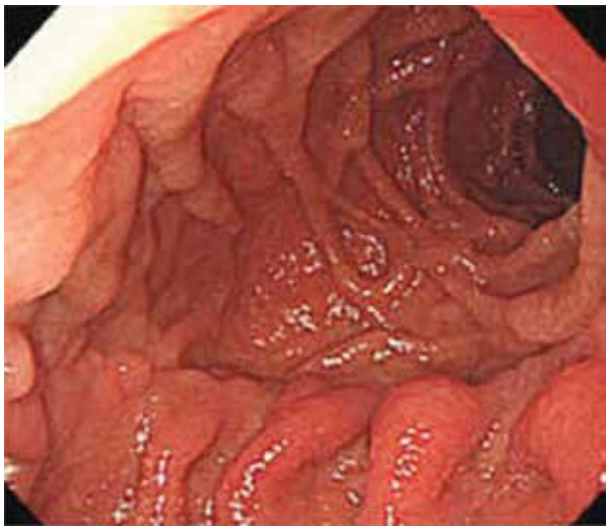

Figure 21. Elliptical anastomotic stoma in postoperative examination.

We performed antecolic isoperistaltic RY reconstruction in 52 consecutive patients who underwent laparoscopic gastrectomy for gastric cancer between April 2015 and December 2017. There were 32 women and 20 men, with a mean age of 70.4 years and mean body mass index of 22.3. D1+ lymphadenectomy was performed in 35 patients, and D2 lymphadenectomy in 17 patients. The mean operation time was 282 min, and the mean blood loss volume was 35.8 ml. All of the procedures were free of intraoperative complications. There were no postoperative complications, such as anastomotic leakage, intestinal obstruction, and duodenal stump leakage.

Conflict of interest

The authors declare no conflict of interest.

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Section 2

Chemotherapy

Chapter 4

Adjuvant Chemotherapy of Gastric Cancer

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Additional information is available at the end of the chapter

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Abstract

Adjuvant chemotherapy is a standard treatment for operable gastric cancer. However, the preferred treatment varies by geographical region. Southwestern Oncology Group (SWOG) conducted a, randomized trial of adjuvant chemotherapy for patients with surgically resected gastric cancer. The 3-year survival rates were 50% in the chemoradiotherapygroup and 41% in the surgery group. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial that compared perioperative chemotherapy with the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil) and patients with surgery alone had a 5-year survival rate of 36 and 23%. The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) showed that the 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group in stage II or III gastric cancer patients who underwent a D2 gastrectomy. An analysis of the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study showed 3-year disease-free survival, 74% in the chemotherapy and surgery group and 59% in the surgery-only group in the patients with stage II–IIIB gastric cancer who had D2 gastrectomy. In conclusion, for all patients with stage II and III gastric cancer, standard D2 gastrectomy and adjuvant chemotherapy are strongly recommended for improved survival rates.

Keywords: gastric cancer, D2 lymph node dissection, chemotherapy

1. Introduction

Gastric cancer is the second most common cause of cancer-related death worldwide [1]. Radical operation is the main treatment for gastric cancer, but the recurrence rate following surgery is high due to the early dissemination of cancer cells via the lymphatic system (about 40–80% in advanced gastric cancer) [1, 2]. In East Asia, especially Japan and Korea, D2 lymph node dissection is the standard treatment for operable gastric cancer [3, 4].

However, in the Western world, D2 gastrectomy is not as widely performed as in Japan and Korea [5]. Western surgical studies have shown that most patients present with tumors that penetrated the submucosa; they have a 5-year survival rate of 20–30% [6]. Postoperative chemotherapy is a standard treatment component of resectable gastric cancer and has improved patient outcomes [3, 4]. Treatment results of adjuvant chemotherapy may depend on the interaction between residual cancers and anticancer drugs. The Japanese recommendation for adjuvant chemotherapy is based on the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) study, which showed a survival benefit with adjuvant chemotherapy after D2 gastrectomy compared with surgery alone [4]. This study showed a survival benefit for stage II and IIIA gastric cancer [4]. However, the FLAGS trial for advanced gastric cancer or gastroesophageal cancer that compared cisplatin and S-1 versus cisplatin and fluorouracil in non-Asian countries did not prolong overall survival [7]. In Korea, adjuvant immunochemotherapy in advanced gastric cancer patients, who had undergone radical subtotal gastrectomy for stage III gastric cancer has been performed. For immunotherapy, a *Streptococcus pyogenes* preparation (picibanil) was followed by MF (mitomycin C and 5-FU) in the late 1990s and early 2000s [3, 8]. The Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study was designed to compare the effect of adjuvant capecitabine plus oxaliplatin after D-2 gastrectomy with stage II or III gastric cancer [1]. Although adjuvant chemotherapy is a standard treatment option for operable gastric cancer, there have been some differences concerning methods of chemotherapy and survival data between the Western world (Europe and North America) and East Asia (Korea and Japan). Therefore, this article summarizes the adjuvant chemotherapy for resectable gastric cancer using a medical literature review.

2. Treatment results with adjuvant chemotherapy

Treatment results of adjuvant chemotherapy may depend on the interaction between residual tumor and anticancer drugs. The tumor burden should be reduced as much as possible to obtain the most optimal survival benefit of adjuvant chemotherapy [10]. As compared to Western countries, the high survival rate in East Asia might have resulted from a selection of early-stage patients and radical operations, including systematic lymph node dissection [10]. The Southwestern Oncology Group (SWOG) conducted a two-armed prospective, randomized trial of adjuvant chemotherapy for patients with gastric adenocarcinoma surgically resected to negative margins (**Table 1**). Most patients (54%) had undergone a D0 dissection, which is less than a complete dissection of the N1 nodes. The chemotherapy regimen included fluorouracil, 425 mg/m^2 of body-surface area per day, and leucovorin, 20 mg, followed by radiotherapy of 4500 cGy of radiation at 180 cGy/day. The median survival time in the surgery group was 27 months as compared with 36 months in the chemoradiotherapy group [5]. The 3-year survival rates were 50% in the chemoradiotherapy group and 41% in the surgery-only group [5, 11]. The 503-patient United Kingdom National Cancer Research Institute (NCRI) Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial was the first randomized trial to demonstrate the survival benefit from the use of perioperative chemotherapy for patients with resectable gastric cancer compared with surgery alone.

Study	Regimen (surgery + chemotherapy surgery alone)	No. of patients	3-YSR (%)	5-YSR (%)
Macdonald et al. [5]	5FU + leucovorin + radiotherapy	281	50	40
	Control	275	41	30
Cunningham et al. [6]	Epirubicin + cisplatin +5FU	250	45	36
	Control	253	30	23
Sakuramoto et al. [4, 9]	S-1	529	80	71
	Control	530	61	70
Bang et al. [1, 2]	Capecitabine + oxaliplatin	520	83	78
	Control	515	78	69

YSR, year survival rate.

Table 1. Adjuvant chemotherapy compared to the surgical control of curative resection of stomach cancer.

The patients who received perioperative chemotherapy with the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil, 5FU) had a 5-year survival of 36%, compared with 23% in patients treated with surgery alone [12] (**Table 1**). Kim et al. evaluated 10,783 consecutive patients who underwent operation for gastric cancer [3]. The prognostic significance of treatment modality (surgery alone, surgery + chemotherapy, surgery + immunotherapy + chemotherapy <immunochemotherapeutic treatment>) was evaluated for stage III gastric cancer. The protocol for immunochemotherapy was as follows: Picibanil (a *Streptococcus pyogenes* preparation; Tokyo, Japan), mitomycin C 4 mg/50 kg, and 5-FU 500 mg/50 kg. They concluded that radical lymph node dissection, with more than 25 resected lymph nodes, improved survival in patients with stage II and IIIc disease; as postoperative adjuvant therapy, immunochemotherapy was most effective in patients with stage III disease. There were significant differences in survival in stage III patients; the 5-year survival rates were 44.8% for the immunochemotherapy group, 36.8% for the surgery + chemotherapy group, 36.8% for the surgery + chemotherapy group, and 27.1% for the surgery-alone group [3]. In the meta-analysis, which assessed entitled adjuvant chemotherapy after curative resection for gastric cancer in Non-Asian patients, Earle et al. concluded adjuvant chemotherapy may produce a small survival benefit of borderline statistical significance in patients with curatively resected gastric carcinoma [13]. Sakuramoto et al. reported that patients with stage II or III gastric cancer who underwent gastrectomy with extended (D2) lymph node dissection were randomly assigned to undergo surgery followed by adjuvant chemotherapy with S-1 or to undergo surgery only. The analysis of the follow-up data showed that the 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group [4]. Consecutive results of the ACT-GC trial showed the overall survival rate at 5 years was 71.1% in the S-1 group and 61.1% in the surgery-only group (**Table 1**) [9]. In the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) trial, the patients with stage II–IIIB gastric cancer who had curative D2 gastrectomy were randomly assigned to receive adjuvant chemotherapy of eight cycles of oral capecitabine (1000 mg/m^2 twice daily on days 1–14 of each cycle) plus intravenous oxaliplatin (130 mg/m^2 on day 1 of each cycle) for 6 months or surgery only. The 3-year disease-free survival was 74% in the

chemotherapy and surgery group and 59% in the surgery-only group. They concluded that adjuvant capecitabine plus oxaliplatin treatment after curative D2 gastrectomy should be considered as a treatment option for patients with operable gastric cancer [1].

3. Discussion

Adjuvant chemotherapy is a standard treatment option for operable gastric cancer and improves patient outcomes, but the preferred treatment differs by geographical region [10]. The recommended adjuvant treatment is chemoradiotherapy in the United States and perioperative chemotherapy in the United Kingdom and some parts of Europe [1, 5, 12]. The Japanese ACT-GC trial was the first large-scale randomized trial of adjuvant chemotherapy after curative resection with D2 gastrectomy [4]. In the Republic of Korea, the CLASSIC trial was the second large-scale randomized trial after D2 gastrectomy [1]. The survival rate of two Asian large-scale randomized trials was substantially higher than in the US Intergroup-0116 and UK MAGIC trials (78% in the CLASSIC trial, 80% in ACT-GC vs. 30–40% in the Intergroup-0116 and MAGIC trials) [1, 4, 5, 12]. Most recurrences after surgery of gastric cancer occurred within 3 years of surgery [14]. The duration of adjuvant chemotherapy differed from previous studies. Kim et al. had adjuvant chemotherapy for 24 months [3]. The ACT-GC trial had adjuvant chemotherapy for 12 months [4]. CLASSIC trial had adjuvant chemotherapy 6 months [1]. The duration of adjuvant chemotherapy after surgery was different, although similar survival results were present in two clinical trials. Kim et al. reported that radical lymph node dissection, with more than 25 resected lymph nodes, improved survival in patients with stage II and IIIa disease [3]. Postoperative immunochemotherapy was most effective in patients with stage II and III disease [3]. The favorable outcomes of Asian studies were a result of the consistent adoption of D2 gastrectomy and the quality control of surgery using video techniques [1, 4]. But postoperative chemoradiotherapy in the United States and perioperative chemotherapy in Europe is not based on D2 gastrectomy. In the Intergroup-0116 study, quality assessment was done for radiotherapy before the initiation of this treatment [5]. However quality control of surgery was not done, because patients were usually identified postoperatively, and they could not require specific surgical procedures. Only 10% of the patients underwent a D2 dissection, while 36% had a D1 dissection, and 54% had a D0 lymphadenectomy (a resection in which not all of the N1 nodes were removed) [5]. The low long-term survival rate of stomach cancer patients in Western studies might result from excessive residual tumor left behind during surgery. The high survival rate in countries such as South Korea and Japan might be the reflection of the small amount of residual tumor due to radical gastrectomy and extensive lymph node dissection [10]. Songun et al. [15] reported that after a median follow-up of 15 years, D2 lymphadenectomy with strict quality control is associated with lower locoregional recurrence and gastric cancer-related death rates in patients with stage II and IIIa disease than D1 surgery; they recommended D2 resection as the standard surgical approach to resectable gastric cancer [15]. The CLASSIC and ACT-GC trials showed the effectiveness of postoperative adjuvant chemotherapy with S-1 and XELOX for stage II and III gastric cancer patients who underwent D2 gastrectomy [1, 4]. Biological aspects may cause the different gastric cancer results between

East Asia and the Western world. However, no significant differences in prognostic factors were reported between these two regions of the world. In conclusion, for all patients with stage II and III gastric cancer worldwide, standard D2 gastrectomy and adjuvant chemotherapy are strongly recommended for a better rate of survival.

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GIST

Chapter 5

Gastric GIST

Tamer Saafan

Additional information is available at the end of the chapter

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Abstract

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. The stomach is considered the most common site of GIST, and the most common histopathological type of GISTs is spindle cell. Mutational analysis may help in defining the management of GIST. Multiple stratification modules are available for the estimation of GISTs' prognosis. Surgery is considered the only curative option for GISTs. The discovery of KIT protein has allowed better identification of GISTs and has allowed creation of selective tyrosine kinase inhibitors which dramatically affected GIST management. Results of trials on neoadjuvant imatinib therapy are promising. Adjuvant imatinib therapy is recommended for 3 years and has proven to improve outcome in high-risk GISTs. New therapeutic agents are now available in case of imatinib resistance. Follow-up of patients with GISTs depends on the type of GIST.

Keywords: GIST, gastric GIST, imatinib, tyrosine kinase inhibitors, primary GIST, metastatic GIST, recurrent GIST, imatinib resistance, KIT, PDGFRA

1. Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract (GIT) [1, 2]. All GISTs are considered to have some degree of malignant potential [3]. The most common site of GISTs is the stomach (60%) [4]. Other common sites are jejunum and ileum (30%), duodenum (5%), rectum (2–3%), colon (1–2%), and esophagus (<1%) [4].

It has been estimated that GISTs comprise about 18% of all sarcomas and 80% of mesenchymal tumors found in the GIT [5]. GIST's true incidence has been underestimated as they were usually misdiagnosed as leiomyomas, leiomyosarcomas, and leiomyoblastomas [6]. A study which used the Surveillance, Epidemiology and End Results (SEER) data from the National Cancer Institute, reported that the incidence of GIST has increased from 0.028 cases

per 100,000 in 1992 to 0.688 cases per 100,000 in 2002, which is a 25-fold increase in incidence. This increase occurred after the availability of diagnostic criteria, especially after the year 2000 [7]. In 1992, 93% of mesenchymal tumors of GIT were identified as smooth muscle neoplasm and 6% as GISTs. In 1995, Miettinen et al. [8] discovered that 70% of GIST are positive for CD34, a myeloid progenitor cell antigen. Furthermore, CD34 were also found in Schwann cell tumors and some smooth muscle tumors [6]. In the late 1990s, Hirota et al. [9] discovered that GIST expresses KIT (CD117), a receptor tyrosine kinase encoded by the proto-oncogene c-kit. Subsequent studies showed that mutations in c-KIT are present in 85–100% of GIST cases, but not in leiomyomas or leiomyosarcomas. These findings made a breakthrough in identifications and management of GISTs. In the SEER data published by Perez et al. [7], 82% of mesenchymal tumors of GIST were classified as GIST and 17% were classified as smooth muscle neoplasms in 2002, which shows how GISTs were poorly identified and were underdiagnosed [7]. GISTs appear to be more common in African Americans, Asians, and Pacific Islanders than in Caucasian patients, and men appear to have a slightly increased incidence [7, 10]. GISTs tend to be infrequent before the age of 30 and are most common after the age of 60 [7]. The median age of diagnosis is between 58 and 65 years [7, 10–13]. Two studies from Europe have shown that GIST incidence is about 1.1 cases/100,000/year [11, 14].

Though rare, GISTs can also affect the pediatric population. A study carried out by Miettinen et al. which included 1782 patients with gastric GIST, reported 44 cases under the age of 21 (2.6%) [15] with an age range from 5 to 21 and a median age of 14.5 years [15]. Prakash et al. [16] reported six cases of gastric GIST with a mean age of 12.8 and an age range from 10 to 18. Pediatric GISTs are commonly of epithelioid type, occur more in females, and have a higher incidence of multifocal presentation and lymph node metastasis. Pediatric GISTs also tend to lack a KIT or a platelet-derived growth factor receptor-α (PDGFRA) mutation [17, 18].

2. Risk factors

There are no known risk factors for GIST. Though most of GISTs are sporadic, the minority occur as part of hereditary syndrome.

Familial GIST syndrome: several family members with hereditary mutations in either the KIR or PDGFRA genes have been reported in the study [19–28]. These families have a higher risk to develop multiple gastric and small bowel GISTs. Some patients may have skin hyperpigmentation, dysphagia, gastrointestinal autonomic nerve tumors, intestinal fibromatosis, and inflammatory fibroid polyps [19–28].

Carney-Stratakis syndrome is an autosomal-dominant disease which is characterized by dyad of multifocal GISTs and paragangliomas [29]. Patients do not have KIT or PDGFRA mutations, but do have mutations of succinate dehydrogenase subunits (SDH) A, B, C, or D [30].

Carney's triad: a very rare non-heritable syndrome characterized by gastric GIST, paraganglioma and pulmonary chondromas. These patients are characterized by mutations succinate dehydrogenase subunit (SDH) C [29] but lack mutations of KIT and PDGFRA.

Neurofibromatosis type 1: patients with NF1 are more predisposed for multifocal GISTs that mainly affect the small intestine [31].

3. Molecular biology

GISTs are characterized by mutations in KIT and PDGFRA genes that encode tyrosine kinase receptor type III [32].

3.1. KIT-mutant GIST

Though 95% of GISTs are positive for KIT, only 60–85% have mutations in KIT. The most common mutations encountered are mutations of exon 11 (juxtamembrane domain) [4] which is found in about two-thirds of GISTs. Exon 9 (extracellular domain) is less common (9–20%) and is principally correlated with GIST of the small bowel and has a greater malignant potential [4, 33].

3.2. PDGFRA-mutant GIST

About 5–10% of GISTs have PDGFRA mutations which have a tendency for localized gastric GIST and epithelioid type [4]. The most common type of mutation is the PDGFRA exon 18 mutation D842V, which is associated with imatinib resistance and has a lower risk of recurrence than GIST with KIT mutations as well as a more benign course 9 [34].

3.3. Wild-type GIST

Approximately 12–15% of adult GIST and 90% of pediatric GIST do not have KIT and PDGFRA mutations [33]. Wild-type (WT) GISTs comprise GISTs that arise in NF1, Carney-Stratakis syndrome, and Carney triad [4]. WT GISTs may have other forms of mutations. BRAF V600E substitution has been described in 7–13% of WT GISTs [35, 36]. About 30% of WT GISTs are SDH deficient and occur solely in the stomach. They mainly affect children and young adults and have a variation in their nature from being indolent to progressive [4].

4. Histopathology

The three main histopathologic subtypes of GIST are spindle cell, epithelioid, and mixed types, with spindle cell type being the most common constituting about 70% of GISTs, while the other two subtypes, epithelioid and mixed, are less common, accounting for 20 and 10% of all GISTS, respectively [6]. Epithelioid GIST is commonly observed in the stomach and omentum [6]. About 95% of GIST will be immunohistochemical positive for CD117(c-KIT) [4]. Epithelioid type has a weaker KIT positivity than spindle cell type [37]. In addition, 70–90% are positive for CD34, 20–30% for actin, 8–10% for S-100, and 2–4% for desmin [38]. DOG1 marker, also known as ANO1, has more than 95% sensitivity for GIST and is expressed in more than 35% of GISTs negative for c-kit [39, 40].

5. Clinical picture

About 60% of GISTs occur in the stomach, 30% in the jejunum and ileum, 5% in the duodenum, 2–3% in the rectum, 1–2% in the colon, and < 1% in the esophagus [4]. About 70% of GISTs are symptomatic, 20% are asymptomatic, and 10% are discovered at autopsy [41]. The main symptoms of GIST are GI bleeding, abdominal discomfort, and abdominal mass. GISTs are highly vascular tumors and may grow quickly and cause massive gastrointestinal or intraperitoneal hemorrhage [42]. Obstruction symptoms such as dysphagia, obstructive jaundice, and small bowel obstruction may also occur [42].

Extragastrointestinal GISTs occur in less than 10% of GISTs and mainly occur intra-abdominally and affect omentum and mesentery. Such tumors are considered more aggressive than gastric GIST and have a poorer prognosis similar to small bowel GISTs [43, 44].

About 50% of patients will present with metastatic disease with the most common site of metastasis being liver at about 65%. Other common metastatic sites are omentum and peritoneum. Extra-abdominal metastasis, lung bone, and lymph node metastasis are not common [13].

6. Prognosis

Various risk stratification models (**Table 1**) have been proposed that are based on site, size, mitotic index, and tumor rupture. Gastric GISTs are known to have better prognosis than non-gastric GIST [46].

Tumor rupture is known to be associated with a very high risk of GIST recurrence [47]. TNM staging is also available for GIST staging [48]. However, these stratification systems are not commonly used in clinical practice.

As an alternative to the risk classification systems that stratify patients into distinct groups, others have quantified the risk of disease recurrence after complete resection as a continuous variable through the use of a GIST nomogram that includes the disease site [49]. Different nomograms have been developed by others as well.

GIST nomograms [49, 50] have been used to assess the risk of disease recurrence after complete resection as a continuous variable instead of the risk stratification systems that stratify patients into separate groups. Recently, a new risk stratification system has been developed in which tumor size and mitotic counts were assessed as continuous, nonlinear variables, and prognostic contour maps were then generated based upon these data plus site and tumor rupture [51]. These prognostic contour maps resulting from nonlinear modeling are used for the assessment of individualized outcomes.

Deletion type of mutations affecting codons 557 and 558 in KIT gene is considered a risk factor for recurrence regardless of different classification systems [4].

Pfetin is a prognostic biomarker which is still under investigation with promising results. Lack of Pfetin expression seems to be associated with a higher GIST recurrence [52]. Orita et al. [52]

Classification system	Prognostic criteria	Risk definition	Risk groups	Comments
NIH [6]	Tumor size Mitotic index	Aggressive behaviors of GISTs	Very low risk Low risk Intermediate risk High risk	Does not differentiate between malignant and benign tumors knowing the fact that even small-size tumors with a low mitotic count may metastasize Does not take GIST site into consideration
Modified NIH [45]	Tumor size Mitotic index Primary tumor site Tumor rupture	Risk of recurrence	Very low risk Low risk Intermediate risk High risk	Tumor location outside the stomach is a prognostic factor for survival independent of the mitotic count and tumor size
AFIP [46]	Tumor size Mitotic index location	Risk of recurrence	Very low risk Low risk Intermediate risk High risk	This classification considered a total area of 5 mm^2 in 50 fields HPF characterized by the use of different optical components, while in practice, 50 HPF typically corresponds to a total area of 10 mm^2 This classification is recommended by GEIS guidelines

Table 1. Different stratification systems for GISTs.

had 45 GIST cases, of which 37 were in the stomach. All GIST patients had R0 resection. There were seven recurrences with five recurrences being gastric GIST recurrences. Thirteen GIST patients were Pfetin negative and 5/13 Pfetin negative GISTs had recurrences [52].

7. Diagnostic evaluation

A computed tomography (CT) scan (**Figure 1a** and **b**) is considered the first imaging to be done to evaluate anatomic location, extension, and metastasis of GISTs. Oral and IV contrast should be given to delineate bowel margins. GISTs can display endophytic and exophytic growth, and large GISTs may appear heterogeneous due to focal areas of hemorrhage or necrosis [53]. Magnetic resonance imaging (MRI) is used to further evaluate liver metastasis or rectal GIST [54]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) is highly sensitive but not specific for GIST, and it is mainly useful to monitor response to tyrosine kinase inhibitors [55, 56].

Upper GI endoscopy may be useful for gastric GIST. Both GISTs and leiomyomas will appear as a submucosal mass with normal overlying mucosa and bulging into gastric lumen. Mucosal ulceration may occur. Endoscopic ultrasound (**Figure 2**) may not be useful, however, when combined with FNA sensitivity, and accuracy may reach 82 and 86%, respectively [57]. Routine biopsy is not needed routinely for local resectable gastric GISTs proved by imaging studies.

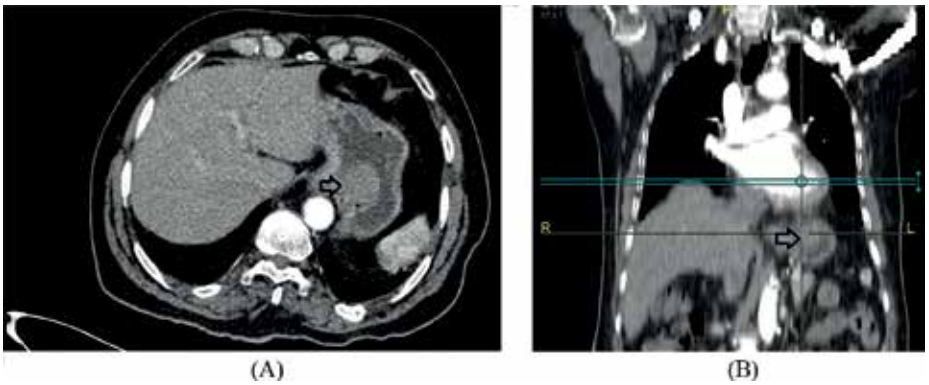

Figure 1. An axial (A) and coronal (B) CT image showing a well-defined mass lesion (arrow) in the anterior gastric wall in the proximal stomach measuring 2.9x2.5x2.7.

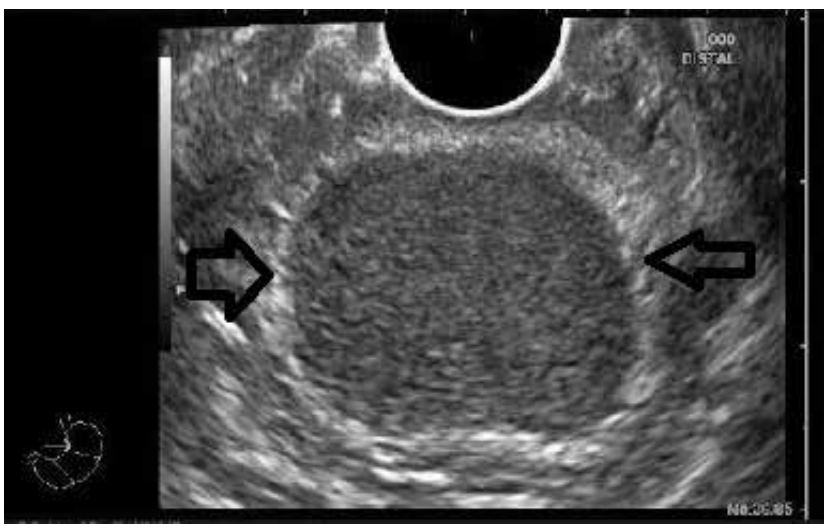

Figure 2. Gastric EUS showing a well-defined hypoechoic gastric submucosal lesion (between the two arrows) from the fourth layer of the stomach wall suggestive of GIST.

8. Management

Complete surgical resection is the recommendation of choice for localized GIST with a target of R0 resection with complete surgical removal of the tumor without disturbing the capsule [4]. Though surgery is considered the only curative option for GISTs, a multidisciplinary approach is needed for best medical and surgical management. Segmental resection of the stomach as wedge resection is accepted, and extensive resection is usually not needed. Lymphadenectomy is also not required as GISTs rarely metastasize to lymph nodes [4]. The discovery of KIT(CD117) (receptor tyrosine kinase) in GISTs has revolutionized GISTs management. Imatinib mesylate is a selective tyrosine kinase inhibitor that selectively inhibits KIT and had a significant impact on the prognosis of GISTs as will be discussed subsequently.

8.1. Management of primary resectable disease

8.1.1. Preoperative therapy for primary GISTs

There is still no consensus on the role of neoadjuvant imatinib therapy in resectable GISTs [4]. However, imatinib therapy might be considered for advanced or borderline resectable tumors. Multiple prospective and randomized trials have shown that neoadjuvant imatinib therapy (with a dose of 400 mg/day) in cases of advanced GIST will cause a reduction in tumor size and enable an R0 resection with an increased chance of organ preservation (**Table 2**). However, if KIT exon 9 mutation is detected and neoadjuvant therapy is planned, the dose may be increased to 800 mg per day as recommended by the European Society for Medical Oncology (ESMO) guidelines.

Study	Published year	Type of study	Type of patients assessed	Dose of imatinib given	Median follow-up	Primary end point	Results
RTOG (Radiation Therapy Oncology Group) 0132 [1, 116]	2009	Phase II prospective	1. Advanced primary GIST of >5 cm (Group A, 30 p) 2. Recurrent or metastatic tumors of ≥2 cm (group B, 22 p)	Neoadjuvant 600 mg/day for 8–12 weeks of treatment with a median of 65 days then 600 mg/day adjuvant therapy for 2 years	1. Group A 4.9 y 2. Group B 5.5 y	RFS	1. The 2-y estimated overall survival was 93.3 and 90.9% in Group A and Group B, respectively, with a median follow-up of 3 y 2. The 5-y PFS and OS were 57% in group A, 30% in group B, and 77% in group A, 68% in group B, respectively
McAufliffe et al. [117]	2009	Phase II randomized	Primary GIST Metastatic GIST of ≥1 cm 3. 19 patients involved	Neoadjuvant 600 mg/day given at 3, 5, or 7 days; then adjuvant 600 mg/day for 2 years	32 m	Tumor cell apoptosis	All patients had a radiographic response with 1 week of imatinib therapy. In addition, the rate of tumor cell apoptosis had a positive correlation duration of imatinib therapy where the maximum tumor cell apoptosis was seen with 7 days neoadjuvant imatinib therapy
APOLLON [118]	2012	Prospective open-label phase II	1. KIT or PDFRA positive GIST. Tumors had to be locally advanced, potentially resectable, and no metastasis 2. 45 patients involved	Neoadjuvant for 6 months 400 mg/day with no postoperative adjuvant therapy	36 m	Overall tumor response	1. R0 resection was achieved in 30/34 patients and PFS at 3 years was 85.2%. 2. Predicted operation was downsized with imatinib therapy

Study	Published year	Type of study	Type of patients assessed	Dose of imatinib given	Median follow-up	Primary end point	Results
Kurokawa et al. [59]	2017	Phase II prospective	1. Primary GISTs in the stomach with tumor size of ≥10 cm with no metastasis 2. 53 patients enrolled	1. Neoadjuvant 400 mg/day for 6 months 2. Adjuvant 400 mg/day for at least 1 year	32 m	R0 resection rate	1. The R0 resection was achieved in 91% of patients (48/53) and at least half of the stomach was spared in 42/48 patients who had R0 resection. 2. After R0 resection, all patients received imatinib 400 mg/day for at least 1 year. The 2-year OS and PFS were 98 and 89%, respectively

RFS, recurrence-free survival; OS, overall survival; y, years; m, months.

Table 2. Summary of studies assessing the role of neoadjuvant imatinib in treatment of GIST.

8.1.2. Surgery for primary GISTs

Surgical resection with negative margins is the recommended treatment for localized primary GISTs and is the only curative treatment for GIST [58, 59]. A published study that contained 200 GIST patients [13] with 46.5% of the cases being primary local GISTs and 39% of the cases gastric GIST, which was the most common type, reported that complete resection was achieved in 80 patients (86%) with primary disease, and those patients had a 54% of a 5-year survival rate with a median survival of 66 months, while patients with incompletely resected or unresectable disease had a median survival of 22 months. Complete resection of even a locally advanced disease is associated with improved survival [60].

Surgical resection is recommended for GISTs with a size of 2 cm or more [61]. However, there is still no consensus on the management of GIST less than 2 cm [62, 63]. Multiple studies have reported the occurrence of microscopic gastric GIST [64–67]. Agaimy et al. [68] discovered microscopic GISTs in 22.5% of consecutive autopsies for adults of >50 years old with all lesions detected in cardia, fundus, and proximal body. Kawanowa et al. [67] reported 35% of microscopic GISTs in patients who had gastric resection for stomach cancer. Ninety percent of these microscopic GISTs were in the upper body.

GISTs have been reported as an incidental finding discovered by routine OGDs and in gastric specimens post sleeve gastrectomy [69, 70] and have caused a dilemma about whether routine preoperative gastroscopy should be done before each bariatric procedure to avoid missing such incidental tumors [70]. Sepe et al. [71] had developed an algorithmic approach for gastric GIST which was adopted by The National Comprehensive Cancer Network (NCCN). They proposed that GISTs with no high-risk EUS features (irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity) can be followed up by EUS. NCCN adopted this approach and suggested that EUS surveillance every 6–12 months may be done for GISTs of <2 cm with no high-risk features [72].

Endoscopic resection of gastric small submucosal tumors is a promising technique with a favorable outcome. Andalib et al. [73] described endoscopic resection of 12 cases with gastric GISTs arising from muscularis propria with an average size of 2.4 cm and no complications of bleeding or perforation. However, 50% of cases had positive microscopic margins but there is no evidence that a positive microscopic margin after macroscopic resection requires re-excision [74], and with an average follow-up of 12 months, none of the patients had recurrence. Zhou et al. [75] described endoscopic resection of 26 cases of gastric submucosal tumors, out of which 16 were gastric GISTs. The mean tumor size was 2.8 cm and all of the tumors were resected completely without interruption of capsule. None of the patients had severe complications as bleeding perforation or abdominal abscess [75]. No recurrence was found with a mean follow-up of 8 months. Nevertheless, tumor spillage and perforation after endoscopic resection had been described [76], and the technique needs to be validated by prospective multicenter trials and cannot be routinely recommended.

As mentioned before, surgery is the main and only curative option for primary localized resectable GISTs [77]. The primary technical goal of surgery is complete macroscopic resection with an intact pseudocapsule and a negative microscopic margin (R0 resection) [77]. Routine lymphadenectomy is not needed as adult GISTs rarely metastasize to lymph nodes [78]. Pediatric GISTs, however, have a higher incidence of lymph node metastasis [78] and lymphadenectomy may be needed for this population [79, 80].

Wedge resection with negative margins is the usual treatment for gastric GISTs [81] unless the tumor is found invading the surrounding tissues where en bloc resection of involved surrounding organs may be appropriate [81]. Patients with low-grade tumors may have a 5-year survival up to 80%. It is still important to avoid tumor rupture and spillage, as this is associated with an increased risk of recurrence and low survival rates [47, 60]. The role of laparoscopy in gastric GISTs is developing with promising outcomes. Two meta-analysis studies have concluded that, when compared to open, laparoscopy seems to result in shorter hospital stays with no difference in operative time, adverse events, estimated blood loss, margin positivity, or overall survival (OS) and recurrence rates [82, 83]. Current NCCN guidelines [84] recommend that a laparoscopic wedge resection for gastric GISTs of 5 cm or less is appropriate and tumor resection may be done using a laparoscopic or a laparoscopic-assisted technique with hand port for GISTs more than 5 cm.

8.1.3. Adjuvant therapy for primary GISTs

Unlike neoadjuvant imatinib therapy, the role of adjuvant imatinib therapy is better established. Recurrence rates of 50% have been reported in localized GISTs that have been completely resected [4]. Multiple randomized trials have proven the efficacy of adjuvant imatinib.

The first randomized phase II trial done on the role of adjuvant imatinib was The American College of Surgeons Oncology Group (ACOSOG) trial Z9000 [85] which assessed the role of adjuvant imatinib dose of 400 mg/day for 1 year for patients with a high-risk GIST. High risk was defined in this study as a tumor diameter of >10 cm, intraperitoneal tumor rupture, or up to four peritoneal implants. The study involved 106 patients with GISTs, 50% of the cases were gastric GISTs. After a median follow-up of 7.7 years, the 1-, 3-, and 5-year overall survivals (OS) were 99, 97, and 83%, respectively, which is much better than historical controls (35%) [85]. The 1-, 3-, and 5-year RFS rates were 96, 60, and 40%, respectively. Recurrence free survival (RFS) was lower with a larger tumor size, KIT exon 9 mutation, a high mitotic rate,

and older age. They concluded that adjuvant imatinib for 1 year prolongs RFS and OS, but the optimal duration of adjuvant imatinib was still to be decided.

Three phase III trials have assessed the efficacy of adjuvant imatinib, ACOSOG Z9001 [86], SSG XVIII trials [87], and EORTC 62024 [88]. Only ACOSOG Z9001and EORTC 62024 had no treatment control arm. The American College of Surgeons Oncology Group (ACOSOG) trial Z9001 [86] is the first randomized phase III, double-blinded, placebo-controlled, multicenter trial done regarding the role of adjuvant imatinib therapy. A total of 359 patients were randomized to receive imatinib 400 mg/day for 1 year, and 354 patients were randomized to receive placebo for 1 year following surgical resection of the tumor. The trial reported that imatinib therapy significantly prolonged RFS when compared to placebo (98 versus 83%) in all risk categories (based upon size, mitotic rate, and location in the GI tract) [86]. Overall survival was similar at 1 year with 99.2 versus 99.7%, and imatinib therapy was tolerated with low side effects. The trial planned a minimum follow-up of 3 years for the patients but it was stopped early with a shorter median follow-up of 19.7 months. The lack of difference in overall survival in this trial may be explained by a short duration follow-up, a limited number of relapses, and a high degree of efficacy of imatinib in relapsed disease [89]. As a result of this study, The U.S. Food and Drug Administration approved adjuvant imatinib in the adjuvant setting by the U.S. Food and Drug Administration for GISTs of ≥3 cm, without guidance as to the optimal duration of treatment or which patients are most likely to benefit. The long-term results of this study were published with a median follow-up of 74 months with no difference in the 5-year RFS and OS.

Another phase III prospective, randomized, open-label trial was done by The Scandinavian Sarcoma Group (SSG) XVIII [87]. This trial compared 36 versus 12 months therapy of adjuvant imatinib (400 mg daily) in 400 patients with a high-risk-resected GIST with a median follow-up of 54 months. A high-risk GIST was defined as a tumor size of >10 cm, a mitotic count of >10/50 high-power fields (HPF), a tumor size of >5 cm with a mitotic rate of >5/HPF, or a tumor rupture. About 50% of the patients had gastric GIST in this study. The study reported prolonged 5-year RFS and OS rates for patients assigned for 36 months imatinib adjuvant therapy compared with patients assigned for the 12-month group, 65.6 versus 47.9% and 92% versus 81.7%, respectively. The results of this trial resulted in NCCN guidelines recommending adjuvant imatinib for at least 3 years for patients with intermediate or high risk of GIST recurrence [90]. In a latter follow-up report for the Scandinavian trial with a median follow-up of 90 months, patients assigned to a 3-year group had a persistent favorable outcome with significantly greater RFS (71 versus 52% and overall survival (92 versus 85%) [91].

The EORTC 62024 trial [88] is a phase III open-label randomized trial which assessed the efficacy of adjuvant imatinib for 2 years in localized surgically resected high- or intermediate-risk GISTs [88]. After surgical resection, 908 patients were randomized to either receive 2 years of imatinib 400 mg/day or observation alone. After a median follow-up of 4.7 years, RFS at 3 years was 84% in imatinib group versus 66% in control group and 69 versus 63% at 5 years ($P < 0.001$). No difference was detected in a 5-year OS. The 5-year imatinib failure-free survival (IFFS, the time to death or starting a TKI other than imatinib) was 87% in imatinib group and 84% in control group ($P = 0.23$). Among patients with a high-risk GIST (528 patients), there was a trend favoring adjuvant imatinib ($P = 0.087$).

As a result of the findings of the previous trials, both NCCN and ESMO guidelines as well as consensus of the scientific community recommend 3 years of adjuvant treatment with imatinib

in high-risk patients [4]. By contrast, adjuvant therapy is not needed in low-risk patients, and there are no sufficient data to support adjuvant imatinib therapy in intermediate-risk patients [4]. Whether doses higher than 400 mg/day should be used is still questionable. Moreover, whether the imatinib dose should be continued more than 3 years is not known. A single-arm phase II 5-year adjuvant imatinib trial, PERSIST5, has completed its accrual, and still survival data reports are pending. Whether patients who had R1 resection for their GISTs should receive adjuvant imatinib is also not clear as there are no data to support adjuvant imatinib therapy in such cases. Re-excision may be appropriate in these situations.

8.2. Management of metastatic and recurrent GIST

GISTs mostly recur in the first 5 years after surgical resection, while less recurrence is observed after 10 years [92]. A study, with pooled analysis from 10 series and included 1625 patients, reported that 5-year, 10-year, and 15-year RFS were 70.5, 62.9, and 59.9%, respectively [92]. It was observed that the larger the size of the tumor, the higher the risk of recurrence. Compared with tumors of <1.1 cm in size, tumors with sizes of 1.1–2, 2.1–5, 5.1–10.0, 10.1–15.0, and > 15 cm were associated with a hazard ratio (HR) of 2.19, 4.45, 21.56, and 27.98, respectively. There was also a positive correlation between tumor mitosis rates and risk of recurrence. Compared with tumors with a very low mitosis count (<2/50 HPF), tumors with a low count (2–5/50 HPF), a moderate count (6–10/50 HPF), and a high count (>10/50 HPF) were associated with HR of 3.78, 11.1, and 22.09, respectively. Gastric GISTs had better RFS than other types of GISTs. Tumor rupture was associated with a worse prognosis. About two-third and half of patients with recurrence had liver metastasis and peritoneal disease, respectively [93].

Patients with advanced (primary unresectable or metastatic GIST) are treated initially with imatinib rather than surgery.

A phase III randomized trail (EU-AUS trial) [94] included 946 patients randomized to either receive imatinib once or twice daily. At a median follow-up of 760 days, the trial reported that 56% of 473 patients receiving imatinib 400 mg/day had progressed while 50% (235) of 473 patients assigned to imatinib 400 twice/day had progressed. OS was 69 and 74%, respectively. There was no significant difference in response rates between the two groups. The study concluded that, although a daily dose of 400 mg of imatinib is enough, a dose of 400 mg twice daily significantly prolongs PFS.

In a phase II open-label multicentric randomized trial, B2222 study, which included 147 patients with advanced GIST, 73 patients received imatinib 400 mg/day and 74 patients received imatinib 600 mg/day. The study reported equal response rates, median progression-free survival, and median overall survival among both groups with a median survival of 57 months for all patients. No advantage was seen with using a higher dose of imatinib (600 mg/day) in this study. This study was followed by another phase III open-label multicentric randomized trial, S0033 study [95], which compared imatinib dose 400 mg/day to imatinib dose 400/mg twice daily. The study included 746 patients with advanced GIST with a median follow-up of 4.5 years. Similar findings were found with no statistically significant difference in response rates, PFS, or OS between either doses of imatinib. However, after progression on imatinib dose of 400 mg/day, 33% of the patients who were crossed over to receive a higher imatinib dose 400 mg twice daily achieved either an objective response or a stable disease [95].

Further analysis of data from EU-AUS and S0033 trials reported that tumor genotype has a significant prognostic impact on PFS and OS, with tumors with mutation of KIT exon 9 having a worse prognosis when compared to tumors with mutation of KIT exon 11 [96, 97].

A subsequent meta-analysis combining S0033 and EU-AUS trials [98] reported a minor albeit significant PFS advantage for a higher imatinib dose of 400 mg twice daily for patients with advanced GIST. The PFS benefit was only evident in patients with KIT exon 9 mutations treated with a high-dose imatinib without difference in OS between the two groups, while patients with KIT exon 11 had a more favorable prognosis. Thus, genotype is required for the treatment of advanced or metastatic GISTs.

The findings of the results of the previous studies [94, 95, 98] designated imatinib dosage of 400 mg/day to be the standard treatment for patients with advanced GISTs, and patients with advanced GISTs with KIT exon 9 mutations to be started on the higher imatinib dose (400 mg twice daily), keeping in mind that the toxicity of imatinib is dose-dependent [99]. Imatinib treatment should be life long as interruption of treatment has a higher rate of disease progression as proven by the phase III randomized trial [100–102]. Indications of surgery in advanced GISTs are still debatable. Multiple retrospective studies have shown that debulking surgery may be beneficial in patients with a stable disease without generalized progression as surgery may improve the prognosis. However, patients should be treated with imatinib first before attempting surgery [103–108].

8.3. Alternatives of imatinib in case of resistance or progression of disease with imatinib therapy

Most patients with advanced GISTs will show improvement with imatinib therapy, although a subgroup of patients will fail to show a response. Resistance to imatinib may be primary or secondary. Primary resistance is defined as continuous growth or growth within 6 months of therapy, and occurs in 15–20% of patients with advanced GIST [109] and occurs frequently in patients with wild-type (WT) GIST or KIT exon 9 mutations or D842V mutation in PDGFRA exon 18 [110]. Unfortunately, most patients develop secondary resistance, which is defined as patients who received treatment with imatinib for longer than 6 months and had an initial response and then developed progressive disease. Secondary KIT mutations occur frequently in KIT exons 13, 14, and 17 and a D842V mutation in PDGFRA exon 18 [111–113].

If a patient develops resistance, escalating imatinib dosage to 800 mg daily or shifting to a second-line therapy like sunitinib may be recommended.

Sunitinib is considered a second-line therapy for patients with advanced GIST refractory to imatinib therapy. Outcomes of a randomized phase III trial versus placebo reported a prolongation of the time to progression from 1.5 to 6.3 months in patients with GIST who progressed on imatinib treatment [114]. It is approved by the EMA and the FDA for the treatment of patients with GIST resistant to imatinib therapy and for patients who are not tolerant to imatinib therapy.

In case of progression on imatinib and sunitinib, regorafenib is considered a third-line therapy [4]. It was recently approved by EMA and FDA for the treatment of patients with unresectable or metastatic GISTs who are resistant or intolerant to imatinib and sunitinib, and

it was tested in a phase III randomized trial which included patients with advanced GIST who progressed after imatinib and sunitinib failed. The study reported that regorafenib, when compared to placebo, has significant improvement in PFS [115]. Inadequate data are available for the efficacy of other tyrosine kinase inhibitors (e.g., sorafenib, pazopanib, and ponatinib) for imatinib and sunitinib refractory GISTs [4].

9. Follow-up

There are no studies assessing the efficacy of different follow-up modules. Nevertheless, follow-up strategies were created based on the fact that most recurrences occur within the first 5 years after surgery.

A follow-up schedule frequency is based on the risk of aggressiveness and recurrence of GISTs [4]. CT is favored over other imagings, such as MRI and FDG-PET scan, because it is more readily obtainable, although other modalities can be used in case CT is inconclusive.

9.1. Follow-up for localized resectable GISTs

Very low-risk patients with surgically removed tumor do not require a follow-up. Low-risk patients require an annual CT. Intermediate- and high-risk patients require CT every 4 months for the first 1–2 years, every 6 months for 3–5 years, and then CT every year thereafter [4].

9.2. Follow-up for unresectable/metastatic GISTs

Follow-up should be done at the start of every 3 months and can be delayed to every 6 months if there is response to the treatment.

10. Conclusion

Surgery is the only curative option for GISTs. The discovery of KIT protein had allowed the development of tyrosine kinase inhibitors which considerably affected the diagnosis and management of GISTs. A multidisciplinary approach is required for optimal management. Neoadjuvant imatinib therapy has produced favorable results so far; however, more studies are needed to define the optimal dose and duration of imatinib therapy. Adjuvant imatinib therapy for 3 years improves outcome in patients with high risk. Mutational analysis has an important role in the management of GISTs. New therapeutic agents have been developed for patients with imatinib resistance.

Conflict of interest

The author declares that there is no conflict of interest.

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This book, *Gastric Cancer - An Update,* is a collection of reviewed and relevant research chapters, offering a comprehensive overview of recent developments in the field of gastric cancer. The book is comprised of single chapters authored by various researchers and it is edited by experts active in this field of study. All chapters are complete in itself but united under a common research topic. This publication aims at providing a thorough overview of the latest research efforts by international authors on gastric cancer, and opening new possible research paths for further novel developments.

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